NDA 18830

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-830

OCT 31 1985

Riker Laboratories
Attention: Florence N. Wong, Pharm.D.
270-3A 3M Center
St. Paul, Minnesota 55144

Dear Dr. Wong:

Please refer to your December 21, 1982 new drug application resubmitted on February 25, 1985 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide acetate, R-818) 100 and 200 mg Tablets.

We also acknowledge receipt of your amendments dated September 5 and 27, 1985; and October 14 and 24, 1985.

We have completed the review of this application including the submitted draft labeling and the application is approved effective on the date of this letter.

The labeling should be revised exactly as in the enclosed draft. Twelve copies of the final printed version of the revised labeling must be submitted to FDA prior to marketing. Marketing of the drug before the changes specified above are made and submitted to FDA renders the product misbranded under 21 U.S.C. 352.

Should additional information relating to the safety and effectiveness of these drug products become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

We would be pleased to meet with you to discuss the design of post-marketing trials that would potentially lead to less restrictive labeling.

Please submit one market package of the drug when available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact:

Mr. Denver Presley, Jr.
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

Summary Basis of Approval

JUL 25 1989

NDA 18-830

Applicant:
Riker Laboratories, Inc./3M
St. Paul, Minnesota 55144

Drug Generic Name:
Flecainide Acetate

Drug Trade Name:
Tambocor

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I. Indications for Use:

Flecainide is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

Flecainide is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of flecainide, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, flecainide, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients depending on their cardiac status and underlying cardiac disease.

The effects of flecainide in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including flecainide, has been shown to have a favorable effect on mortality or sudden death.

II. Dosage form, route of administration and recommended dosage:

A. Dosage Form: Oral Compressed Tablet

B. Dosage Strength: 100 and 200 mg

C. Recommended Dosage: For patients with sustained ventricular tachycardia, no matter what their cardiac status, flecainide, like other antiarrhythmics, should be initiated in-hosptial with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions.

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels, in patients with normal renal and hepatic function, may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, increases in dosage should be made no more frequently than once every four days, since during the first 2 to 3 days of therapy the optimal effect of a given dose may not be achieved.

For sustained ventricular tachycardia patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day, and the plasma level is below 0.6 µg/ml, the dosage may be cautiously increased to a maximum of 600 mg/day.

Use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and congestive heart failure particularly during the first few days of dosing. Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occassionally with flecainide while awaiting the therapeutic effect of flecainide. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen. An occasional patient not adequately controlled by (or intolerant to) a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients efficacy at the lower dose should be evaluated.

Flecainide should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction. The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg bid every four days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

In patients with renal impairment, the initial dosage should be 100 mg every 12 hours. Dosage increases should be made cautiously, at intervals greater than 4 days, observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change. It is recommended that plasma level monitoring be used to guide dosage adjustments (see below).

Based on theoretical considerations, rather than experimental data, the following suggestion is made: when transferring patients from another antiarrhythmic drug to flecainide allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting flecainide at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

Plasma Level Monitoring: The large majority of patients successfully treated with flecainide were found to have plasma levels between 0.2 and 1.0 µg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Because elimination of flecainide from plasma may be slower in patients with severe chronic renal failure or severe congestive heart failure, plasma level monitoring may be especially helpful in these patients.

III. Manufacturing and Control:

A. Manufacturing and Controls

The synthesis of the new drug substance is described in the application in sufficient detail to permit a determination that the assigned chemical structure is valid and that the specifications and test methods for the new drug substance are suitable. The specifications include limits on total and individual impurities as determined by specific assay methods. Adequate information has been provided to explain the various steps involved in the synthesis, and the organic chemical reactions employed are reasonable for the synthesis of this type of chemical compound. Raw materials and intermediates are satisfactorily characterized and their purity well controlled.

Controls over the manufacturing procedures, including specifications and test methods for the new drug substance, excipients, and the drug product, give sufficient assurance of the identity, strength, quality, and purity of the drug product.

B. Stability

The stability of the drug substance has been characterized. Stability studies have been conducted on the products in the proposed container/closure systems under room temperature and accelerated conditions. The data support the use of a two year expiration time. The data were obtained using a stability-indicating assay method, whose suitability has been demonstrated.

In addition, the applicant has stated their intention to place initial production lots on stability studies when they become available.

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C. Methods Validation

The analytical methods for control of the new drug substance and drug product have been independently validated by two FDA laboratories and found suitable for their intended purpose.

D. Labeling

The immediate container label and carton labels are in compliance with technical requirements pertaining to the following: established name, ingredients statement, control number, expiration date, prescription caution, applicant's name and address, and net contents statement. Likewise, the "Description" and "How Supplied" sections of the package insert are satisfactory with respect to the technical requirements of the regulations.

E. Establishment Inspection

Inspections of Riker Laboratories facilities in Northridge, California; Decatur, Alabama; and Loughborough, England have been performed to determine their compliance with Current Good Manufacturing Practice Regulations. A satisfactory report was received from the Office of Compliance, indicating no reason to withhold approval of the application.

F. Environmental Impact Analysis Report

A report on the impact on the environment was submitted. The manufacture of Tambocor tablets is expected to have little or no impact on the environment.

IV. Pharmacology

A. Antiarrhythmic Studies

Flecainide demonstrated antifibrillatory action both orally and parenterally in mice exposed to toxic concentrations of chloroform and showed greater potency than the reference antiarrhythmic agents, quinidine, lidocaine and procainamide. Intravenously administered flecainide had a wide spectrum of antiarrhythmic action in completely suppressing atrial and ventricular arrhythmias induced experimentally in pentobarbital anesthetized dogs by hydrocarbon-epinephrine, ouabain or aconitine administration and in conscious dogs by coronary ligation. Flecainide showed 100% effectiveness in suppressing these arrhythmias with average effective doses ranging from 1 mg/kg (against ouabain-induced tachycardia) to 7.2 mg/kg (against aconitine-induced atrial arrhythmia) and was approximately two to three times more potent than the reference agents.

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Flecainide was effective in blocking atrial arrhythmias induced by direct application of methacholine chloride to the right atrium of open-chest, pentobarbital anesthetized dogs. An intravenous dose of 2.5 mg/kg was required to completely block the arrhythmia. An intravenous dose of approximately 5.0 mg/kg was required to convert an established atrial arrhythmia to sinus rhythm. An intravenous infusion of flecainide at the rate of 0.2 mg/kg/min in two dogs (average total of dose of 4.5 mg/kg) was effective in blocking the methacholine-induced arrhythmia for approximately 30 minutes.

Five dogs with stable ventricular tachycardia induced by ouabain were infused with flecainide (0.25 mg/kg/min) to a total intravenous dose of 18.0 to 50.0 mg. Based on an average weight of the dogs of 28.5 kg, the dose of flecainide administered was estimated to be 0.5 to 2.0 mg/kg. In three dogs no effect was obtained. In one dog there was a conversion to sinus rhythm and in one a conversion to A-V dissociation. When the study was repeated using a similar protocol, efficacy was demonstrated in four of five dogs treated with an average intravenous dose of 2.8 mg/kg.

When compared to some of the new antiarrhythmic compounds, e.g., disopyramide, tocainide, encainide, mexiletine and lorcainide, i.v. flecainide was one of the most effective, (in terms of % arrhythmias converted) in treating ectopic ventricular tachycardia induced by toxic doses of ouabain in male and female pentobarbital anesthetized dogs. Only encainide showed greater potency than flecainide in treating this arrhythmia. All compounds showed minor effects on arterial blood pressure. Disopyramide, encainide and lorcainide showed greater bradycardic effects than the other compounds.

Five and 10.0 mg/kg doses of flecainide, injected directly into the duodenum of pentobarbital anesthetized dogs, suppressed ectopic ventricular tachycardia induced by ouabain with a 100% conversion rate achieved at the higher dosage. Time to onset of suppression and duration of suppression were also dose related (at 10.0 mg/kg all arrhythmias were fully suppressed within about 30 minutes with response lasting about two hours). In conscious dogs with arrhythmias induced by ouabain, intraduodenally administered flecainide generally suppressed the arrhythmia within 15 minutes and for greater than one hour after a 10.0 mg/kg dose (67% conversion rate). Flecainide administered by intramuscular injection at doses of 5.0 and 10.0 mg/kg was also effective in suppressing arrhythmias induced by ouabain (about an 80% conversion rate at 10.0 mg/kg). The onset of action was approximately 20 minutes and the duration of action was generally greater than one hour, irrespective of dose level.

Ventricular arrhythmias induced by coronary artery ligation were suppressed by flecainide administration either by oral gavage or by intraduodenal injection at a dose of 10.0 mg/kg (100% conversion at 15.0 mg/kg i.d.). Prolonged antiarrhythmic activity (greater than one hour) was observed only after

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intraduodenal administration. Flecainide administered in gelatin capsules was effective in suppressing this arrhythmia; however, a dose of 20.0 mg/kg was required (for a 100% conversion rate). At 10.0 mg/kg, transient suppression of the arrhythmia was observed in 1/4 dogs tested and traces of flecainide were found in the stomach and duodenum indicating incomplete absorption in these experiments. Flecainide, administered by intramuscular injection at a dose of 10.0 mg/kg, was generally effective in suppressing ventricular arrhythmias induced by coronary artery ligation with conversion achieved 50% of the time. The onset of action was less than 15 minutes while the duration of action was generally less than 30 minutes.

Pretreatment of coronary ligated dogs with reference cardiovascular compounds revealed that propranolol, phentolamine, procainamide and quinidine seemed to enhance the antiarrhythmic potency of flecainide, whereas digoxin and diphenylhydantoin seemed to diminish its antiarrhythmic potency. Slight cumulative toxicity was observed with the combinations of flecainide with chlordiazepoxide, diphenylhydantoin, procainamide, quinidine or lidocaine. The combinations of flecainide with propranolol or digoxin showed greater cumulative toxicity resulting in death after small to moderate doses of flecainide (average of 7.0 mg flecainide/kg fatal in three of three propranolol pretreated dogs with deaths attributed to respiratory depression; average of 14.5 mg flecainide/kg fatal in two of four digoxin pretreated dogs with deaths attributed to ventricular fibrillation). These same doses of flecainide produced no serious toxic effects in control flecainide experiments.

A meta-o-dealkylated metabolite of flecainide was effective on intravenous administration in suppressing ectopic ventricular tachycardia induced by ouabain; however the metabolite was considerably less potent than flecainide in treating this arrhythmia (average converting dose 5.0 mg/kg vs less than 2.0 mg/kg for flecainide). The metabolite showed rather weak antiarrhythmic action compared to flecainide when administered intravenously to coronary artery ligated dogs (at an average dose of 5.0 mg/kg) with ventricular arrhythmias.

A second metabolite of flecainide, the meta-o-dealkylated lactam, was not effective (at a dose of 10.0 mg/kg i.v.) in suppressing ectopic ventricular tachycardia induced by ouabain in pentobarbital anesthetized dogs.

B. Electrophysiological Studies

In isolated dog Purkinje fibers, a bath concentration of 1.0 µg/ml of flecainide had the following electrophysiological effects: alterations in the contour of the action potential included a decrease in the rising velocity, a shortening of the plateau (phase 2 repolarization), a decrease in the overshoot and no change in the duration; the effective refractory period was lengthened; local premature responses were abolished; the

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rate of spontaneously beating fibers was decreased (a concentration of 2.0 µg/ml rendered these fibers quiescent); no effect on the slope of diastolic depolarization (phase 4) was observed in concentrations up to 5.0 µg/ml; there was a decrease in the ability of fibers to undergo depolarization; the period during an action potential when premature responses could be elicited was shortened; the increased slope of diastolic depolarization and other changes induced by ouabain (2.1×10^{-7}M) and epinephrine (1.0 µg/ml) were abolished at concentrations of 2.0 to 10.0 µg/ml of flecainide. The electrophysiological effects of flecainide in isolated atrial and ventricular muscle fibers were similar to those observed in Purkinje fibers except that the duration of the ventricular action potential was increased. Flecainide did not alter the changes in the ventricular action potential induced by relative hypoxia.

In open-chest pentobarbital anesthetized dogs, flecainide infused intravenously at 0.1 and 0.25 mg/kg/min had the following electrophysiological effects: conduction was depressed in all tissues of the heart and the degree of depression was related to the plasma concentration of the drug; depression of conduction was most pronounced in the His-Purkinje system and in the ventricular muscle. Flecainide did not greatly depress sinus node function or junctional rhythms even at high plasma concentrations (up to 10 µg/ml and 8 µg/ml, respectively). Ectopic atrial and ventricular rates were slowed by flecainide and this slowing was related to plasma concentrations of the drug. The slowing of ectopic ventricular rate was less than that reported for lidocaine, but similar to that reported for propranolol. Mean aortic blood pressure was not greatly changed even at high plasma concentrations of flecainide. Flecainide increased ventricular fibrillation threshold; however, the increase was not consistent and was of less magnitude than values reported for lidocaine or propranolol. Results of experiments carried out in pentobarbital anesthetized open chest dogs indicate that flecainide may be more effective in increasing ventricular fibrillation threshold during premature ventricular beats than during supraventricular pacing.

In pentobarbital anesthetized open chest dogs, flecainide, at plasma concentrations of 0.4 to 0.7 µg/ml, prolonged atrioventricular conduction. Both flecainide and ouabain slowed intra-atrial conduction, ventricular activation time and A-V nodal conduction during atrial fibrillation. Used in combination, the effects of the two drugs were additive. Propranolol pretreatment potentiated the actions of flecainide by further prolonging intra-atrial conduction, A-V nodal conduction and His-Purkinje conduction. A-V conduction may be slowed to such an extent that A-V block could be a complication.

Intravenous doses of 5.0 or 10.0 mg/kg of flecainide administered to pentobarbital anesthetized closed chest dogs significantly decreased sinus rate and prolonged His-Purkinje conduction. No significant effect was seen on either intra-atrial or atrioventricular conduction. Ouabain and propranolol induced conduction changes were variably affected by flecainide. However, these changes were proportionate to the changes of flecainide alone. Hence, conduction abnormalities induced by digitalis and propranolol were not exaggerated.

C. Myocardial Studies

When tested in isolated guinea pig atria, flecainide showed greater myocardial depressant action than either quinidine or lidocaine. No cholinergic receptor stimulant or beta-adrenergic receptor blocking actions were observed.

Studies in isolated cat papillary muscle on the effects of flecainide on sodium kinetics, sodium and potassium content and contractile characteristics showed that higher concentrations of flecainide increased the half-time (t 1/2) of the faster of two sodium influx kinetic pools, depressed the developed tension and increased the stimulation threshold in a dose-related manner. It is believed that, because of the crudeness of the technique used and inadequate stabilization of the muscle preparations, the true changes in sodium flux caused by flecainide were not seen in these experiments.

Flecainide had a mild negative inotropic action after 1.0 mg/kg iv in the open chest vagotomized dog. However, subsequent higher doses generally had a slight positive inotropic effect. The 1.0 mg/kg iv dose also produced an apparent slight decrease in ventricular function. There was no further decrease with higher doses of flecainide; rather, there was some recovery of the apparent loss of function after the first dose. A mild negative inotropic response to flecainide was also observed with relatively large intracoronary doses in the isolated perfused rabbit heart.

In a comparative cardiovascular study in open chest, vagotomized, pentobarbital anesthetized male and female dogs, encainide had greater hypotensive and bradycardic effects than either flecainide or disopyramide at an intravenous dose of 5.0 mg/kg. Flecainide had a mild negative inotropic effect at 5.0 mg/kg, whereas both disopyramide and encainide showed negative inotropism at 3.0 mg/kg and greater negative inotropism than flecainide at 5.0 mg/kg.

D. Cardiovascular Studies

Evidence of depressed nerve conduction and/or ganglionic blockade was observed in anesthetized dogs where attenuation of responses to carotid occlusion, right vagal stimulation and cardiac nerve stimulation were [illegible]onstrated after intravenously administered flecainide, 5.0 [illegible] body weight.

Flecainide infused (15 mg/min) intravenously in conscious dogs at doses of 1.0 mg/kg/day for 14 consecutive days showed no significant electrocardiographic changes. Increasing the daily dose to 5.0 or 15.0 mg/kg resulted in increases in heart rate, PR interval, QRS duration, QT interval and T-wave amplitude (effects were of dosage dependent severity) during dosing on day 14 (not on days 1, 4 or 7). Values returned to normal following termination of the infusion. There was a significant (p less than 0.05) positive correlation between plasma concentrations (determined 15 minutes after completion of infusion) and electrocardiographic changes. Retching and/or emesis and marked muscle tremors were frequently observed in all of the high dose animals. There were no deaths.

At 5.0 mg/kg of flecainide, administered intravenously to anesthetized dogs, there was no apparent effect on cardiovascular hemodynamics including mean aortic, pulmonary arterial and central venous pressures, cardiac output and total peripheral resistance.

In experiments designed to measure changes in coronary arteriovenous oxygen differences and plasma potassium levels in normal pentobarbital anesthetized dogs and in conscious coronary ligated dogs (24 hours post ligation), a 5.0 or 7.5 mg/kg intravenous dose of flecainide did not alter either coronary arteriovenous blood gas or plasma potassium concentrations.

No apparent vasodilatory activity was observed for flecainide given intra-arterially in doses up to 1.2 mg in the dog perfused hind limb at constant blood flow. At an effective intravenous antiarrhythmic dose of 5.0 mg/kg, flecainide had no apparent effect on regional blood flow in carotid, femoral, renal and superior mesenteric vascular beds. Coronary blood flow in isolated perfused rabbit heart showed minimal variable changes at relatively high intracoronary doses of flecainide.

Large cumulative intravenous doses of flecainide administered to pentobarbital anesthetized dogs by constant infusion gradually depressed heart rate and blood pressure and finally caused respiratory failure and death. The lead II electrocardiographic changes observed during flecainide infusion were an increased amplitude of the T-wave and a decreased amplitude of the QRS

complex. Similar cardiopulmonary effects were seen with lidocaine and quinidine; however, the average fatal dose of flecainide was considerably less than the fatal doses of lidocaine and quinidine (infusion rates for all drugs 1 mg/kg/min). Some idea of the relative margin of safety of flecainide may be assessed from a ratio of the fatal intravenous dose found in this study to the average effective antiarrhythmic intravenous dose derived from three experimentally induced arrhythmias in the pentobarbital anesthetized dog. The table below shows values computed for this ratio (or relative safety margin) for flecainide, lidocaine and quinidine and indicates that flecainide may have greater safety potential than either lidocaine or quinidine.

	Fatal Dose mg/kg	Effective Dose mg/kg	Dose Fatal/Effective
Flecainide	31.0	3.9	7.9
Lidocaine	60.0	9.3	6.5
Quinidine	86.0	11.7	7.4

Procainamide was considerably less toxic than the other compounds including flecainide and though it showed some similar cardiovascular effects, they were generally less severe. Procainamide has been omitted from the above table as it was not fatal in the one dog in which it was infused at 1 mg/kg/min. At 2 mg/kg/min it was fatal in only 1/4 dogs (total dose of 30 mg/kg). Chronic pretreatment with 5.0 mg/kg daily doses of flecainide for 14 days resulted in a greater sensitivity to the toxic effects of an acute intravenous infusion (1 mg/kg/min) of flecainide on the 15th day with average fatal dose reduced by 29%.

E. Other Pharmacological Studies

In pentobarbital anesthetized male and female dogs with neuromuscular blockade by succinylcholine chloride and mechanical ventilation with room air, intravenous flecainide (5.0 or 10.0 mg/kg) did not block bronchoconstriction induced by intravenous histamine or methacholine.

Local anesthetic action similar to lidocaine was demonstrated for flecainide administered topically to the rabbit cornea. When given intramuscularly flecainide showed regional nerve block of equal intensity but of longer duration than lidocaine in the mouse sciatic nerve preparation.

In isolated smooth muscle tissues (trachea, ileum, uterus and seminal vesicle) taken from rats and guinea pigs, flecainide demonstrated a relatively weak nonspecific spasmolytic action.

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In isolated smooth muscle tissues (trachea, ileum, uterus and seminal vesicle) taken from rats and guinea pigs, flecainide demonstrated a relatively weak nonspecific spasmolytic action.

Dose-related CNS depression was observed in rats administered flecainide intraperitoneally. Death was observed at 100.0 mg/kg. Male and female mongrel dogs administered flecainide orally showed mild CNS depression and mild tachycardia at 10. and 20.0 mg/kg. Vomiting was the limiting factor for the administration of higher oral doses of flecainide to dogs. A slight delayed weight loss was observed in dogs treated with flecainide at all oral doses.

Flecainide did not block electrically induced arterial thrombosis in the pentobarbital anesthetized male rat at an intravenous dose of 5.0 mg/kg body weight.

F. Preclinical Metabolism

Metabolic studies with flecainide in laboratory animals have been conducted with intravenous and/or oral dosage in dogs, rats, mice, cats, monkeys, and swine. Results and conclusions on the primary metabolic aspects of flecainide from these various animal studies are summarized below.

The results from comparative radiochromatographic (TLC) metabolite fraction analyses indicate that flecainide undergoes more routes of biotransformation (more metabolite fractions) in each of the three chronic toxicity animal species (dog, rat, and mouse) than in humans. While at least seven or eight metabolites are detectable in the urine of all three animal species, only two major metabolites and two or three minor ones are detectable in human urine. Although fewer metabolites are found in human urine, all of the metabolites in human urine are also present in the urine of all three animal species; in addition, the two major metabolites in human urine and plasma (both the meta-O-dealkylated metabolite and the meta-O-dealkylated lactam of flecainide) are also major metabolites in the urine from each of the three animal species. Conjugation of flecainide metabolites (glucuronide and/or sulfate) is a major route of biotransformation in all four species. Overall, these results indicate that the three chronic toxicity animal species were exposed to all of the same metabolites of flecainide as are present in human urine and plasma; from a biotransformation viewpoint, the evaluation of chronic drug toxicity in these animal species is a reasonable assessment of flecainide safety for humans.

After multiple oral dosing of pregnant rats with carbon-14 labelled flecainide, the presence of radioactivity in fetal and embryo-placenta tissues on gestation Days 10 and 15 indicates that the lack of teratogenic effects in teratogenicity studies with flecainide in rats cannot be attributed to lack of exposure of the fetuses to flecainide and/or its metabolites during the period of organogenesis.

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Following a single intravenous dose of carbon-14 labelled drug to rats, flecainide and/or its metabolites (radioactivity) distribute extensively to many tissues, but not extensively to the brain; subsequently, carbon-14 is eliminated at a relatively rapid rate. Although cardiac tissue levels of unchanged flecainide are 11- to 12-fold higher than plasma levels, the levels of flecainide in heart and plasma decline at the same rate.

In rats, dogs, cats, and monkeys, flecainide and/or its metabolites (carbon-14) do not appear to be retained in any of the tissues, except for pigmented ocular tissues. In contrast to albino rats (non-pigmented eye), levels of carbon-14 (flecainide and/or its metabolites) are relatively high in the uveal tract of the three species (dog, cat, and monkey) with pigmented eye tissues as compared with non-pigmented eye tissues, other tissues, and plasma. However, long-term toxicity studies in dogs (12-18 months), baboons (six months), albino rats (two years), and mice (18 months) have revealed no evidence of ocular toxicity and no ocular toxicity has been found in humans with administration of flecainide for periods of 12 months and longer.

In the cat, procainamide and/or its metabolites (carbon-14) are also present at relatively high levels in pigmented eye tissues and are also retained. Since procainamide is an antiarrhythmic for which there is a record of extensive chronic use in humans without ocular toxicity, these procainamide results provide additional evidence to include with the growing literature that indicates a lack of relationship between drug binding to pigmented eye tissues and ocular toxicity. Overall, there is no evidence that the presence and retention of flecainide and/or its metabolites in pigmented ocular tissues is of clinical consequence.

After oral dosage, flecainide absorption is prompt and nearly complete in humans, dogs, rats, and mice, based on comparison of oral/IV plasma level data and/or urinary excretion data. In contrast to humans, flecainide undergoes substantial presystemic biotransformation (first-pass effect) in dogs; plasma AUC's of flecainide after oral dosage to dogs are about 50% of those after IV dosage. First-pass effect was not assessed in other animal species. For toxicity assessment, drug-diet feeding used for rodents provides extensive absorption and the solid dosage forms used for dogs provide nearly complete drug absorption.

In comparison to humans, the plasma half-life of unchanged flecainide (Table 1) is relatively short in dogs (about 1 hour), rats (about 2 hours), cats (about 1 hour), swine (about 1 hour), and monkeys (about 4 hours). Although the difference in plasma half-life for flecainide in humans as compared with laboratory

animals is quantitatively striking, it is similar to the differences reported for several other drugs. For flecainide, no definitive, direct explanation for this difference can be given; however, available comparative data (presystemic biotransformation and excretion data) for dogs and rats indicate that this difference in plasma half-life between humans and animals most probably results, at least in part, from differences in rates of flecainide biotransformation (probably hepatic) and, perhaps, in the extent of biliary excretion. Apparently, these animal species possess drug-metabolizing-enzyme systems that can biotransform flecainide at a faster rate than humans.

Flecainide and/or its metabolites (radioactivity) are excreted in both urine and feces of dogs, rats, and monkeys; the drug appears to undergo extensive biliary elimination in dogs and rats. Only about 1 to 2% of a single dose is excreted in dog urine as unchanged flecainide (Table 1); in comparison, excretion of unchanged drug in rat urine accounts for about 25% of the dose and in mouse urine accounts for about 11 to 13% of a single dose.

Table 1

Comparative Pharmacokinetics and Excretion for Unchanged Flecainide in Humans and Laboratory Animals

Species	Healthy Human	Beagle Dog	Albino Rat	Albino Mouse	Mongrel Cat	Yorkshire Swine	Rhesus Monkey
Pharmacokinetics of Unchanged Flecainide							
Dose (mg/kg)[a]	0.5-3.5	5.0	5.0	5.0	5.0	2.0	5.0
Dose Route	Oral & IV	Oral & IV	Oral & IV	Oral & IV	IV	IV	IV
Time to Peak Plasma Level (hrs)[b]	:3 hrs (0.5-6 hrs)	:1 hr (0.5-3 hrs)	0.5 hr	-[c]	-[c]	-[c]	-[c]
Plasma Half-Life	13 hrs (7-22 hrs)	:1 hr (55-85 min)	:2 hrs (95-130 min)	-[c]	:1 hr (45-85 min)	:1 hr	4 hrs (2-5 hrs)
Excretion of Unchanged Flecainide							
Dose (mg/kg)	0.6-3.5	4.0	5.0	5.0	-[c]	-[c]	-[c]
Dose Route	Oral	IV	IV	Oral & IV	-	-	-
Urinary (% dose)	27% (10-50%)	1-2%	:25%	11 & 13%	-	-	-
Collection Period (hours)	48-144	24	24	24			

[a] Single doses.
[b] Oral dosage.
[c] Not available.

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G. Acute Toxicity

Symptoms following acute oral or parenteral administration of flecainide to mouse, rat, dog or cat included, at the higher doses tested, tremors, ataxia, dyspnea and convulsions. Also observed in dogs and cats (only two of the latter species studied) was emesis. Deaths were attributed to respiratory depression and arrest. Surviving animals recovered within hours.

Species	Sex	Route	No. Gps. No./Gp.	Dose Range (mg/kg)	Maximum Non-lethal (mg/kg)	LD_{50} (95%CL) (mg/kg)
Mouse	M	p.o.	4/10	100-400	100	190(151-239)
Mouse	M	i.v.	3/10	20-25	20-23	24(23-25)
Rat	F	p.o.	5/10	100-800	200-400	567(422-763)
Rat	M	p.o.	7/10	250-630	250	498(452-549)
Rat	F	i.v.	4/10	16-50	16-20	23(21-25)
Rat	M	i.v.	5/10	10-50	10-16	20(17-23)
Dog	M&F	p.o.	3/2	25-100	25-50	50*#
Dog	M&F	i.v.	3/2	15-30	15-20	20*

* gross estimate. LD50 not calculated.
# aqueous solution. When drug administered in capsules median lethal dose was over 200 mg/kg (no deaths at any of tested levels, 20-200 mg/kg).

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Mouse	M	i.v.	3/10	20-25	20-23	24(23-25)
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Rat	M	p.o.	7/10	250-630	250	498(452-549)
Rat	F	i.v.	4/10	16-50	16-20	23(21-25)
Rat	M	i.v.	5/10	10-50	10-16	20(17-23)
Dog	M&F	p.o.	3/2	25-100	25-50	50*#
Dog	M&F	i.v.	3/2	15-30	15-20	20*

* gross estimate. LD50 not calculated.
# aqueous solution. When drug administered in capsules median lethal dose was over 200 mg/kg (no deaths at any of tested levels, 20-200 mg/kg).

H. Chronic Toxicity

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Chronic studies were carried out in baboons, dogs, mice and rats. The studies of longest duration in each of these species are outlined below.

Study:	* 18 Month Mouse	** 24 Month Rat	*** 18 Month Dog	**** 6 Month Baboon
Maximum Exposure Evaluated:	60 mg/kg/day for 18 months	60 mg/kg/day for 24 months	20 mg/kg b.i.d. for 18 months	15 mg/kg b.i.d. for 6 months
Animals/ Dose Level:	70/sex	50/sex	4/sex #	2/sex
Mode of Admin.:	diet	diet	tablets	fruit juice

* Charles River CD-1/ICR; 42-44 days of age at start
** Charles River Crl:COBS(WI)BR; 37-39 days of age at start
*** beagles; 7.8-14.3 kg at start
**** Senegalese; 5.5-10 kg 4 days prior to initiation of dosing
\# Not reflected in this number were an additional 2 dogs/sex which were added to the high dose group (only) for the purpose of an interim necropsy @ 12 months. One female and one male from this interim necropsy group plus one female and one male scheduled for terminal necropsy were not dosed during a 2 week recovery interval following 9 months of dosing to determine reversibility of ECG effects.

The only finding associated with treatment in the mouse was a slight reduction in body weight gain relative to controls. This effect was much more pronounced in rats where mean body weight decrement at conclusion of study ranged from 11-30% of control weight (dose-dependent effect with all dosage levels affected). An increased incidence of interstitial cell adenoma in testes at high dose levels in the rat was attributed to increased survival in that group. All of the flecainide-treated male groups had better survival (dose related) than the control male group. (An apparent improvement in female survival at the highest dosage level was of borderline significance). There was a dose-related increased incidence of urinary incontinence in the high and intermediate dosage male groups. There was a decreased incidence of focal degeneration and fibrosis of heart and of chronic nephritis in high dose males and females. A decreased incidence of pituitary chromophobe adenoma was recorded in all treated female groups (dose dependent). Overall incidence of tumor bearing animals was lower in these groups. In high dose females there was a decreased incidence of focal degeneration and hemmorhage of adrenal, and of mammary fibroadenomas.

There was one high dosage death in each of the non-rodent studies. Toxic signs were not observed preceding death and tissue examinations were unremarkable. Expected (and reversible) EKG changes were noted in dogs (EKGs not recorded in baboons). Other findings in dogs included peripheral flushing (all treated groups) which gradually decreased in occurrence after the initial 3-4 months of study and a mean body weight loss or failure to gain weight which occurred at high and intermediate dosage levels during the last six months of study. Mild morphologic changes in the lung (focal inflammation and hemosiderin-containing macrophages) were present (as early as 12 months) in both the intermediate and high dosage levels. These changes were closely linked with elevation in CPK enzyme activity. Other than the one death there were no remarkable findings in baboons.

I. Effects on Reproduction

Segment II studies (for teratogenic potential) were carried out in mice, rats and rabbits.

Species	Route	Period of Admin.	Dosage Levels (mg/kg/day)	Females/ Dose Level
Mouse (OF1)	p.o.	gestation days 6-15	0,5,20,80	28
Mouse (OF1)	i.v.	gestation days 6-15	0,1,2.5,5	25-26
Rat (CRCD)	p.o.	gestation days 6-16	0,10,20,50	21-24
Rat (CRCD)	p.o.	gestation days 6-15	0,10,20,50	22-29
Rabbit (NZ*)	p.o.	gestation days 6-18	0,10,20,25,30,35	15-26
Rabbit (NZ*)	i.v.	gestation days 6-18	0,1,2,4	16-19
Rabbit (DB#)	p.o.	gestation days 6-18	0,10,20,30	15-17

* NZ = New Zealand # DB = Dutch Belted

Adverse effects were observed with oral administration in New Zealand rabbits with increased resorptions noted at 25 or more mg/kg and teratogenic findings (clubbed paws, heart changes, sternebral and vertebral abnormalities) observed at 30 or more mg/kg. Similar findings were not reported with the i.v. route of administration or with oral dosing in the Dutch Belted rabbit. In both rat studies the highest dosage level was associated with a significant increase in the number of fetuses with one or more bipartite bodies in the vertebrae.

A combined fertility/general reproduction and peri/post-natal study was carried out in the (CRCD) rat (up to 50 mg/kg/day administered from before breeding to weaning). There were no adverse effects on fertility, reproductive performance, late fetal development or growth of pups during lactation. The F1

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pups (exposed in utero during gestation and during lactation via milk) exhibited no adverse effects of flecainide on growth, CNS development or subsequent reproductive performance (second generation study in which no further treatment was administered).

J. Mutagenicity

Neither Ames test nor mouse lymphoma test (up to 8,000 mcg/plate in former, up to 500 mcg/ml in latter; both tests conducted with and without metabolic activation) revealed a clearly significant effect of flecainide on the number of revertants, although an equivocal finding (max effect at 4,000 mcg/plate with less than 100% increase in revertants) with Salmonella strain TA 1535 (only without metabolic activation) was reproducible. Nor was the drug associated with cytogenetic abnormalities in a bone marrow cytogenetic study in which rats were dosed for five days at levels of up to 20 mg/kg/day.

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V. Medical

The approval of flecainide rests on the analysis of 38 studies in 923 patients and 354 subjects. A total of 546 patients have been exposed to the drug for at least 30 days, 274 of these patients for at least one year and 99 patients for at least two years. Information on clinical pharmacology was obtained in 26 studies, and information on efficacy and safety was obtained in 12 studies.

Safety information was obtained in an additional 201 patients in clinical studies outside the U.S. (Germany, France, United Kingdom and Norway). Sixty-nine (34%) of these patients were followed for more than one year.

The approval is further supported by analysis of spontaneous adverse reaction reporting in the United Kingdom where flecainide has been marketed since September 1983 with an estimated 1,300 patient-years exposure, and in Germany where flecainide has been marketed since September 1982 with an estimated 65,000 patient-years exposure.

A. Clinical Pharmacology and Metabolism

A list of the studies in which the clinical pharmacology and metabolism of flecainide has been studied is contained in the following Table. This Table lists the purposes, investigator, study design, number of subjects or patients, and the duration of therapy and doses used in each study.

The clinical electrophysiology of flecainide has been defined by both the intravenous and oral routes in studies conducted in the U.S. In addition, a number of studies have been conducted outside the U.S. and reported in the published literature. The clinical hemodynamic effects of the drug have been investigated in patients after single intravenous doses and in both patients and subjects after single oral doses. Assessment of the effects of flecainide on left ventricular function in patients has also been made in conjunction with some of the efficacy studies on the drug.

The pharmacokinetics, metabolism and bioavailability of flecainide have been defined in nine studies in healthy subjects and pharmacokinetics were determined in one multicenter study in patients with premature ventricular contractions. Additionally, the effects of renal insufficiency and congestive heart failure on the single dose kinetics of flecainide have been determined in separate studies in patients with each disease state.

Drug-drug interactions of flecainide have been systematically investigated in two studies in healthy subjects; one investigated the potential interaction with digoxin, and the other studied the effects of propranolol and flecainide when given concurrently.

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818V-001	Drug safety & pharmacokinetics in healthy male subjects	D. Hunninghake	Open	9 subjects	Single iv dose 2 @ 0.5 mg/kg over 5 min 2 @ 1.0 mg/kg over 5 min 2 @ 1.5 mg/kg over 5 min 2 @ 2.0 mg/kg over 5 min 1 @ 5,7.5,10,12.5 mg at 2 hour intervals
R-818V-003	Safety & effect of flecainide on cardiodynamics in patients undergoing diagnostic catheterization	P. Miller	Open	12 patients	Single iv dose 4 @ 0.5 mg/kg over 5-10 min 2 @ 0.75 mg/kg over 5-10 min 3 @ 1.0 mg/kg over 5-10 min 3 @ 1.5 mg/kg over 5-10 min
R-818V-005	Determine rate & extent of absorption of flecainide. Obtain pharmacokinetic data, assess safety & tolerance in healthy male subjects	G. Levis	Open	16 subjects	Single oral & iv doses 4 @ 60 mg oral 7 days later 60 mg iv 4 @ 120 mg oral 7 days later 120 mg iv 4 @ 180 mg oral 6 weeks later 200 mg oral 4 @ 240 mg oral only
R-818V-015	Effect of flecainide on intracardiac conduction system & sinus node function when administered as a single intravenous dose to patients	R. Helfant	Open	15 patients	Single iv doses of 1.0 mg/kg administered over 5-10 min.

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONTINUED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-018	Determine plasma levels of flecainide during seven days of oral dosing. Assess multiple-dose pharmacokinetics of flecainide. Determine safety & tolerance of multiple oral doses of flecainide in subjects	G. Lewis	Open	16 subjects	Seven days of dosage 4 @ 80 mg bid 4 @ 120 mg bid 4 @ 150 mg bid 4 @ 180 mg bid
R-818V-022	Determine the effect of intravenous flecainide on right and left ventricular performance using radionuclide angiography in patients with suspected or diagnosed heart disease	R. Helfant M. Bodenheimer	Open	20 patients	Single iv dose 4 @ 1.0 mg/kg over 5-13 min 5 @ 1.5 mg/kg over 5-13 min 10 @ 2.0 mg/kg over 5-13 min 1 @ 0.7 mg/kg over 5-13 min
R-818V-023	To compare the effects of flecainide & vehicle on left ventricular function using catheter tip sensors in patients with suspected or diagnosed left ventricular disease.	M. Hodges	Double-blind vehicle controlled parallel study	2 patients	Single iv dose 1 @ 2.0 mg/kg 1 @ vehicle control

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONTINUED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
-818-024	Compare the effects of oral flecainide and placebo on left ventricular function using non-invasive techniques.	M. Hodges	Double-blind, placebo-controlled two period crossover	10 subjects 20 patients	Single oral dose 250 mg
-818-026	Compare relative rate & extent of flecainide absorption between a tablet & capsule formulation.	G. Levis	Open, randomized two period crossover	16 subjects	Single dose 200 mg of each formulation
-818-030-01	Dose ranging efficac, of oral flecainide in patients with PVCs. Plasma pharmacokinetics during washout. Short-term (2 weeks) efficacy.	J. Anderson	Open, placebo-controlled.	9 patients	100 mg bid for 3 days; then 200 mg bid for 3 days, if needed; then 250 mg bid for 3 days, if needed. Two-weeks of bid dosage with efficacious regimen.
R-818-030-02	Dose ranging efficacy of oral flecainide in patients with PVCs. Plasma pharmacokinetics during washout. Short-term (2 weeks) efficacy.	M. Hodges	Open, placebo-controlled.	10 patients	100 mg bid for 3 days; then 200 mg bid for 3 days, if needed; then 300 mg bid for 3 days, if needed. Two-weeks of bid dosage with efficacious regimen.

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONTINUED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-030-03	Dose ranging efficacy of oral flecainide in patients with PVCs. Plasma pharmacokinetics during washout. Short-term (2 weeks) efficacy.	R. Woosley	Open, placebo-controlled.	11 patients	100 mg bid for 3 days; then 200 mg bid for 3 days, if needed; then 250 mg bid for 3 days, if needed. Two-weeks of bid dosage with efficacious regimen.
R-818-038	Determine effect of chronic renal impairment on flecainide elimination. Assess influence of hemodialysis on flecainide elimination. Determine if dosage adjustments are necessary in this patient population.	R. Cutler	Open	10 patients with varying degrees of chronic moderate renal failure. 10 patients with end stage renal disease	Single oral dose 200 mg
R-818-039	Pharmacokinetics & cardiodynamics of flecainide in healthy subjects & in patients with congestive heart failure.	J. Francioza	Open	9 subjects 10 patients	Single oral dose 200 mg

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONTINUED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-041	Effects of oral flecainide & propranolol administered alone & concurrently on cardiac function in healthy male subjects.	J. Holtzman	Open	10 subjects	Total of nine days of dosage 200 mg bid
R-818-045	Effects of flecainide on plasma digoxin levels when given concurrently to subjects.	G. Lewis	Open	15 subjects	Five days of oral dosage 200 mg bid
R-818-049	Comparative oral absorption of three flecainide dosage formulations & the effect of food on drug absorption.	A. Cohen	Open, randomized four period crossover	18 subjects	Single dose 200 mg of each formulation; 200 mg as tablet with food
R-818-050-03	Metabolic disposition of carbon-14 labeled flecainide in subjects	A. Cohen	Open	4 subjects	Single dose 200 mg ^{14}C-labeled flecainide

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONTINUED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-053-01	Effects of oral flecainide on the inducibility of ventricular tachycardia during electrophysiologic provocation	J. Stewart	Open	2 patients	200 mg tid on day 1, then bid for three to five days
R-818-053-02	Effect of oral flecainide on the inducibility of ventricular tachycardia during electrophysiologic provocation	J. Anderson	Open	15 patients	200 mg tid on day 1, then four to six days of therapy 300 mg bid
R-818V-054-01	Effects of iv flecainide on left ventricular function (invasive).	B. Singh	Double-blind randomized vehicle controlled parallel study	18 patients	Single iv dose 6 @ 1.0 mg/kg 6 @ 2.0 mg/kg 6 on vehicle
R-818V-054-02	Effects of iv flecainide on left ventricular function (invasive).	P. Troup	Double-blind randomized vehicle controlled parallel study	2 patients	Single iv dose 1 @ 2.0 mg/kg 1 @ vehicle control

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONCLUDED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818V-058-01	Effects of iv flecainide on left ventricular function in patients with reduced ejection fractions (25-45%) (invasive)	B. Singh	Open	10 patients	Single iv dose 5 @ 1.0 mg/kg 5 @ 2.0 mg/kg
R-818-061-01	Plasma level-dose proportionality and absolute bioavailability in healthy male subjects	M. Zinny	Open, randomized four period crossover	12 subjects	Single oral doses of 100, 200, and 300 mg as tablet when fasting and single iv dose of 100 mg
81-152-PRO-BE-002	Effect of food and antacid on flecainide absorption in subjects	T. Tjandramaga	Open, three period crossover	10 subjects	Single oral doses of 200 mg as tablet when fasting, with food, and with antacid

Studies Cited from Published Literature

Hellestrand KJ, Bexton RS, Nathan AW, et al: Acute electrophysiologic effects on flecainide acetate on cardiac conduction and refractoriness in man. Br Heart J 48:140-148, 1982.

Seipel L, Abendroth RR, Breithardt G: Elektrophysiologische effekte des neun anti-arrhythmikums flecainid (R-818) beim menschen (Electrophysiologic effects of the new anti-arrhythmic drug flecainide (R-818) in man.) Z Kardiol 70:524-529, 1980.

Vik-Mo H, Ohm OJ, Lund-Johansen P: Electrophysiologic effects of flecainide acetate in patients with sinus nodal dysfunction. Am J Cardiol 50:1090-1094, 1982.

1. Clinical Electrophysiology

a. Routine Electrophysiological Studies

Studies carried out to determine the electrophysiologic effects of flecainide have shown the following:

- Marked effects on conduction in all parts of the heart which are most prominent in the His-Purkinje system and ventricle.

- Effects on refractoriness are less prominent than those on conduction.

These effects of intravenous flecainide on the intracardiac conduction system were examined in an open-label study of 15 patients with known or suspected cardiac disease, who were undergoing diagnostic catheterization (Study 015). Flecainide lengthened the conduction intervals (AH, HV, and PA), but only demonstrated statistically significant increases in the AH and HV intervals at 20 minutes postdosing (Table 2). Plasma flecainide levels at this time averaged 502 ng/ml (range 134-1784 ng/ml).

These observations were confirmed in a published open-label study of 47 patients using intravenous doses of 2.0 mg/kg (Hellestrand et al). All patients were undergoing routine electrophysiological study for investigation of symptoms or evidence of recurrent arrhythmias or cardiac conduction disturbances. No change was noted in sinus cycle length; PA, AH and HV intervals were prolonged significantly. The duration of the QRS complex increased an average of 23% (range 0% to 79%). The QT interval showed a slight prolongation, but this was entirely due to the increase in QRS duration. Changes in refractoriness were small and were significant only in the ventricular effective refractory period. Plasma flecainide levels, obtained during the time electrophysiological measurements were being made, averaged 335 ng/ml (range 85-785 ng/ml).

Findings were similar in an open-label study of 27 patients undergoing diagnostic catheterization conducted in Germany (Seipel et al). The effects of flecainide in patients with normal baseline values are presented in Table 3. Dose-related increases in AH and HV intervals were observed after intravenous injection of 1.0 mg/kg, or 2.0 mg/kg; increases were also noted in HRA-A and V-RVA intervals, although these did not appear to be particularly dose-related. Only the change in ventricular effective refractory period was statistically significant at both doses. In contrast, there were only small and often

insignificant increases (5% to 15% of control values) in the refractoriness of the atria and AV node. Average plasma flecainide levels obtained with the 1.0 mg/kg dose (n=17) were 366 ± 161 ng/ml at 5 min. and 146 ± 52 ng/ml at 20 min. After 2 mg/kg given as a bolus (n=6) levels were 851 ± 17 ng/ml at 5 min. and 306 ± 4 ng/ml at 20 min. Four patients received the 2.0 mg/kg dose as a 1.0 mg/kg bolus plus a 1.0 mg/kg infusion given over 20 minutes. Plasma flecainide levels from this regimen were 397 ± 266 ng/ml after 5 minutes and 343 ± 81 ng/ml at 20 minutes. Initial plasma levels from 1.0 mg/kg doses and all levels from 2.0 mg/kg doses are within the range accepted as effective for suppression of PVCs (200-1,000 ng/ml). These investigators found no significant effects on sinus node function in this study even in six patients with sinus node dysfunction. However, a Norwegian study found that flecainide depressed sinus node function in 11 patients with pre-existing sinus node dysfunction (Vik-Mo, et al).

The effects of oral flecainide were also studied in 14 patients with inducible ventricular arrhythmias (Study 053-02). Therapeutic response in this open-label study was evaluated using programmed electrical stimulation and effects on intracardiac conduction were measured. Flecainide was given orally, 200 mg or 150 mg bid, for 4-6 days after baseline EP testing. Plasma levels of flecainide at the time of repeat testing averaged 773 ± 222 ng/ml, comparable to those associated with suppression of PVCs. Flecainide significantly increased intracardiac conduction times as well as the ventricular refractory period (Table 4). This indicates that the electrophysiologic effects of flecainide are similar by both the oral and intravenous routes.

As a consequence of its effects on intracardiac conduction, flecainide produces dose-related effects on intervals measured on the surface electrocardiogram. This is illustrated by the changes in ECG intervals (both as absolute values and percentages) produced after three days of flecainide therapy in the dose-ranging trial (Study 030) at 100 mg bid, 200 mg bid and 250 or 300 mg bid. An analysis of the mean interval changes on day three of dosing at each dose level is displayed in Table 5 for the 10 patients who received all three dose levels.

These data indicate that prolongations of the PR and QRS intervals were experienced which became more pronounced as the dose was increased every three days. The QT interval remained fairly constant after an initial small increase at 100 mg bid; JT interval (QT-QRS), however, increased slightly at 100 mg bid and 200 mg bid, but to a lesser extent at the highest dose. No patients discontinued from the study because of interval changes.

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It may be concluded that, in initial flecainide therapy, an apparent positive relationship exists between the daily dose and the increases produced in PR and QRS intervals.

Flecainide has profound effects on myocardial conduction, with minimal influence on refractoriness; in accord with its in vitro electrophysiological actions, it affects primarily depolarization, with scant effects on repolarization. As with all Class I agents, its effects on conduction are magnified when cardiac conduction is impaired.

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Table 2

Study: B-818-015-01
Investigator: R. Holfant, MD

EFFECT OF FLECAINIDE, 1.0 mg/kg IV ON INTRACARDIAC CONDUCTION IN PATIENTS

MEASUREMENT	CONTROL	MEAN DIFFERENCE FROM CONTROL ± STD DEV		
		Minutes Post Dose		
		10	20	30
PA INTERVAL (msec)	24.5	n = 13 0.69 ± 7.50	n = 14 0.93 ± 7.59	n = 13 1.46 ± 6.39
AH INTERVAL (msec)	97.3	n = 14 5.07 ± 10.25	n = 15 6.13 ± 8.60*	n = 15 3.93 ± 8.66
HV INTERVAL (msec)	47.3	n = 14 4.36 ± 7.84	n = 15 6.13 ± 8.93*	n = 15 5.00 ± 9.82

*Significantly different from control, P<0.05

INVESTIGATOR: L. SEIFEL, MD

Table 3

EFFECTS OF FLECAINIDE, 1.0 OR 2.0 MG/KG IV, ON INTRACARDIAC CONDUCTION AND REFRACTORINESS IN PATIENTS WITH NORMAL BASELINE VALUES

INTRAVENOUS DOSE MG/KG	N	Percentage Change From Control Values							
		ERA-A	A-H	H-V	V-RVA	ERP-A	FRP-AVN	ERP-AVN	ERP-V
1.0	12	+10.4	+13.5	+15.7	+29.1*	+4.3	+8.0	+15.0	+5.6
	P =	<0.05	<0.001	<0.001	<0.005	NS	<0.05	NS	<0.05
2.0	6	+9.0	+24.4	+40.2	+16.5	+16.0	+3.4	+12.4**	+10.5
	P =	NS	<0.005	<0.001	<0.05	<0.01	NS	NS	<0.01

*N=5
**N=4

ERA-A = CONDUCTION TIME, HIGH TO BASAL RIGHT ATRIUM
A-H = CONDUCTION TIME, BASAL ATRIUM TO HIS BUNDLE
H-V = CONDUCTION TIME, HIS BUNDLE TO RIGHT VENTRICULAR ACTIVATION
V-RVA = CONDUCTION TIME, VENTRICULAR SEPTAL ACTIVATION TO DEPOLARIZATION OF RIGHT VENTRICULAR APEX
ERP-A = EFFECTIVE REFRACTORY PERIOD OF ATRIUM
FRP-AVN = FUNCTIONAL REFRACTORY PERIOD OF AV NODE
ERP-AVN = EFFECTIVE REFRACTORY PERIOD OF AV NODE
ERP-V = EFFECTIVE REFRACTORY PERIOD OF VENTRICLE

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Table 4

Study: B-818-083-82
Investigator: J. Anderson, MD

ELECTROPHYSIOLOGICAL EFFECTS OF FLECAINIDE, PO, IN PATIENTS WITH VENTRICULAR TACHYCARDIA

	n*	(MSec (SEM)) ± SEM Dev	
		Control	Flecainide
Sinus Cycle	14	865 ± 207	942 ± 178
Sinus Cycle Length Pacing§	13	600	600
PA Interval	13	28 ± 11	38 ± 18°
PA Interval, Pacing	13	30 ± 11	37 ± 6
AH Interval	12	116 ± 34	142 ± 31°°
AH Interval, Pacing	12	113 ± 33	144 ± 40
HV Interval	12	50 ± 11	70 ± 22°°
HV Interval, Pacing	12	53 ± 12	73 ± 24
Atrial ERP	13	283 ± 36	308 ± 55
AVN ERP	13	454 ± 142	411 ± 104
Ventricular ERP	13	263 ± 27	286 ± 25°°

§ Any cycle length, 600 msec
° significantly different from control, $p<0.05$
°° significantly different from control, $p<0.01$
°°° significantly different from control, $p<0.001$

Table 5

Absolute and Percent Changes for ECG Intervals after Three Days of Therapy in Study 030 Dose-Ranging Study for the Ten Patients Who Received all Three Dose Levels

	Mean Percent Increase From Baseline			Mean Absolute Increase From Baseline (sec)		
	Dose (mg bid)			Dose (mg bid)		
	100	200	250/300	100	200	250/300
PR	7.9%	14.9%	24.2%	0.013	0.024	0.038
QRS	12.8%	17.8%	27.1%	0.010	0.014	0.022
QT	3.9%	6.1%	7.0%	0.019	0.032	0.026
JT*	1.4%	2.8%	1.4%	0.005	0.008	0.004

*JT = QT minus QRS

b. Studies Using Programmed Electrical Stimulation (PES)

A limited amount of data are available on the ability of oral flecainide to prevent the induction of ventricular tachycardia (V-Tach) during programmed electrical stimulation (PES). A number of investigators, at their option, have studied the effect of multiple oral doses of flecainide on the inducibility of V-Tach upon retesting after institution of therapy, under open-label protocol R-818-057 Amended. Results from this show that (Table 6) 7/23 patients were fully protected, 7/23 were partially protected and 9/23 were fully inducible after flecainide. Fifteen of the 23 patients were discharged on flecainide. Mean plasma levels (Table 6) were within the therapeutic range and did not differ between responders and partial or non-responders.

Seventeen patients with inducible ventricular tachycardia due to a variety of cardiac diagnoses were studied under protocol R-818-053 (Table 6). Experience in this open-label study was slightly more favorable. Ventricular tachycardia was fully prevented in 9/17 patients, partially prevented in 4/17 patients and was fully inducible in 4/17 patients after four to six days of multiple dose therapy with flecainide. Ten of the 17 patients continued long term flecainide treatment Again plasma levels of flecainide did not differ significantly between groups (Table 6).

From the experience in these two studies, oral flecainide would appear to be effective in preventing the induction of ventricular tachycardia in approximately 40% (range 30%-53%) of patients, and partially effective in another 25% (range 24-26%) of patients. These results in this procedure compare very favorably with the experience with other Class I drugs.

2. Clinical Hemodynamics

Hemodynamic studies on flecainide have shown the following:

- Flecainide possesses a measurable negative inotropic effect.
- In healthy subjects or in the compensated patient, overall left ventricular pump function is maintained after flecainide administration.
- Flecainide has no significant effects on systemic vascular resistance.

TABLE 6

EFFECT OF ORAL FLECAINIDE ON INDUCIBILITY OF VENTRICULAR TACHYCARDIA BY PROGRAMMED ELECTRICAL STIMULATION

STUDY NO	RESPONSE	NO. PTS PATIENTS STUDIED	TOTAL DAILY DOSE MEAN ± SD (range)	DAYS ON FLECAINIDE PRIOR TO PES MEAN ± SD (range)	PLASMA LEVEL AT TIME OF PES NG/ML MEAN ± SD (range)	NO. PTS DISCHARGED ON FLECAINIDE
R-818-057* Amended	V-TACH FULLY PREVENTED	7/23	286 ± 69 (200-400)	8.9 ± 1.8 (6.0-11.0)	626 ± 239† (365-1015)	7
	V-TACH PARTIALLY PREVENTED	7/23	317 ± 41† (300-400)	8.0 ± 3.8 (1.0-14.0)	651 ± 252 (252-1045)	7
	FAILURE	9/23	300 ± 87 (200-400)	10.2 ± 5.5 (3.0-17.0)	534 ± 277 (208-1112)	1
R-818-053**	V-TACH FULLY PREVENTED	9/17	289 ± 105 (200-400)	4.7 ± 0.8 (4.0-6.5)	769 ± 240 (377-1081)	8
	V-TACH PARTIALLY PREVENTED	4/17	350 ± 191 (200-600)	5.1 ± 0.8 (4.5-6.0)	881 ± 252 (654-1152)	2
	FAILURE	4/17	325 ± 96 (200-400)	3.8 ± 1.2 (2.0-4.5)	705 ± 56 (654-755)	0

*MULTIPLE INVESTIGATORS
**INVESTIGATORS - J. STEWART, MD; J. ANDERSON, MD
†N=6

TABLE 6

EFFECT OF ORAL FLECAINIDE ON INDUCIBILITY OF VENTRICULAR TACHYCARDIA BY PROGRAMMED ELECTRICAL STIMULATION

STUDY NO	RESPONSE	NO. PTS PATIENTS STUDIED	TOTAL DAILY DOSE MEAN ± SD (range)	DAYS ON FLECAINIDE PRIOR TO PES MEAN ± SD (range)	PLASMA LEVEL AT TIME OF PES NG/ML MEAN ± SD (range)	NO. PTS DISCHARGED ON FLECAINIDE
R-818-057* Amended	V-TACH FULLY PREVENTED	7/23	286 ± 69 (200-400)	8.9 ± 1.8 (6.0-11.0)	626 ± 239† (365-1015)	7
	V-TACH PARTIALLY PREVENTED	7/23	317 ± 41† (300-400)	8.0 ± 3.8 (1.0-14.0)	651 ± 252 (252-1045)	7
	FAILURE	9/23	300 ± 87 (200-400)	10.2 ± 5.5 (3.0-17.0)	534 ± 277 (208-1112)	1
R-818-053**	V-TACH FULLY PREVENTED	9/17	289 ± 105 (200-400)	4.7 ± 0.8 (4.0-6.5)	769 ± 240 (377-1081)	8
	V-TACH PARTIALLY PREVENTED	4/17	350 ± 191 (200-600)	5.1 ± 0.8 (4.5-6.0)	881 ± 252 (654-1152)	2
	FAILURE	4/17	325 ± 96 (200-400)	3.8 ± 1.2 (2.0-4.5)	705 ± 56 (654-755)	0

*MULTIPLE INVESTIGATORS

**INVESTIGATORS - J. STEWART, MD; J. ANDERSON, MD

†N=6

Single Dose Studies. Several single dose IV studies were conducted in patients to determine the effect of flecainide on left ventricular function (Studies 003, 022, 023, 054). Table 7 shows results from a double-blind vehicle-controlled study which shows a slight negative inotropic effect for flecainide under these conditions. In this controlled study of patients undergoing diagnostic catheterization, the mean changes from baseline for hemodynamic parameters did not differ significantly from those of the vehicle group at any time interval (p greater than 0.05). However, mean ejection fractions tended to decrease more in patients receiving flecainide, and the direction of the changes in other indices (PAWP and LVEDP) was consistent with a negative inotropic effect for the drug compared with drug vehicle.

A similar but open-label, study (058) in patients undergoing diagnostic catheterization, who had impaired left ventricular function demonstrated comparable effects on hemodynamic parameters (Table 8). Changes from baseline in ejection fraction in this study, which lacked a vehicle control group, were statistically significant.

A double-blind noninvasive study (024) comparing the effects of oral flecainide and placebo on left ventricular function (using M-mode and 2-D echocardiography and systolic time intervals) in subjects and patients with cardiac disease confirmed that flecainide reduces myocardial contractility slightly, but also showed that overall pump function is maintained. M-mode indices and systolic time interval changes were consistent with a mild negative inotropic effect. Changes in ejection fraction were most pronounced at early time periods when plasma levels were rising.

Multiple Dose Studies. To substantiate the results of the single dose studies, noninvasive multiple dose hemodynamic measurements were obtained as adjuncts to the dose ranging studies (030-01,02,03) in patients with PVCs. Table 9 shows the results of these studies, which showed no effect on ejection fraction as measured echocardiographically.

Patients with radionuclide ejection fractions (RNEFs) less than 30% at baseline were required to have followup ejection fractions performed at subsequent visits in the acute and chronic study of ventricular tachycardia (057 amended). Multiple dose therapy with flecainide did not change the mean ejection fraction in this group of patients during three months of monitoring (Table 10).

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TABLE 7

Study: R-818V-054-02
Investigator: B.N. Singh, MD, D.Phil.

Hemodynamic Effects of Flecainide in Patients Determined During Diagnostic Catheterization - Double-blind Study With Vehicle Control

	Mean ± Standard Deviation		
	Vehicle (N=6)	Flecainide 1 mg/kg (N=6)	Flecainide 2 mg/kg (N=6)
Cardiac output (L/min)--baseline	5.40 ± 1.1	5.35 ± 0.8	5.48 ± 1.3
30 minutes after dose	4.80 ± 0.3	4.98 ± 0.7	5.05 ± 1.6
Systemic vascular resistance (dynes/sec/cm)--baseline	1451 ± 397	1456 ± 531	1387 ± 446
30 minutes after dose	1595 ± 433	1518 ± 385	1573 ± 684
Left ventricular ejection fraction--baseline	0.60 ± 0.07	0.61 ± 0.15	0.65 ± 0.06
20 minutes after dose	0.58 ± 0.06	0.56 ± 0.13	0.59 ± 0.06
Left ventricular end diastolic pressure (mmHg)--baseline	15.7 ± 4.2	20.0 ± 5.2	15.2 ± 4.1
30 minutes after dose	18.5 ± 5.4	21.5 ± 4.9	16.5 ± 4.6
Pulmonary wedge pressure (mmHg)--baseline	11.5 ± 4.2	12.2 ± 1.6	11.0 ± 2.0
30 minutes after dose	10.5 ± 4.3	13.7 ± 3.3	11.5 ± 3.3

None of the differences is significantly different ($p>0.05$) from those of the vehicle group.

TABLE 7

Study: R-818V-054-02
Investigator: B.N. Singh, MD, D.Phil.

Hemodynamic Effects of Flecainide in Patients Determined During Diagnostic Catheterization - Double-blind Study With Vehicle Control

	Mean ± Standard Deviation		
	Vehicle (N=6)	Flecainide 1 mg/kg (N=6)	Flecainide 2 mg/kg (N=6)
Cardiac output (L/min)--baseline	5.40 ± 1.[illegible]	5.35 ± 0.8	5.48 ± 1.3
30 minutes after dose	4.80 ± 0.8	4.98 ± 0.7	5.05 ± 1.6
Systemic vascular resistance (dynes/sec/cm)--baseline	1451 ± 397	1456 ± 531	1387 ± 446
30 minutes after dose	1595 ± 433	1518 ± 385	1573 ± 664
Left ventricular ejection fraction--baseline	0.60 ± 0.07	0.61 ± 0.15	0.65 ± 0.06
20 minutes after dose	0.58 ± 0.06	0.56 ± 0.13	0.59 ± 0.06
Left ventricular end diastolic pressure (mmHg)--baseline	19.7 ± 4.2	20.0 ± 5.2	15.2 ± 4.1
30 minutes after dose	18.5 ± 5.4	21.5 ± 4.9	16.5 ± 4.6
Pulmonary wedge pressure (mmHg)--baseline	11.5 ± 4.2	12.2 ± 1.6	11.0 ± 2.0
30 minutes after dose	10.5 ± 4.3	13.7 ± 3.3	11.5 ± 3.3

None of the differences is significantly different ($p>0.05$) from those of the vehicle group.

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TABLE 8

Study: R-818V-058-02
Investigator: B.N. Singh, MD, D.Phil.

Hemodynamic Effects of Flecainide in Patients With Reduced Ejection Fractions Determined During Diagnostic Catheterization - Open Label Study Without Vehicle Control

	Mean ± Standard Deviation	
	Flecainide	
	1 mg/kg (N=5)	2 mg/kg (N=5)
Cardiac output (L/min) -- baseline	4.68 ± 0.34	5.00 ± 0.84
30 minutes after dose	4.25 ± 0.31†	4.44 ± 1.00*
Systemic vascular resistance (dynes/sec/cm) before	1667 ± 315	1423 ± 323
30 minutes after dose	1984 ± 521	1635 ± 460
Left ventricular ejection fraction--baseline	0.33 ± 0.07	0.32 ± 0.06
20 minutes after dose	0.28 ± 0.07*	0.27 ± 0.06*
Left ventricular end diastolic pressure (mmHg)--baseline	24.6 ± 9.0	20.2 ± 7.4
30 minutes after dose	25.6 ± 8.4	19.6 ± 6.0

*$p<0.01$, significantly different compared to predose values
†$p<0.05$, significantly different compared to predose values

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Table 9

Effect of Flecainide on Ejection Fractions in Patients With PVCs After Daily Administration for 14 Days (Median Daily Dose of 400 mg)

Investigator	Study No	No. Patients	Ejection Fraction Baseline	Ejection Fraction During Therapy
Anderson	030-01	9	63.0 ± 6.1[a]	65.2 ± 6.5[a]
Hodges	030-02	10	55.4 ± 12.0[a]	59.5 ± 9.3[a]
Duff	030-03	10	52.0 ± 8.0[b]	53.0 ± 12.0[b]

[a] Determined using M-mode echocardiography.
[b] Determined using 2-dimensional echocardiography.

Table 10

Study 057 Amended (Acute and Chronic Ventricular Tachycardia): Follow-up Results for Patients With Baseline RNEFs < 30%

	RNEF Values			
	Baseline	Week 1	Month 1	Month 3
	19%	11%	9%	11%
	22%	24%		25%
	17%	19%	[b]	
	29%	24%	31%	30%
	22%	25%	[b]	
	18%	19%	[b]	
	29%	30%		27%
	15%	16%		18%
	25%	41%[a]		34%
	20%	27%		21%
	23%	24%	17%	19%
	20%	28%	[b]	
	27%	22%		25%
	16			15%
Mean ± SD	21.6 ± 4.6	23.9 ± 7.3	19.0 ± 11.1	22.5 ± 7.0

[a] Week 2 RNEF
[b] Patient discontinued

3. Metabolism

Comprehensive metabolic information on flecainide has been obtained in humans and laboratory animals. Results and conclusions from studies in humans on the principal metabolic aspects of flecainide are summarized below by topic and in Drug-Drug Interactions. Results from metabolism studies in animals are summarized in the preclinical metabolism section.

Metabolic information for flecainide on absorption, pharmacokinetics, biotransformation, and excretion was obtained in nine open-label studies in healthy human subjects and pharmacokinetic data for patients with premature ventricular contractions were obtained in a multicenter efficacy study. In addition, the effects of renal failure and congestive heart failure on the pharmacokinetics and excretion of flecainide were assessed in separate single dose open-label studies in patients with each disease state. The potential metabolic interactions of flecainide with digoxin and propranolol were evaluated in separate multiple dose open-label studies in healthy subjects with each other drug.

a. Oral Absorption

After oral administration of the tablet formulation, peak plasma levels of flecainide are attained at about three hours, on average, with a range of one to six hours.

Figure 1 shows a plot of mean plasma levels versus time for 18 subjects after a single, 200 mg oral dose (Study R-818-049-01). As shown, plasma levels of flecainide increase promptly after dosage with the tablet, with a peak level attained at three hours. In comparison to a solution of flecainide in the same subjects, absorption is only slightly slower from the tablet than the solution, and the extent of absorption is comparable (not statistically different) for the two dosage forms (Table 11).

When plasma level data after oral dosage are compared to data after intravenous dosage in the same subjects (Study 005-01), the extent of absorption of unchanged flecainide into the systemic circulation (absolute bioavailability) was shown to be greater than 90% (Table 11). Thus, flecainide does not undergo any consequential presystemic biotransformation (first-pass effect) during absorption in humans. In addition, when flecainide is given with a meal, food does not appreciably affect absorption (Studies 049-01

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Figure 1A (Scatterplot)

Mean Plasma Flecainide Levels After 200 mg
Oral Dose (18 Subjects)
Bioavailability Study (049)

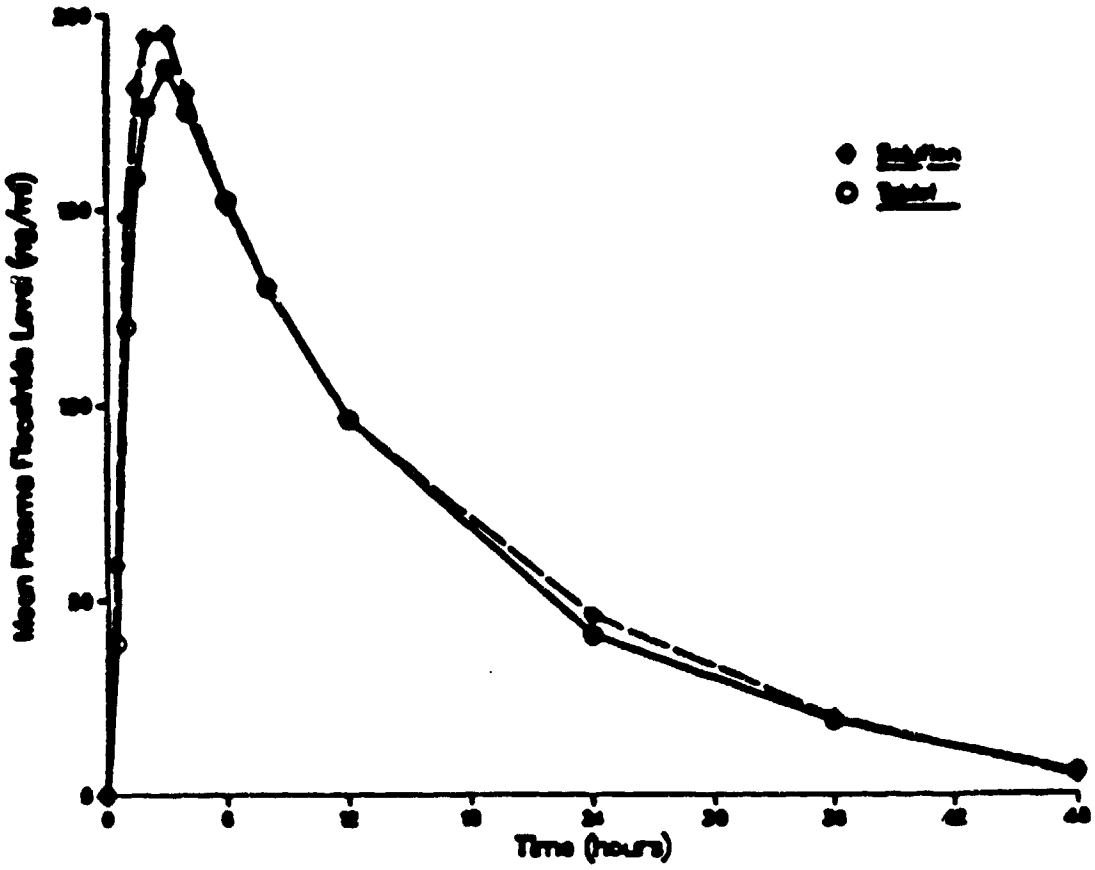

Figure 1B (Semilog Plot)

Mean Plasma Flecainide Levels After 200 mg
Oral Dose (18 Subjects)
Bioavailability Study (049)

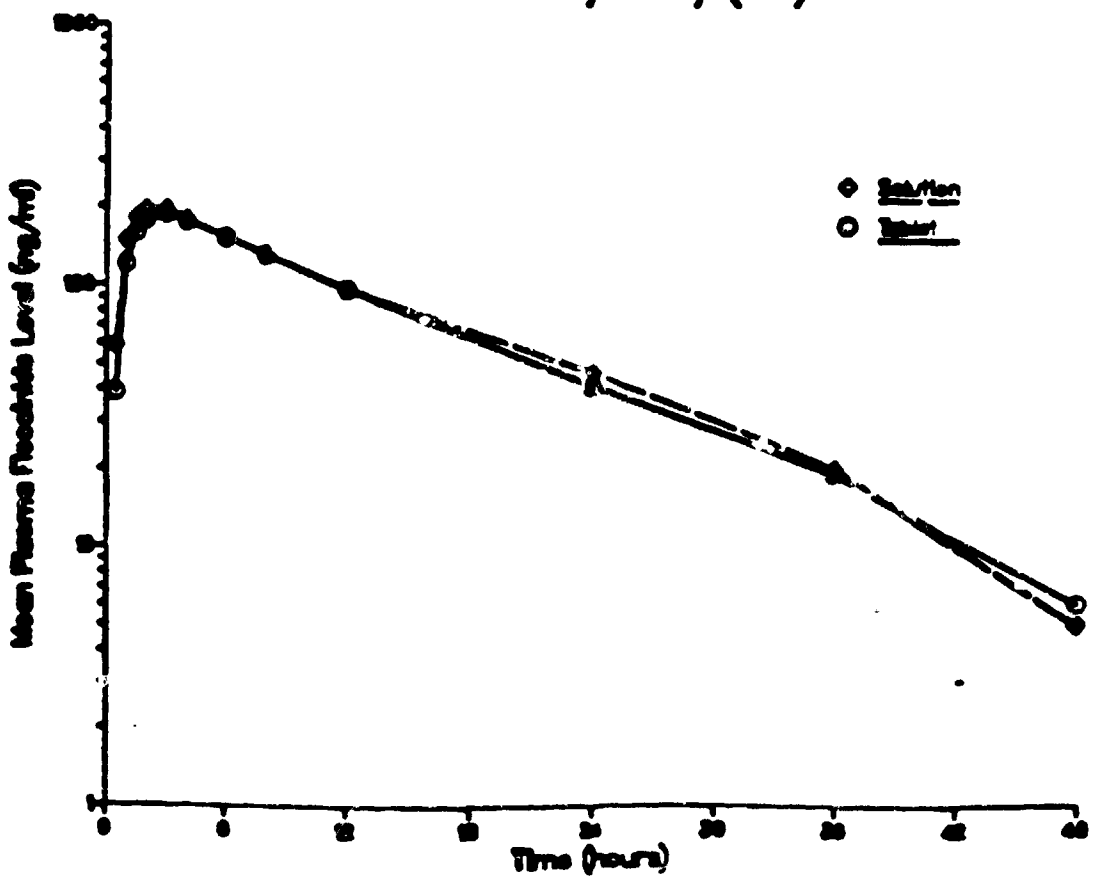

Table 11

Absorption in Healthy Human Subjects
Absolute (005) and Relative (049) Bioavailability Studies

Study Number	Dose[a]	N[b]	Formulation Reference	Time to Peak Level (hours)[c] Reference	Time to Peak Level (hours)[c] Solid Dosage Form	Plasma Half-life (hours)[c] Reference	Plasma Half-life (hours)[c] Solid Dosage Form	Plasma AUC (0 to Infinity) Ratio[c]: Solid Dosage Form/ Reference	Difference[d]
005	60 or 120 mg	8	IV	N/A	2.6±0.8	14±4	14±4	0.95±0.21	n.s.
049	200 mg	18	Solution	2.2±0.8	2.8±1.1	11±2	10±3	0.93±0.17	n.s.

[a] All single doses.

[b] All subjects were male.

[c] Mean ± Standard Deviation.

[d] Results of statistical comparison of treatment difference in plasma AUC values (n.s. indicates $p > 0.05$).

Figure 2A (Semilinear Plot)

Mean Plasma Flecainide Levels After 200 mg Oral Dose With Meal and Fasted (18 Subjects) Bioavailability Study (049)

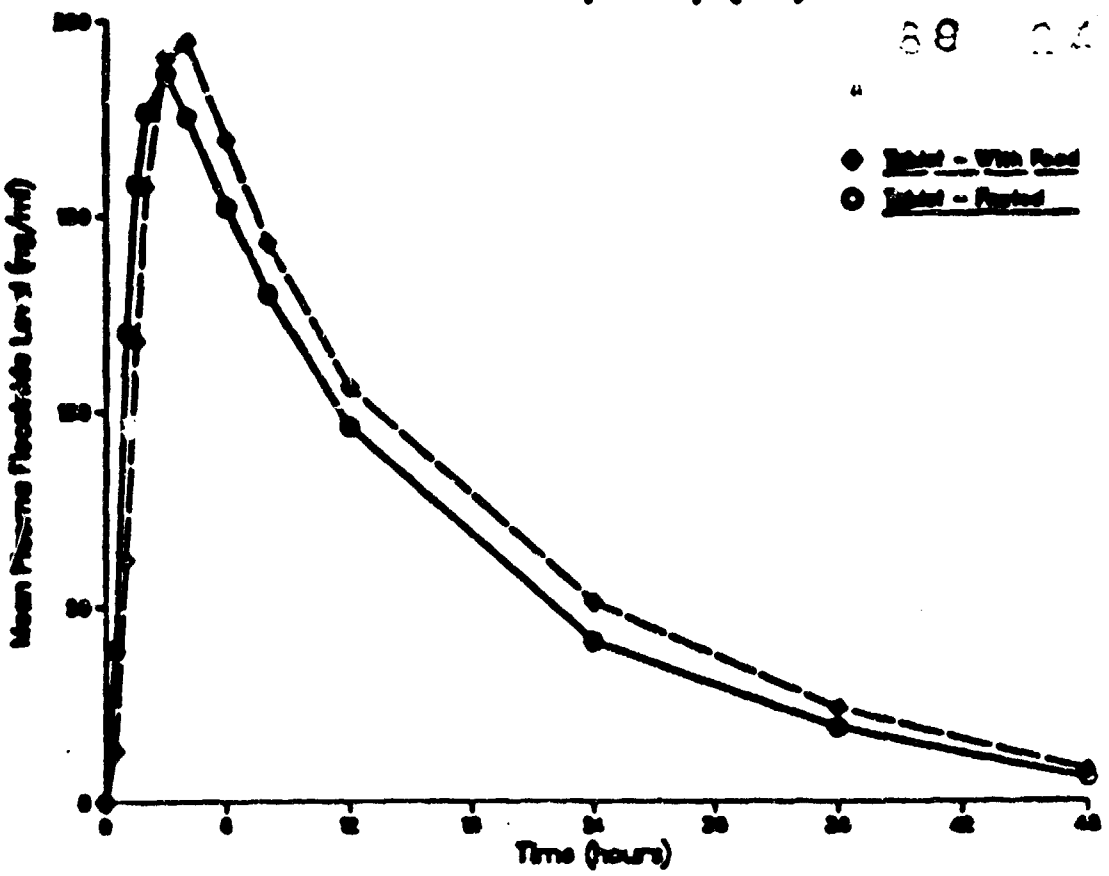

Figure 2B (Semilog Plot)

Mean Plasma Flecainide Levels After 200 mg Oral Dose With Meal and Fasted (18 Subjects) Bioavailability Study (049)

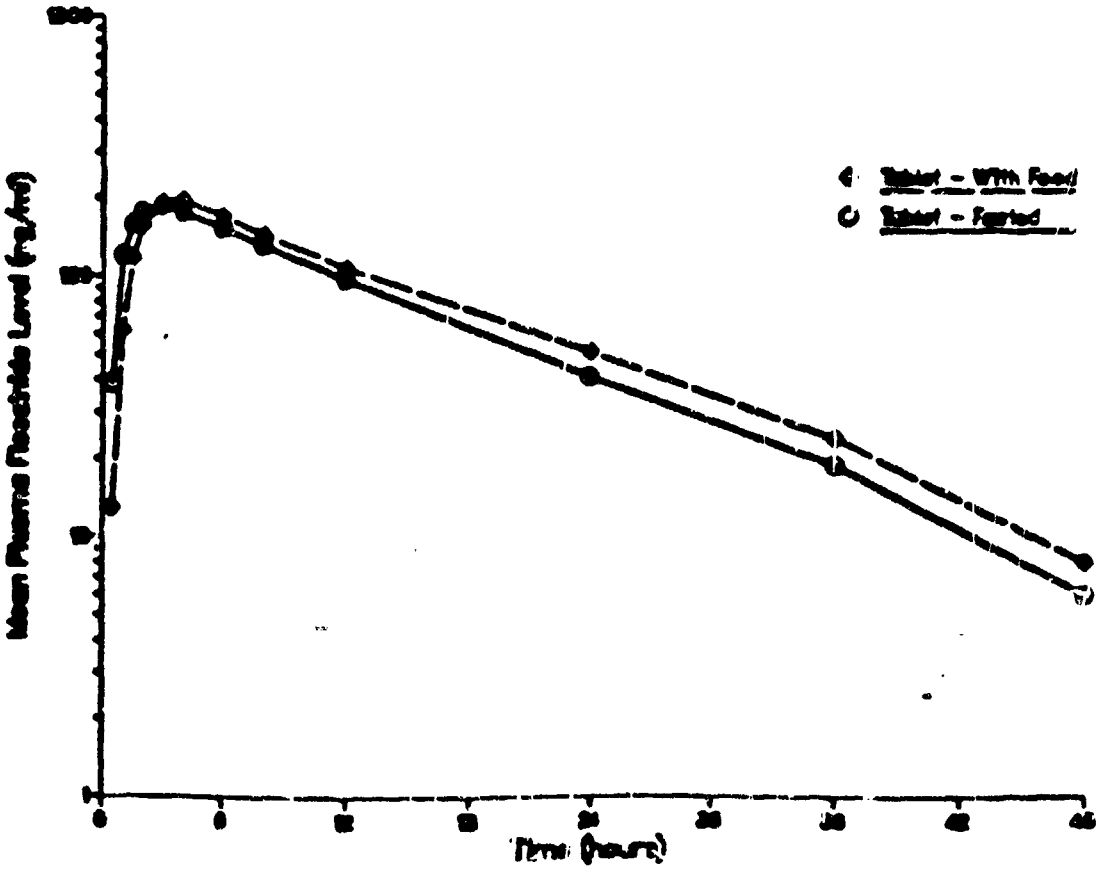

Figure 2A (Curvilinear Plot)

Mean Plasma Flecainide Levels After 200 mg Oral Dose With Meal and Fasted (18 Subjects) Bioavailability Study (049)

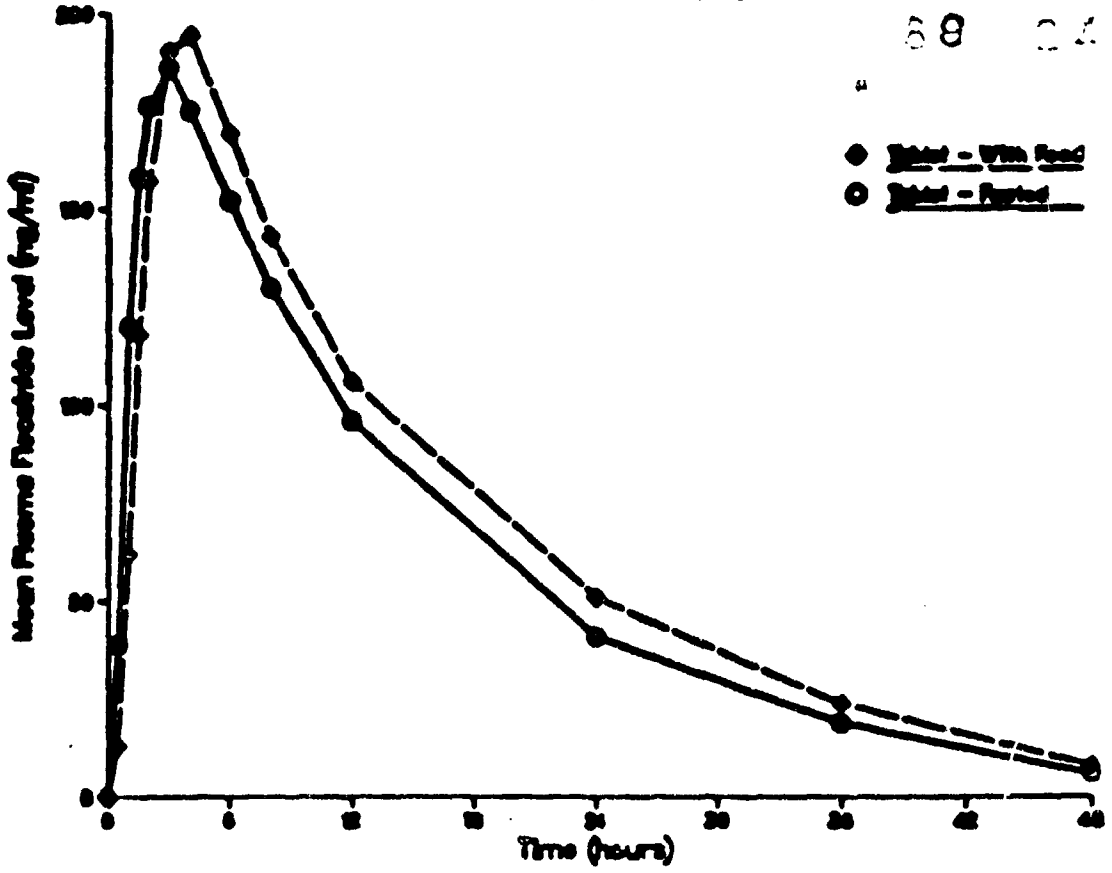

Figure 2B (Semilog Plot)

Mean Plasma Flecainide Levels After 200 mg Oral Dose With Meal and Fasted (18 Subjects) Bioavailability Study (049)

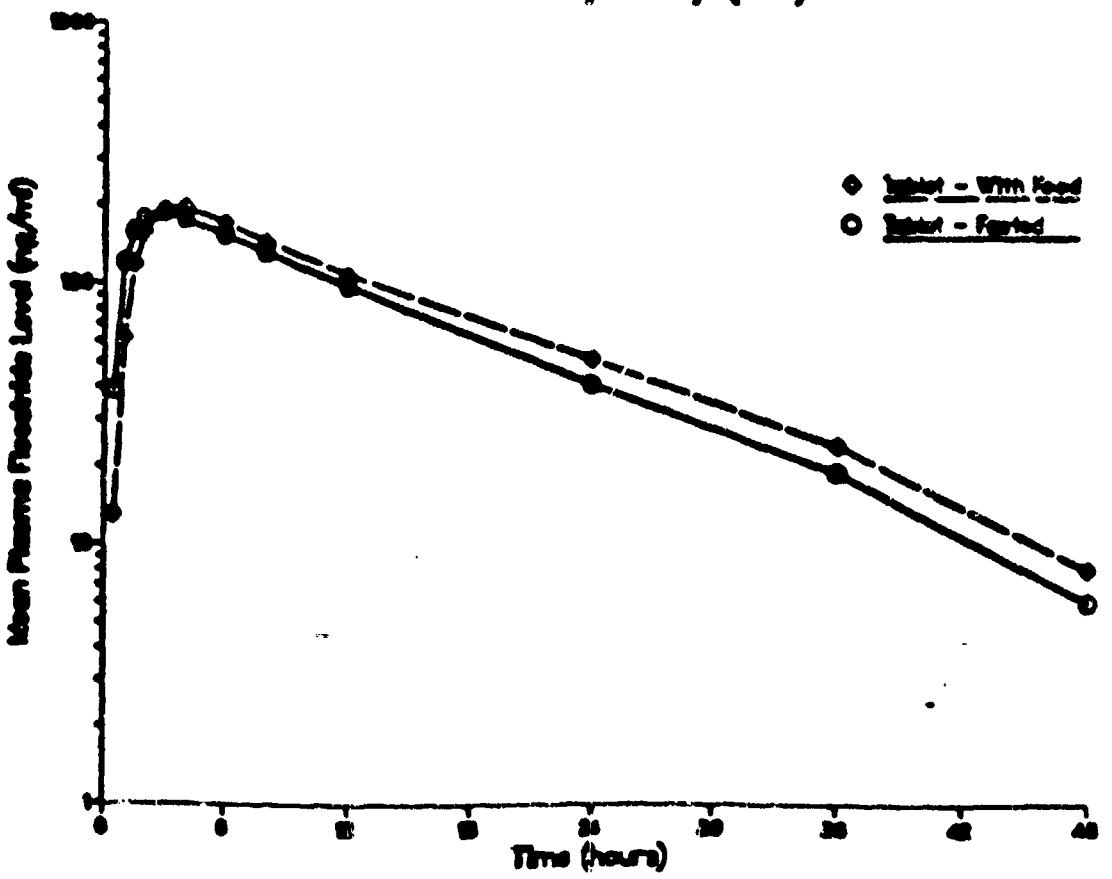

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Figure 3A (Rectilinear Plot)

Mean Plasma Flecainide Levels After 200 mg Oral Dose With Antacid and Fasted (9 Subjects) Absorption Study (81-152)

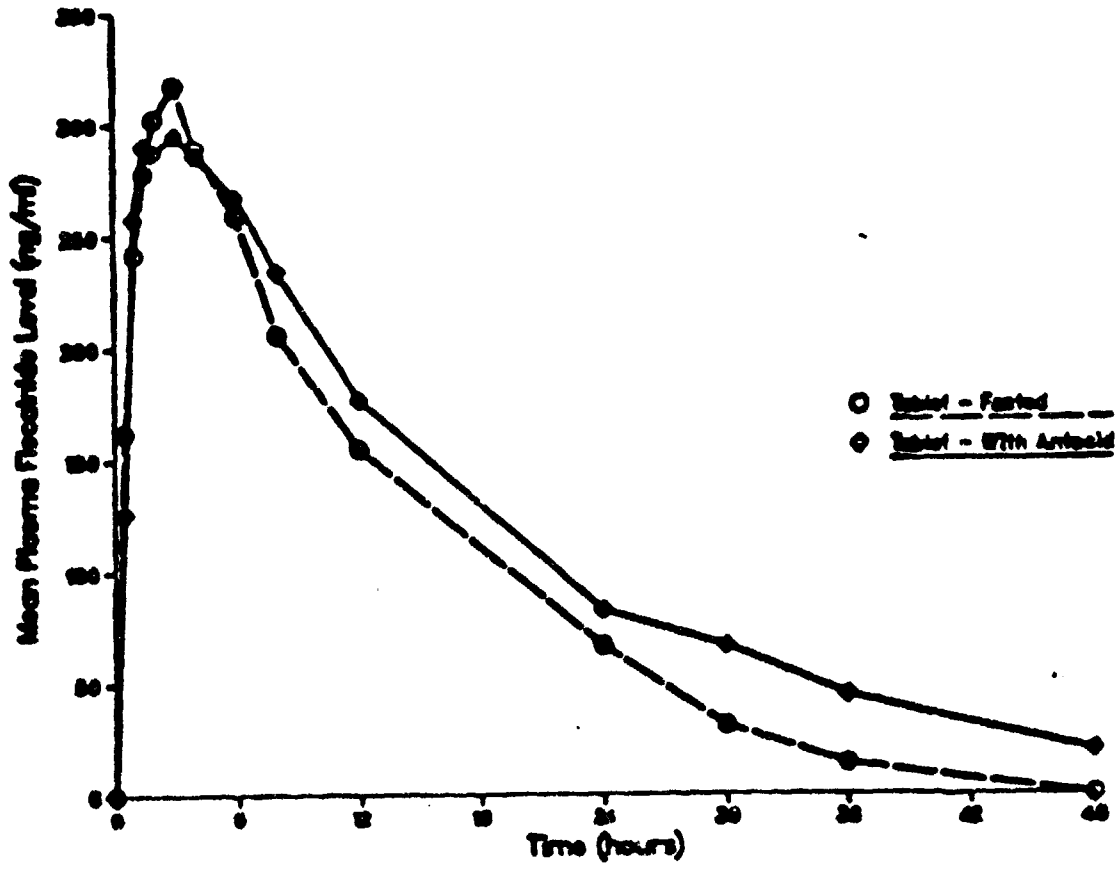
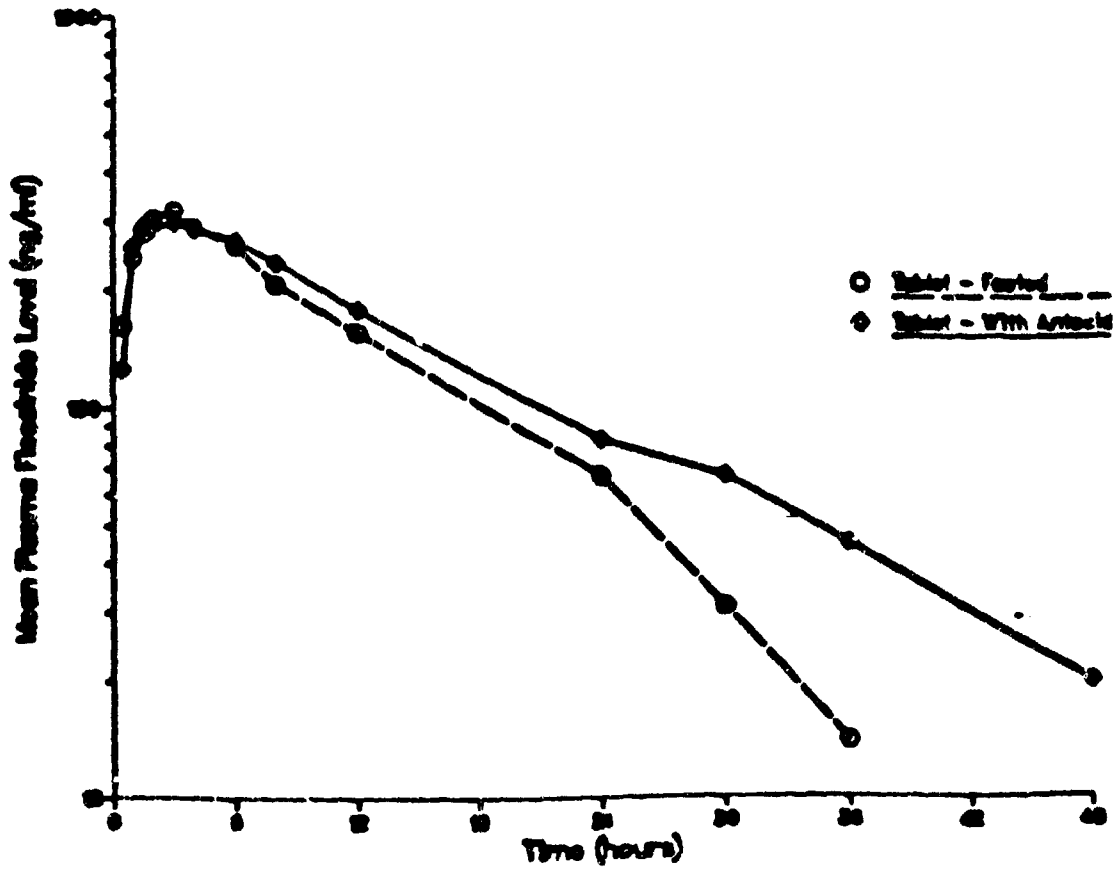


Figure 3B (Semilog Plot)

Mean Plasma Flecainide Levels After 200 mg Oral Dose With Antacid and Fasted (9 Subjects) Absorption Study (81-152)



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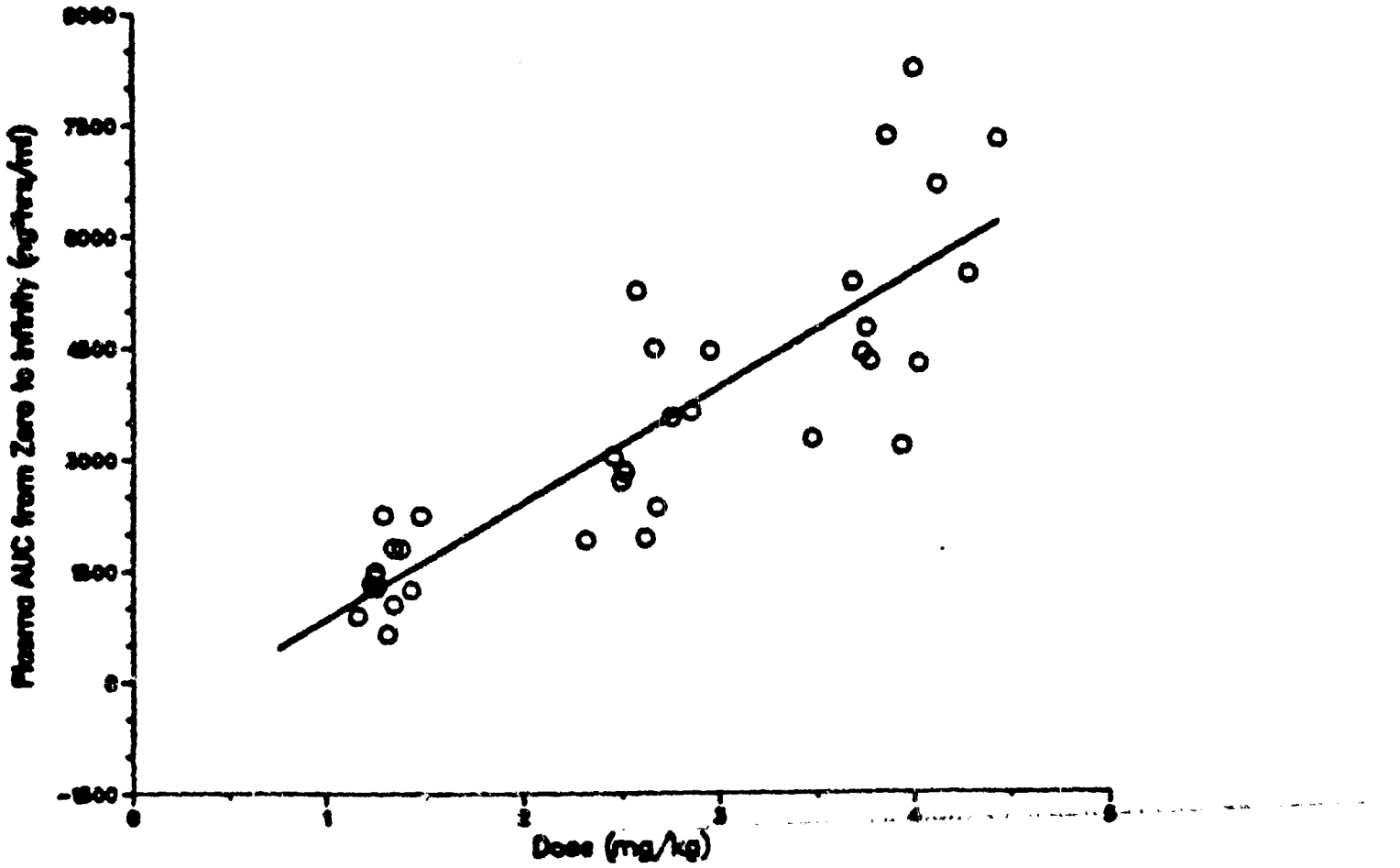
and 81-152-FRO-BE-002); the rate of absorption is only slightly slower, but the extent of absorption is not altered (Figure 2). Similar results (Figure 3) were found when flecainide is given with an antacid (Study 81-152-FRO-BE-002).

Within the range of usual therapeutic doses, plasma levels of flecainide are nearly proportional to dose levels. In an intrasubject comparison study (Figure 4), plasma levels (AUCs) of drug deviate upward from direct proportionality by only about 10 to 15% per 100 mg dose increment (Study 061-01).

Figure 4

Plasma AUC Versus Dose Following Single Oral Doses of 100, 200 and 300 mg (12 Subjects) Dose Proportionality Study (061)



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b. Plasma Pharmacokinetics

For 30 patients with chronic PVCs and an average age of 54 years (Table 12), the apparent plasma half-life of flecainide averages about 20 hours, with a range of 12 to 27 hours, after multiple oral dosage regimens (Multicenter Study 030); eight of these patients had evidence of left ventricular dysfunction, including four with CHF. With the long half-life, plasma levels of flecainide are sustained, which allows twice daily dosage for treatment of most patients. Plasma pharmacokinetic data for younger healthy human subjects, (half-life and clearance) are summarized in Table 13.

With multiple dosage, flecainide accumulates to steady-state plasma levels within three to five days, based on its long half-life. This is illustrated in Figure 5. Shown are mean plasma levels of flecainide in four different subjects at two dose levels over a seven day period of dosage (Study 018-01); doses are indicated by the arrows and dosage regimens are either 180 mg bid or 80 mg bid. As expected, plasma levels increase to steady-state levels in a few days; this is evident by about the third day. In addition, measured plasma levels at steady-state are in good agreement with those predicted by superposition from first dose data. Also in this study (018-01), similar results were found for eight other subjects (four at 120 mg bid and four at 150 mg bid).

Once at steady-state with multiple dosage in patients, no more (or unexpected) accumulation of drug in plasma occurs during chronic therapy over long periods of time. For 78 patients with up to 43 months of flecainide therapy (mean, 19 months), trough plasma levels of flecainide remain reasonably constant with time on drug. Overall, regression analyses show a slight nonsignificant (p greater than 0.05) decrease in trough plasma level (adjusted for dose changes) over time. For a daily dose of 400 mg, the average decrease is estimated to be about 1.5 ng/ml per month on therapy.

Information (Table 13) on the relationship of the plasma pharmacokinetics of flecainide to dose is available from three studies (005-01, 018-01, and 061-01). In two intersubject comparison studies (005 and 018), plasma half-life is not related to dose level and plasma levels (AUCs) are proportional to dose. In study 018-01 (Table 13), plasma half-life is somewhat longer after 7 days of dosage (mean, 16 hours) than after the first dose (mean, 13 hours), but plasma clearance is not different after multiple dosage. In an intrasubject comparison study (061), plasma half-life tends to be somewhat longer with

increasing doses (Table 13) and plasma clearance appears to be modestly slower (on average, about 10% per 100 mg dose increase). In addition, plasma levels (AUCs) deviate slightly upwards from direct proportionality to dose (Figure 4). Overall, the data indicate that the plasma pharmacokinetics of flecainide are reasonably linear (not greatly affected by dose or plasma concentration) over the range of usual therapeutic doses.

The elimination of drug from plasma is only slightly reduced in older patients; when trough plasma levels are related to age, levels ranging up to about 1,500 ng/ml are only about 3 to 4 ng/ml greater per year of age, for a population of patients receiving an average total daily dose of about 300 mg and ranging in age from about 20 years to over 80 years.

Table 12

Plasma Pharmacokinetics for Patients with Premature Ventricular Contractions
Dose-Ranging Study (030)

Study Number	Dose[a]	N[b]	Plasma Half-life (hours) Mean±S.D.	Range	Plasma Clearance (ml/min/kg) Mean±S.D.	Range
030-01	100-250 mg bid Wash-out	9	19±4	14-26	-- [c]	--
030-02	100-300 mg bid Wash-out	10	20±5	12-27	-- [c]	--
030-03	100-250 mg bid Wash-out	11	20±4	13-27	6.2±2.8	3.1-12.6

[a] Twice daily oral dosage for 3 to 12 days.

[b] Both sexes.

[c] Blood sampling schedule did not permit determination of plasma clearance.

Table 13

Plasma Pharmacokinetics for Healthy Human Subjects
Pharmacokinetic and Metabolism Studies

Study Number	Dosage Route	Dose[a]	N[b]	Plasma Half-life (hours) Mean±S.D.	Plasma Half-life (hours) Range	Plasma Clearance (ml/min/kg) Mean±S.D.	Plasma Clearance (ml/min/kg) Range
001	IV	0.5-2.0 mg/kg	8	11±2	7-15	-- [c]	--
005	IV	0.6-1.7 mg/kg	8	14±4	7-19	7.6±2.5	4.6-12.1
005	Oral	60-240 mg	16	14±4	7-22	7.9±2.7	4.1-13.7
026	Oral	200 mg	16	12±2[d]	8-16[d]	9.8±2.7[d]	6.0-14.1[d]
039	Oral	200 mg	9	14±3	10-18	10.2±3.8	5.4-17.0
049	Oral	200 mg	18	11±2[e]	7-14[e]	15.2±4.6[e]	7.8-22.0[e]
050	Oral	200 mg	4	16±5	9-21	6.1±2.3	4.2- 9.4
061	Oral	100 mg	12	10±3	5-16	17.0±6.7	9.6-34.3
061	Oral	200 mg	12	11±3	7-20	14.7±4.3	8.2-22.7
061	Oral	300 mg	12	12±3	7-20	13.3±3.8	8.1-20.9
018	Oral	80-180 mg	16	13±3	9-19	7.3±2.3	4.1-11.7
018	Oral	80-180 mg bid[f]	16	16±4	9-23	6.9±2.7	4.1-14.5

[a] All single doses, except as indicated for Study 018.

[b] All subjects were male, except for 1 female in Study 050.

[c] Blood sampling schedule did not permit determination of plasma clearance.

[d] Average values for 2 single doses (capsule and tablet) in each subject.

[e] Average values for 3 single doses (capsule, tablet, and solution) in each subject.

[f] Twice daily dosage for 7 days.

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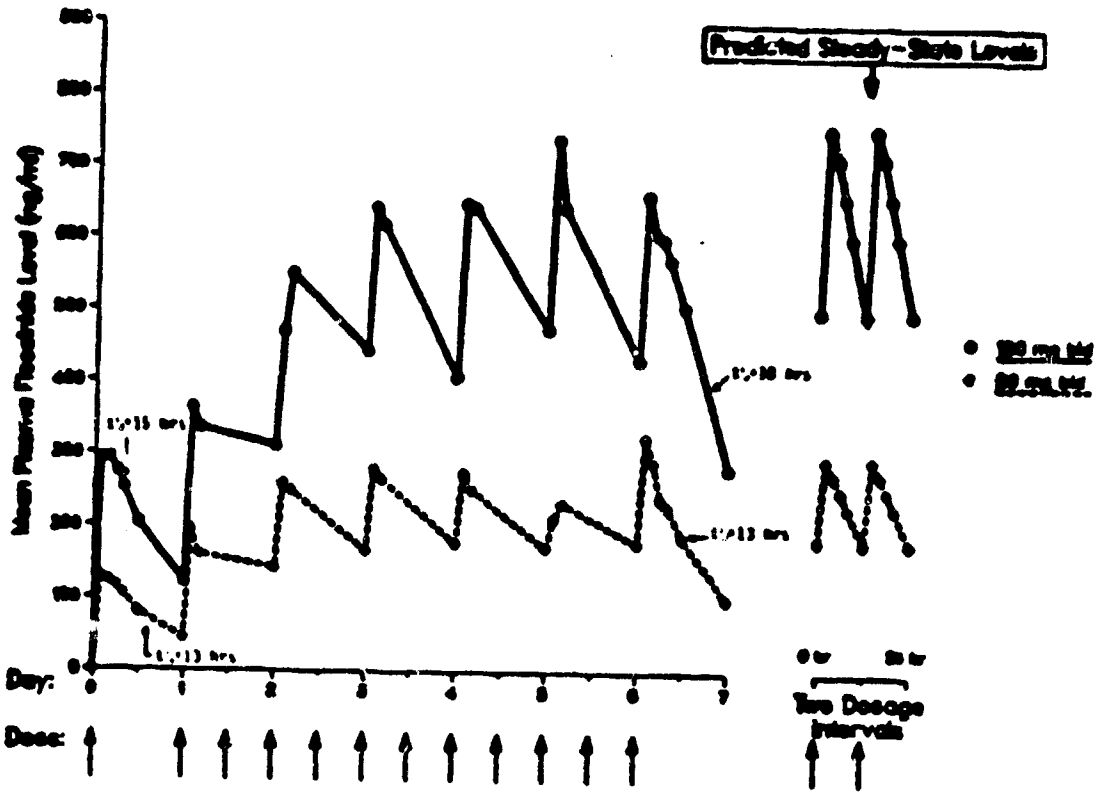
Figure 5A (Rectilinear Plot)

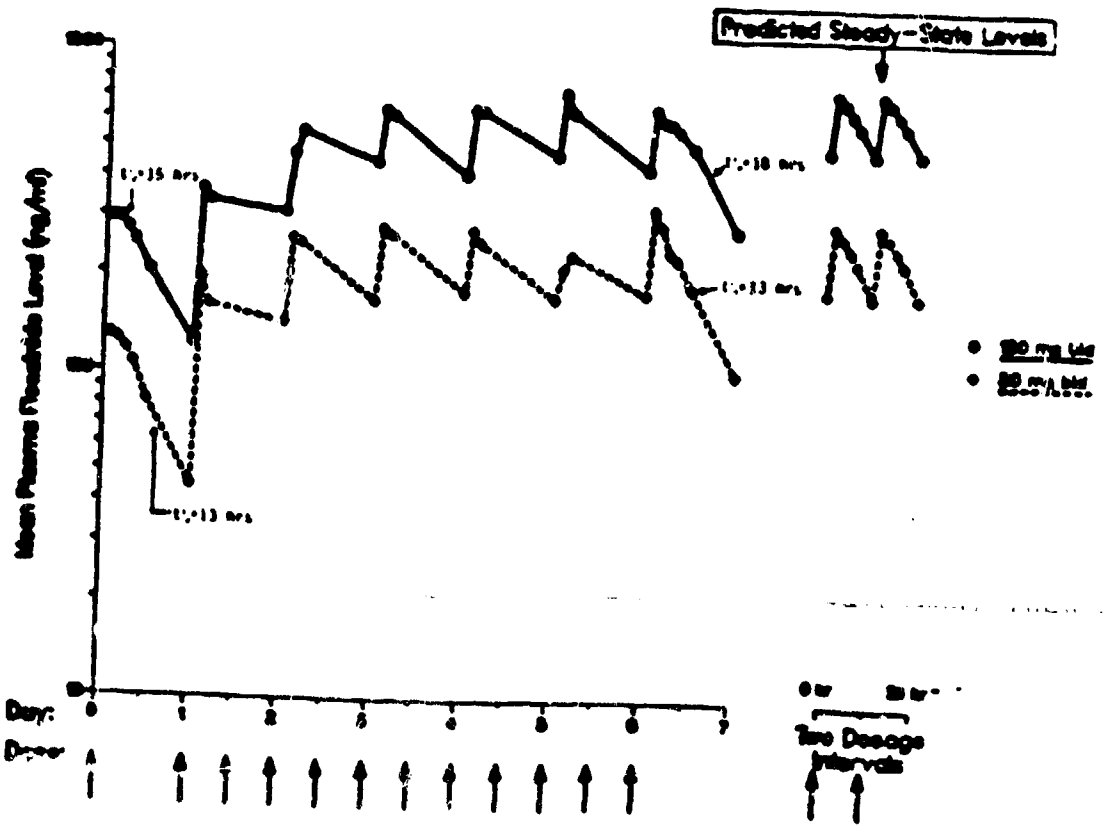
Mean Plasma Flecainide Levels During Multiple Oral Dosage (4 Subjects)*
Multi-Dose Pharmacokinetic Study (018)



* Four different subjects at each dose

Figure 5B (Semilog Plot)

Mean Plasma Flecainide Levels During Multiple Oral Dosage (4 Subjects)*
Multi-Dose Pharmacokinetic Study (018)



* Four different subjects at each dose

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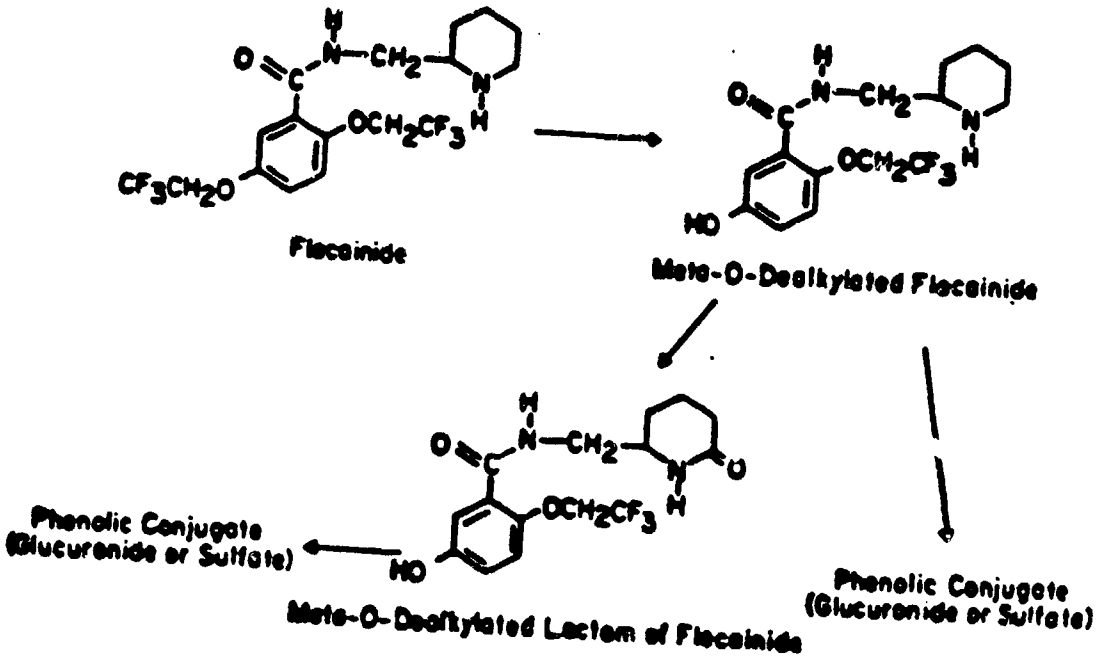
c. Biotransformation

In addition to urinary excretion of unchanged drug, flecainide undergoes extensive biotransformation in humans. Only two major metabolites, however, are found in human urine and plasma.

Figure 6 shows the major pathways of flecainide biotransformation in humans. Flecainide undergoes O-dealkylation, selectively in the meta (or 5) position of the molecule, to form meta-O-dealkylated flecainide; this phenolic metabolite is extensively conjugated as either the glucuronide or sulfate. In addition, the piperidine ring undergoes oxidative metabolism to form the lactam of the meta-O-dealkylated metabolite; this second major phenolic metabolite is also extensively conjugated.

FIGURE 6

Major Pathways of Flecainide Biotransformation in Humans



Both of the two major metabolites are found primarily in the conjugated form in both urine and plasma of humans. In addition, these two metabolites were tested in animal models; results indicate that they have a lack of or markedly reduced antiarrhythmic and electrophysiologic actions, when compared to flecainide. Also, free (unconjugated) plasma levels of these metabolites are very

low (less than 50 ng/ml) in humans, even after multiple dosage to patients, when plasma levels of flecainide are in the therapeutic range of 200 to 1,000 ng/ml and higher. Thus, the metabolites of flecainide are not likely to contribute any consequential pharmacologic activity.

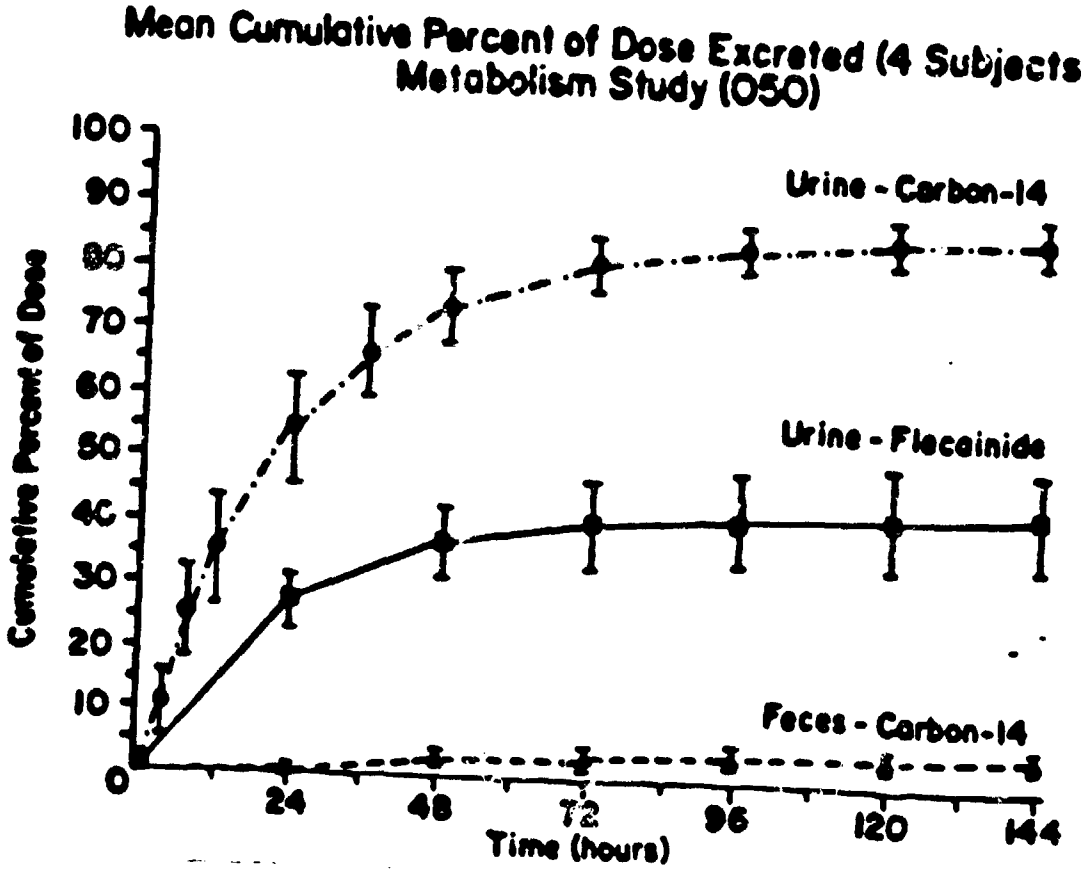
As an indicator of the relevance of laboratory animal toxicity results to flecainide safety for humans, urinary metabolite fractions were compared using radiochromatographic (TLC) analyses. Results show that the three chronic toxicity species (dogs, rats, and mice) were exposed to all human metabolites; in addition, the two major human metabolites are also major metabolites in all three animal species. Thus, the laboratory evaluation of chronic toxicity in these animal species is a reasonable assessment of flecainide safety for humans.

d. Excretion of Flecainide and Its Metabolites

After an oral dose of carbon-14 labelled drug, flecainide and its metabolites (carbon-14) are primarily excreted in human urine; only a small proportion of the dose is found in feces.

Shown in Figure 7 are mean data for four subjects who received an oral, 200 mg dose of carbon-14 labelled flecainide (Study 050-03); cumulative percent of dose is plotted versus time. As indicated, most of the carbon-14 is excreted in urine (on average, 86% of the dose) while little of the carbon-14 (5% of the dose) is excreted in feces. Thus, biliary elimination of flecainide is apparently not extensive in humans. In addition, there is extensive excretion of unchanged flecainide in human urine, as well as extensive urinary excretion of metabolites as indicated by the difference between carbon-14 and flecainide.

FIGURE 7



As shown, a substantial amount of unchanged flecainide is excreted in human urine. Data for a larger group of subjects from several studies shows that the range is from about 10 to 50% of the dose, with a mean of 27%. In addition, urinary excretion of the two major metabolites, in both the free and conjugated forms, accounts for most of the balance of the dose in urine.

Also, the renal clearance of unchanged flecainide averages about 175 ml/min and accounts for about 25% of total body clearance. Compared to normal inulin clearance values, these data suggest that flecainide undergoes some active renal secretion.

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e. Effect of Disease States on Pharmacokinetics and Excretion

Congestive Heart Failure Table 14 shows results from a study in patients with congestive heart failure after a single, 200 mg oral dose (Study 039-01). In this table, plasma pharmacokinetic and urinary excretion data for ten patients with CHF (primarily New York Heart Association functional Class III) are compared to data for nine healthy subjects, who were age and weight matched, and free of cardiac disease.

TABLE 14

Plasma Pharmacokinetics and Urinary Excretion
Congestive Heart Failure Study (039)

	CHF Patients (N=10)[a]		Healthy Subjects (N=9)	
Plasma Pharmacokinetics:				
Half-life (hours)	19	(14-26)	14	(10-18)
Clearance (ml/min/kg)	8.1	(3.1-13.4)	10.2	(5.4-17.0)
Urinary Excretion:				
Extent (% dose)	24.1	(13.4-58.8)	24.7	(11.8-43.3)
Clearance (ml/min)	133		176	

[a] 9 in NYHA Class III and 1 in Class II.

As shown, plasma half-life, on average, is about 35% longer in CHF patients, and plasma clearance is about 20% slower than in the subjects. Overall, the rate of elimination of flecainide from plasma is about 25% slower in patients with CHF than for control healthy subjects. In addition, the extent of unchanged flecainide excretion in urine is not altered, but renal clearance of flecainide is somewhat slower (about 25%) in patients with CHF. Therefore, patients with congestive heart failure may require somewhat lower maintenance doses, particularly if their left ventricular dysfunction is severe.

Chronic Impairment of Renal Function Results from a study in two groups of patients with renal disease after a single, 200 mg oral dose are shown in Table 15 (Study 038-01). Plasma pharmacokinetic and urinary excretion data for 10 patients with moderate renal failure (creatinine clearances of 4 to 41 ml/min/m^2) and 10 patients with

end-stage renal disease (creatinine clearances of 2 ml/min/m^2 or less) are compared to data for healthy, young subjects with normal renal function from several other studies.

TABLE 15

Plasma Pharmacokinetics and Urinary Excretion
Renal Failure Study (038)

	Moderate Patients[a] (N=10)		End-Stage Patients[b] (N=10)		Healthy Subjects (N=79)	
Plasma Pharmacokinetics:						
Half-life (hours)	17	(12-26)	26	(9-58)	13	(7-22)
Clearance (ml/min/kg)	6.7	(2.2-13.9)	5.1	(1.5-10.0)	10	(4-20)
Urinary Excretion:						
Extent (% dose)	15.3	(5.7-29.8)	0.8	(0-3.1)	27	(10-50)
Clearance (ml/min)	90		<4		175	

[a] Creatinine clearance of 4 to 41 ml/min/m^2.
[b] Creatinine clearance of 0 to 2 ml/min/m^2.

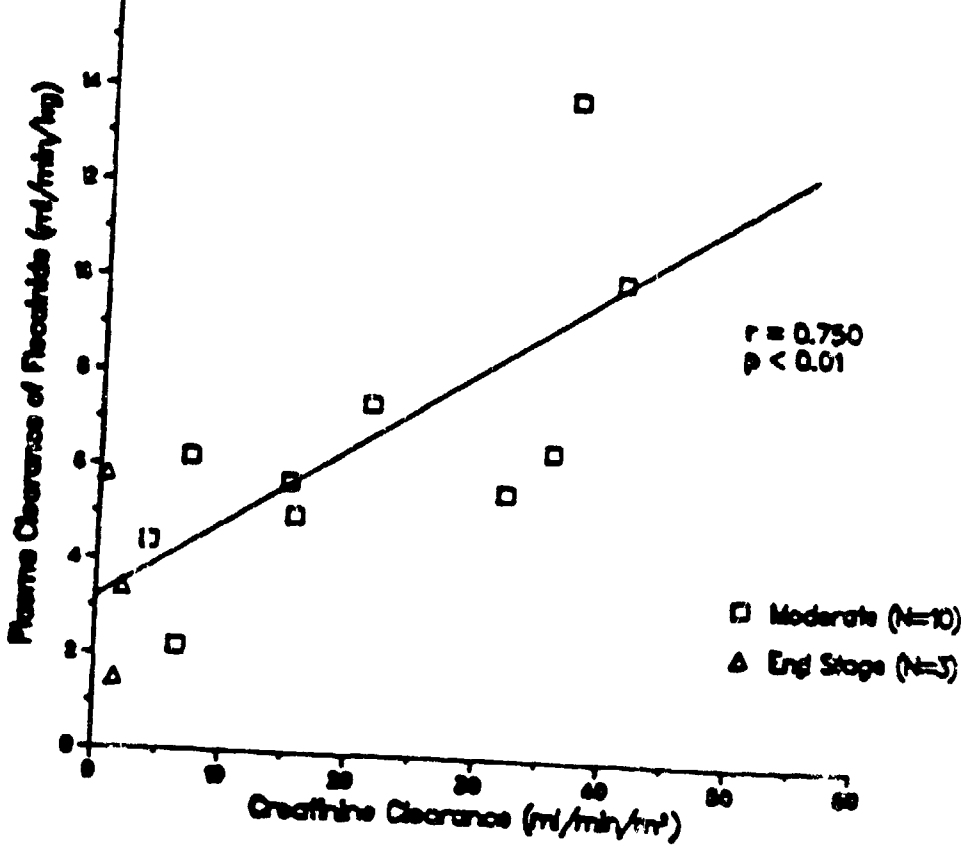
For patients with moderate renal failure, plasma half-life, on average, is about 30% longer and plasma clearance is about 35% slower than for healthy subjects; overall, flecainide elimination from plasma is about 30% slower than for subjects with normal renal function. In addition for the moderate group, the extent of flecainide excretion in urine is less extensive (about 40%) and renal clearance is slower (about 50%); on average, the excretion of flecainide in urine is about 45% less.

For patients with end-stage renal disease, plasma half-life is longer and clearance is slower than for the moderate group; this was particularly the case for two patients with end-stage renal disease, who had half-lives of about two days. Thus, the elimination of flecainide from plasma is markedly slower in some end-stage patients. In addition, the extent of urinary excretion is markedly less and renal clearance of flecainide is markedly slower in the end-stage group.

Although plasma and renal clearance of flecainide are correlated with creatinine clearance, the latter alone (creatinine clearance) is not predictive of flecainide clearance in a given patient; Figure 8A shows a plot of plasma clearance of flecainide versus creatinine clearance (Study 038-01) for the 10 patients with moderate renal failure and three patients with end-stage renal disease (creatinine clearance could not be determined in the other seven end-stage patients). Since flecainide is also extensively biotransformed (in addition to being excreted unchanged in urine), there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. For patients with more severe renal impairment, lower maintenance doses may be required. Upward dosage titration should be undertaken cautiously, bearing in mind that it may take longer to achieve a new steady-state plasma level in these patients.

FIGURE 8A

Relationship Between Plasma Clearance of Flecainide and Creatinine Clearance Renal Failure Study (038)



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Hemodialysis does not effectively remove unchanged flecainide from the body (only about 1% of the dose). Removal of metabolites by hemodialysis, however, is more substantial (about 10% of the dose as total meta-O-dealkylated flecainide).

f. Plasma Protein Binding

The plasma protein binding of flecainide has been assessed in vitro using equilibrium dialysis. Results indicate that flecainide is not extensively bound to human plasma proteins (only about 40%, on average). In addition, the binding is independent of total plasma drug level over a wide range that includes and markedly exceeds therapeutic concentrations.

No consequential effect or interaction on binding has been found with other drugs that are protein bound. Also, flecainide binding is not greatly increased in patients after an acute myocardial infarction, at a time when alpha$_1$-acid glycoprotein levels are elevated. Thus, consequential changes in free (unbound) drug levels in vivo would not be expected with concomitant drugs or with changes in plasma proteins.

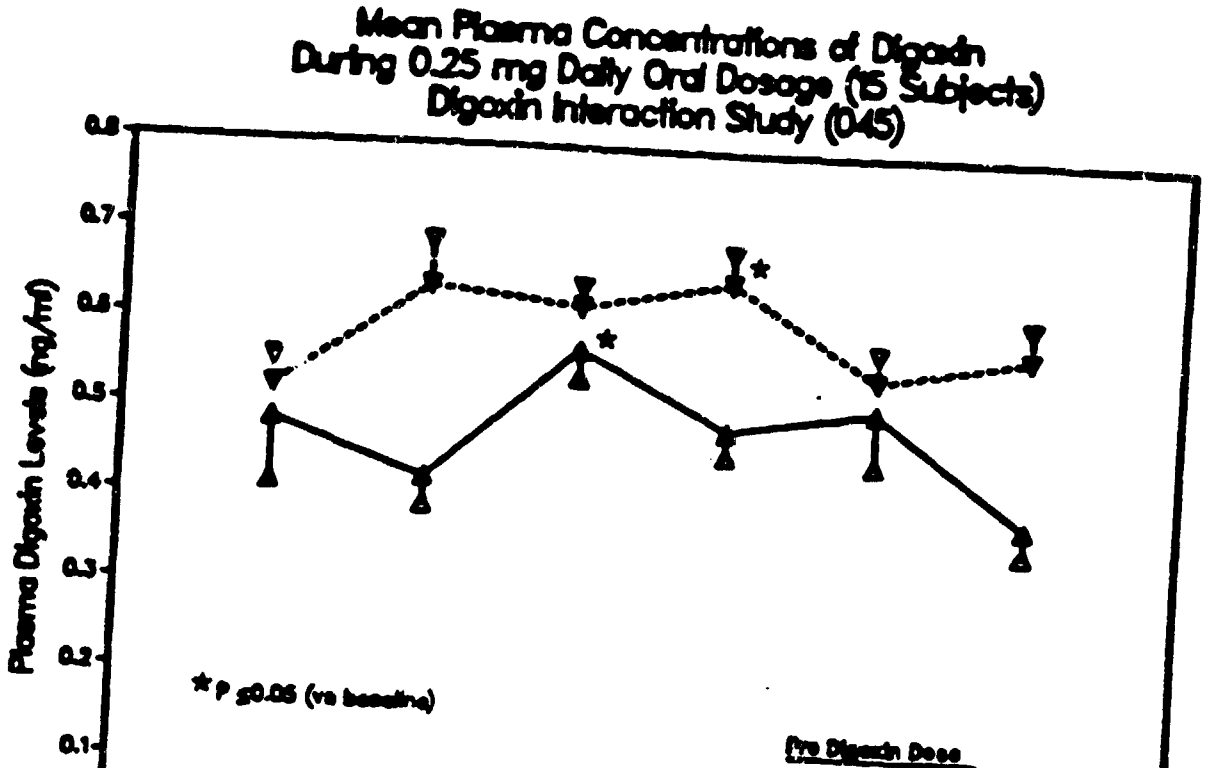
4. Drug-Drug Interactions

a. Digoxin

The effect of multiple dosage of flecainide (200 mg bid for five days) on steady-state plasma levels of digoxin has been assessed (Study R-818-045-01). As shown in Figure 8B, coadministration of therapeutic doses of flecainide was found to cause a small, but sometimes statistically significant, increase in plasma digoxin levels when values on days 13 and 15 were compared with baseline (average of days 9 and 10) values.

On average, digoxin levels were 13% higher at six-hours postdose; this is markedly less than that reported for quinidine.

FIGURE 8B



No increase was noted in the incidence of side effects reported by the subjects in this study, nor were unexpected adverse reactions observed. Increases were noted in the PR interval when both drugs were administered concurrently, but these were of the magnitude generally reported for flecainide given by itself. The small changes in digoxin levels should be of little clinical consequence for most patients on chronic digoxin therapy.

b. Propranolol

In another study (041-01), the pharmacodynamic and pharmacokinetic interactions of flecainide (200 mg bid) and propranolol (80 mg tid) were assessed. Each drug alone demonstrated a mild negative inotropic effect, the negative inotropic effects of flecainide and propranolol being comparable in this study. The coadministration of the two drugs produced effects that were, at most, additive. Effects on PR interval were less than additive. During

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coadministration, plasma levels were elevated about 30% for propranolol and about 20% for flecainide as compared to control levels. These somewhat higher levels were associated with no greater than additive pharmacodynamic effects, and the plasma half-lives of both drugs did not appear to be affected by coadministration. While these effects were of little clinical consequence in the healthy subjects in this study, there remains the possibility of exaggerated negative inotropic effects in patients with reduced left ventricular function.

ACUTE AND CHRONIC CONTROLLED STUDIES

Protocol	No of Sites	Study Design	Condition(s) Studied	No of Qualifying Patients Enrolled	Completed	Conclusions
030 Dose-Ranging Trial	3	Single-blind trial, 3 day dosing of flecainide 200, 400, and 600 mg/day followed by open-label 2-week trial in responders	Chronic PVCs, nonsustained VT	35	30	Flecainide was highly effective in suppressing PVCs and nonsustained ventricular contractions. 31/35 patients achieved ≥ 80% suppression: 9 required 200 mg/day, 15 required 300 mg/day or 400 mg/day, and 7 required 500 mg/day or 600 mg/day.
032 Flecainide (F) - Quinidine (Q) Comparison Trial	16	Double-blind, parallel, randomized, 4 week trial comparing flecainide 200-300 mg bid with quinidine 300 to 600 mg qid	Chronic PVCs, nonsustained VT	F = 141 Q = 139 280	F = 119 Q = 114 233	Oral flecainide (200 to 300 mg every 12 hours) compared with oral quinidine (300 to 600 mg every six hours) showed greater suppression of PVCs and nonsustained VT.
057 Amended, Acute Chronic Study of Ventricular Tachycardia	16	Open-label, long-term safety and efficacy study using an initial dose of 100 mg bid with controlled upward titration of dosage	Refractory ventricular tachycardia and significant cardiac disease	96	47 ongoing (mean, 8 months)	An initial dose of 100 mg bid with careful upward titration to optimize efficacy and tolerance is appropriate when treating patients with severe heart disease and associated complex ventricular arrhythmias.
058 Flecainide - Disopyramide Comparison Trial (Norway)	6	Double-blind, crossover, randomized, placebo-controlled trial comparing flecainide 200 mg bid with disopyramide 150 qid for a 7 week duration	Chronic PVCs, Nonsustained VT	32	26	Flecainide (400 mg per day) when compared to disopyramide (600 mg per day) was more effective in the suppression of simple and complex PVCs.

CHRONIC SAFETY AND EFFICACY TRIALS

Protocol	No of Sites	Study Design	Condition(s) Studied	No of Qualifying Patients Enrolled	No ongoing/ Duration of Therapy	Conclusions
031 Chronic followup of Dose-Ranging Trial	3	Open-label, long-term followup of responders from 030 trial	Chronic PVCs, nonsustained VT	29	23 patients at 24 mos	Flecainide continued to be effective in suppressing ventricular arrhythmias, without limiting side effects in 23/29 patients who completed at least 24 months of long-term therapy.
033 Chronic followup of Flecainide - Quinidine Comparison Trial	16	Open-label, long-term followup of patients from 032 trial	Chronic PVCs, nonsustained VT	198	117 patients at 6 to 24 mos	For the 117 (59%) patients who completed 6 to 24 months of long-term therapy (mean exceeding one year), flecainide continued to be successful in suppressing ventricular arrhythmias without limiting side effects.
035 Chronic Controlled Trial/Ventricular Ectopy (Netherlands)	4	Open-label, 6-day inpatient period followed by long-term followup of responders	Chronic PVCs, nonsustained VT	66	37 patients at 12-28 mos	Flecainide continued to be effective in suppressing ventricular arrhythmias without limiting side effects in patients treated approximately 17 months (median, 15 months).
COMPASSIONATE-USE TRIALS						
028	45	Open-label long-term safety and efficacy trial	Refractory ventricular tachycardia	228	89 patients for a mean of 13.5 mos	Flecainide was an effective antiarrhythmic in this refractory population. 39% of patients were effectively treated for a mean of 15.5 months. Flecainide did appear to be associated with potentially serious cardiac side effects.
057	13	Open-label long-term safety and efficacy trial	Refractory ventricular tachycardia significant cardiac disease	39	14 patients for a mean of 11.6 mos	Flecainide was effective in 14 of 39 high risk patients for 10 to 12 months. This trial was suspended in November 1982. An amended protocol of this study was initiated which used lower initial doses, upward dose titration, and plasma level monitoring (057, Amended).

OTHER STUDIES

Protocol	No of Sites	Study Design	Condition(s) Studied	No of Qualifying Patients Enrolled	Completed	Conclusions
019 Efficacy, tolerance, and plasma levels of flecainide in patients	3	Open-label, inhospital, divided doses within a six hour period to a total dose of 240 mg	Non-life-threatening cardiac arrhythmias	25	25	Antiarrhythmic effects were demonstrated in patients with vaoble data.
053 Effect on intracardiac conduction and induced ventricular tachycardia	2	Open-label, 200 mg bid, 4 to 6 days inhospital	Ventricular tachycardia	17	16	From the induction of ventricular tachycardia, flecainide protected 9/17 (53%) patients, partially protected 2/17 (24%) patients, and failed in 4/17 (24%) of patients. This indicates that flecainide is safe and effective in the suppression of VT as evaluated by PES testing.
056 Effect of multiple oral doses on the inducibility of VT during EP testing	1	Open-label, inhospital, safety and efficacy trial for VT inducibility by EP testing	Ventricular tachycardia	8	8	EP testing results have not been evaluated. Safety analyses showed that a loading dose regimen should not be recommended.

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B. Efficacy

1. Controlled Trials

This section discusses:

a. A dose-ranging trial (Study 030) performed in 35 patients with simple and complex ventricular ectopy. This study identified doses that significantly suppressed (greater than 80%) PVCs in this population, and supported the recommended effective and maximum doses used in subsequent trials. Data from this trial that are used to support the relationship of plasma level to drug effect and to support the adequacy of a bid dosing regimen are discussed separately in Section D (Dosing Rationale).

b. A double-blind efficacy comparison trial (Study 032) in which 280 patients with ventricular ectopy were randomized to either flecainide or the commonly prescribed antiarrhythmic drug, quinidine.

c. An efficacy and safety study (amended 057 Study) of flecainide treatment in 96 patients with ventricular tachycardia most of whom had significant coexisting cardiac disease, risk of congestive heart failure and various conduction disturbances, and who were refractory to or intolerant of marketed or investigational antiarrhythmic drugs. In this trial, patients were initially treated with the lowest recommended dose of flecainide, then had limited and controlled dose adjustments based on efficacy and safety evaluations.

d. A double-blind crossover comparison study (Study 060) in 32 patients with ventricular ectopy who received both flecainide and disopyramide, in a randomized order.

a. Dose-Ranging Trial (Study 030)

STUDY DESIGN: Three centers participated in this study. Forty patients with chronic ventricular arrhythmias were screened and 35 patients qualified for participation in this study to determine the range of effective multiple oral dosage regimens for flecainide in suppressing PVCs (part 1) and to determine safety and continued effectiveness of the dosage regimen determined effective for each patient in part 1 for a two-week period (part 2). Pharmacokinetic parameters and plasma level efficacy relationships were studied to establish dosing rationale.

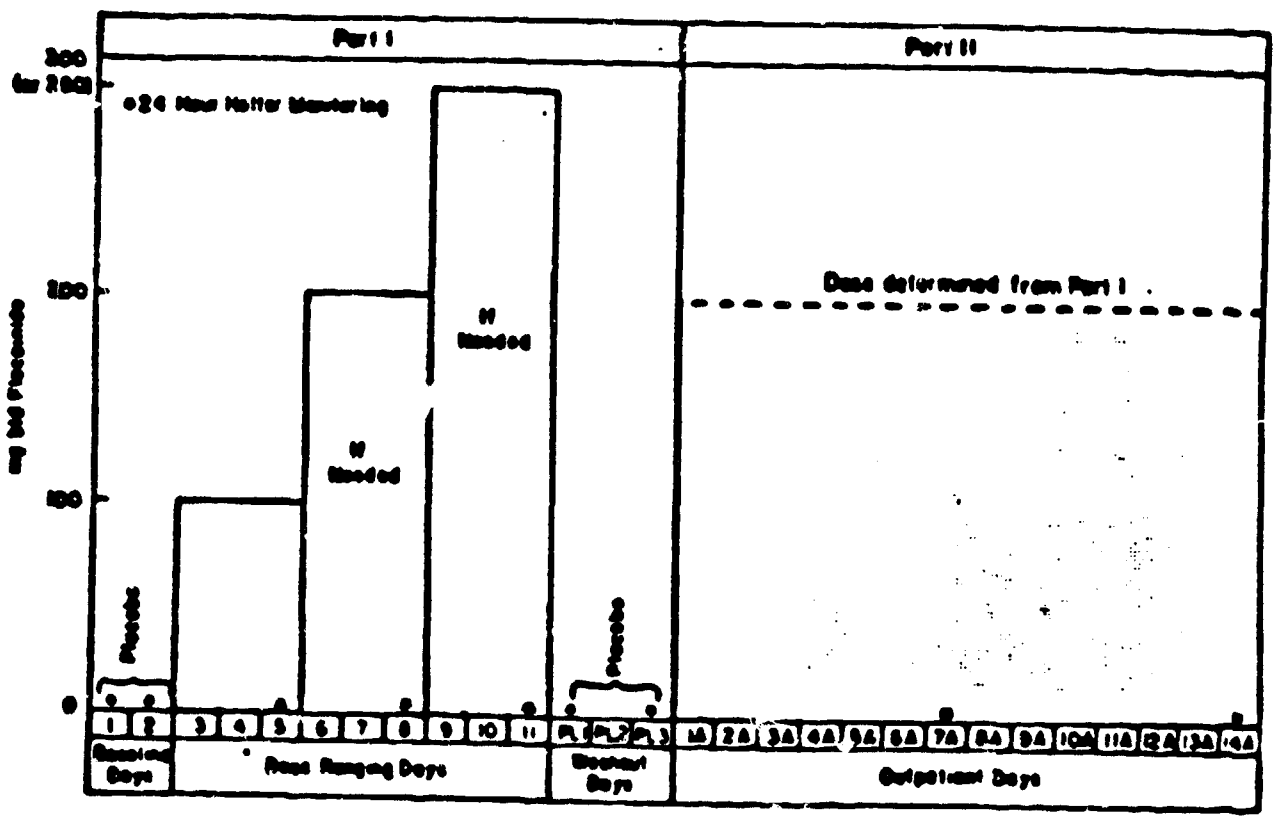
Patients with a history of chronic stable PVCs (greater than 600/12 waking hours), including unifocal, multifocal and nonsustained salvos of three or more PVCs could be entered into the study. Patients were excluded if they had digitalis intoxication arrhythmias, grade 2 or greater A-V block, a recent myocardial infarction, bundle branch block, unstable angina, ventricular tachycardia with a history of syncope or presyncope, or Class III or IV CHF.

Study design is displayed in Figure 9. Although there is no concurrent control, the washout period allows assessment of spontaneous improvement; Holter tapes are read by persons not involved in a trial and are thus effectively blinded.

Figure 9

Dose-Ranging Study (030)

STUDY DESIGN



Part 1 (single blind, inpatient) started with two days of placebo dosing followed by three days of flecainide dosing at each dose level (100 mg bid, 200 mg bid and either 250 or 300 mg bid) until greater than 80% suppression of the patient's placebo control PVC frequency was obtained, unless precluded by the occurrence of limiting side effects. Decisions by the investigator to increase dosage or to proceed to part 2 were made using 12-hour Trendscriber data (suppression of PVCs greater than or equal to 80% in comparison with placebo). Twenty-four-hour Holter recordings performed on the third day of each dosing regimen provided the basis for analysis of arrhythmia suppression.

A placebo washout period of three days was performed between parts 1 and 2.

In part 2 (open label, outpatient), patients were continued for an additional two weeks to assess multiple dose safety and efficacy on the previously determined effective and safe dose. Non-responders (patients having less than 80% suppression of PVCs) at the highest dose used in part 1 were not continued into part 2. Holter recordings were performed on the seventh and fourteenth days of part 2.

RESULTS: Eighteen males and 17 females entered the study. Ages ranged from 27 to 72 years with a mean of 54.1 years. These patients were treated with a mean of 2.5 previous antiarrhythmic agents (range 0 to 8). Table 16 lists the distribution of cardiac diagnoses.

Thirty-two of 35 qualifying patients completed part 1 of this study, 31 (89%) achieving greater than or equal to 80% suppression of PVCs. Nine of 35 patients (26%) required 100 mg bid; 14 (40%) required 200 mg bid, and seven (20%) required 250 or 300 mg bid. One patient who did not respond to 100 mg bid received 100 mg tid and achieved greater than 80% suppression. One patient completed part 1 without achieving 80% suppression of PVCs. This patient, therefore, did not enter part 2.

Three patients discontinued during part 1. One patient discontinued at 200 mg bid due to stomach pain, headache, abdominal cramps, and nausea; one due to an increase in PVCs on Trendscriber at 100 mg bid; one due to a nondrug-related transient ischemic attack.

Of the 31 patients who qualified for entry into part 2 (greater than or equal to 80% suppression of PVCs in part 1) 30 entered and all completed this two week outpatient portion of the study. The remaining patient was mistakenly determined to be a nonresponder by Trendscriber; Holter data later showed 82% suppression at 300 mg bid. Of the 30 patients entered in part 2, 26 achieved greater than or equal to suppression of PVCs at the end of the two-week outpatient portion of the study. Three other patients achieved 63% to 79% suppression and one patient's Holter was not analyzable. The mean and median percent suppression of baseline PVCs and repetitive beats (couplets and nonsustained VT) are given in Tables 17 and 18, respectively.

Figure 10 shows the mean number of PVCs/hour for the 32 patients who completed part 1 of the study. The figure shows the mean PVCs/hour at baseline, at the effective dose, at washout, and on outpatient days 7 and 14. Figure 11 shows the same information for repetitive PVCs (couplets plus VT beats) for these 32 patients. The off-on-off-on pattern, as well as the very large response seen, leaves no doubt, despite lack of a concurrent control group, that the change in VPB rates is drug-related.

CONCLUSION: Flecainide was effective in this population of patients with chronic ventricular ectopy. Eighty-nine percent of qualifying patients (31/35) responded to daily doses of 200 to 600 mg/day with greater than or equal to 80% suppression. Eighty-seven percent (26/30) of patients entering the outpatient phase of the study achieved greater than or equal to 80% suppression of PVCs at two weeks. Flecainide was well tolerated in this population with only two patients discontinuing because of drug-related adverse effects.

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TABLE 16

Cardiac Diagnoses

	Number of Patients[a]	% of Patients (n = 35)
Atherosclerotic heart disease	14	40%
Previous MI	5	14%
Cardiomyopathy	3	9%
Valvular disease	11	31%
Hypertensive heart disease	7	20%
Primary rhythm disorder	3	9%
History of CHF	4	11%

[a] Patients may have more than one cardiac diagnosis.

TABLE 17

Efficacy Summary

Mean and Median Percent Suppression of Baseline PVCs

Center	Dose-Ranging Effective Dose Mean	Dose-Ranging Effective Dose Median	Outpatient Day 7A Mean	Outpatient Day 7A Median	Outpatient Day 14A Mean	Outpatient Day 14A Median
01	94.9% (n=10)	99.6%	96.1% (n=9)	99.8%	95.3% (n=9)	98.8%
02	96.3% (n=11)	100%	94.1% (n=10)	99.6%	93.2% (n=9)	100%
03	96.9% (n=11)	97.2%	92.6% (n=11)	95.9%	95.8% (n=11)	98.2%
Overall	96.1% (n=32)	98.8%	94.2% (n=30)	98.8%	94.9% (n=29)	98.8%

TABLE 18

Efficacy Summary - Couplets and Nonsustained VT

Mean and Median Percent Suppression of Baseline Couplets and Nonsustained VT

Center	Dose-Ranging Effective Dose		Outpatient Day 7A		Outpatient Day 14A	
	Mean	Median	Mean	Median	Mean	Median
01	98.5% (n=9)	100%	98.4% (n=8)	100%	92.8% (n=8)	100%
02	87.2% (n=11)	100%	92.5% (n=10)	100%	96.0% (n=9)	100%
03	99.9% (n=11)	100%	99.5% (n=11)	100%	99.2% (n=11)	100%
Overall	98.2% (n=31)	100%	96.8% (n=29)	100%	96.4% (n=28)	100%

Center 01 had one patient with zero couplets and zero nonsustained VT beats at both baseline and followup visits.

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Figure 10
Study 030 Holter Analysis
Mean PVCs/Hour ± Standard Error of the Mean

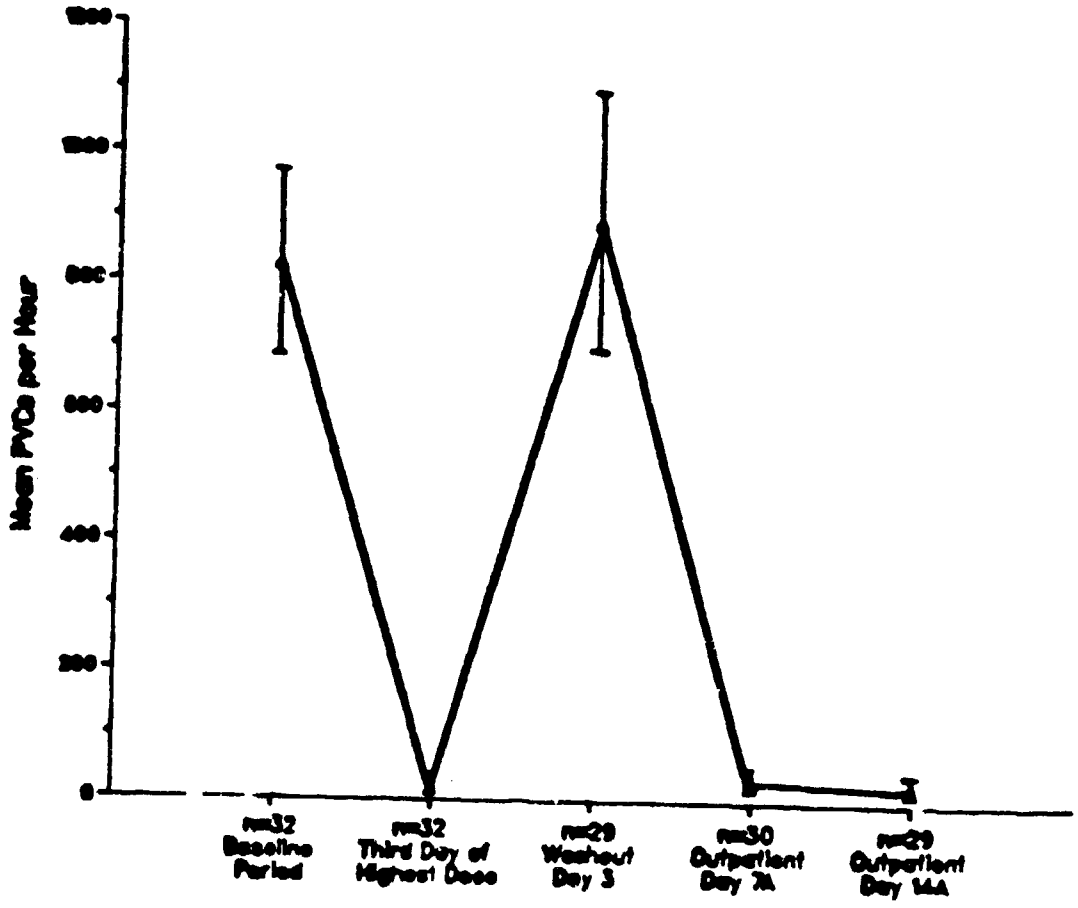
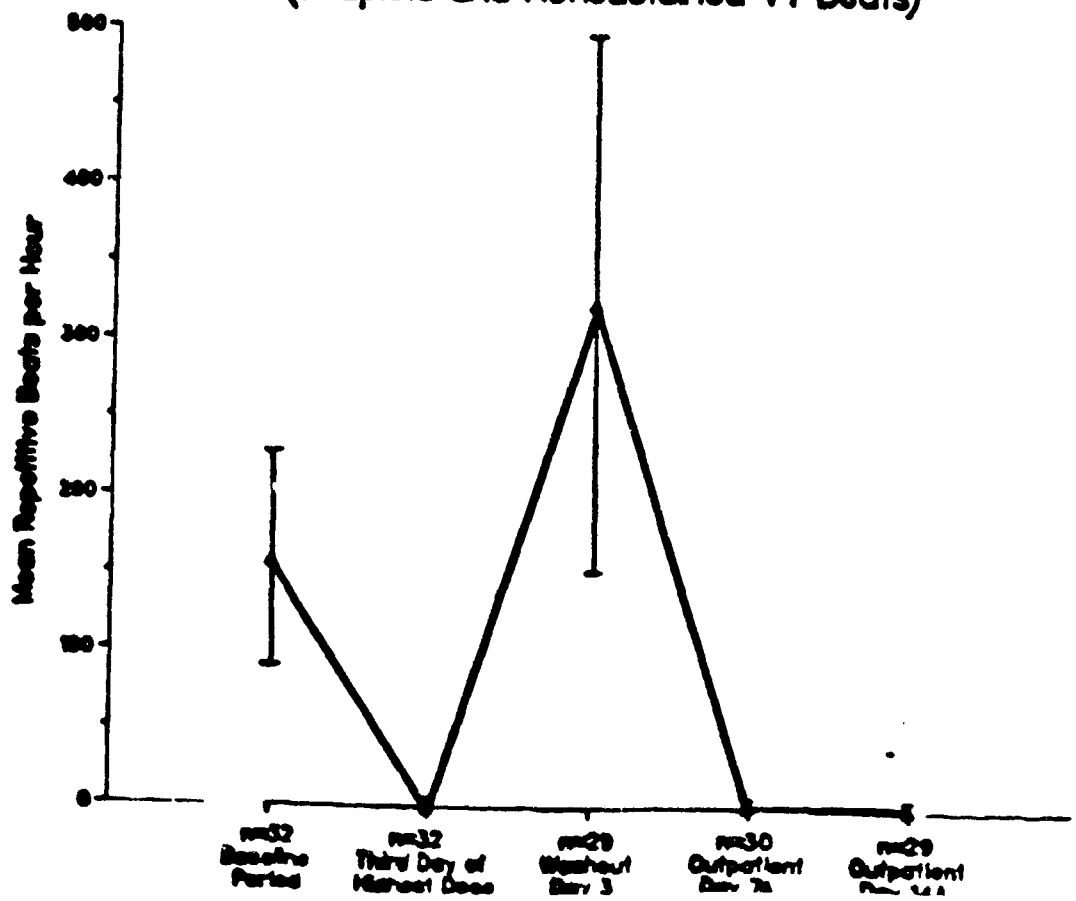


Figure 11

Study 030 Holter Analysis
Mean Repetitive Beats/Hour ± Standard Error of the Mean
(Couplets and Nonsustained VT Beats)



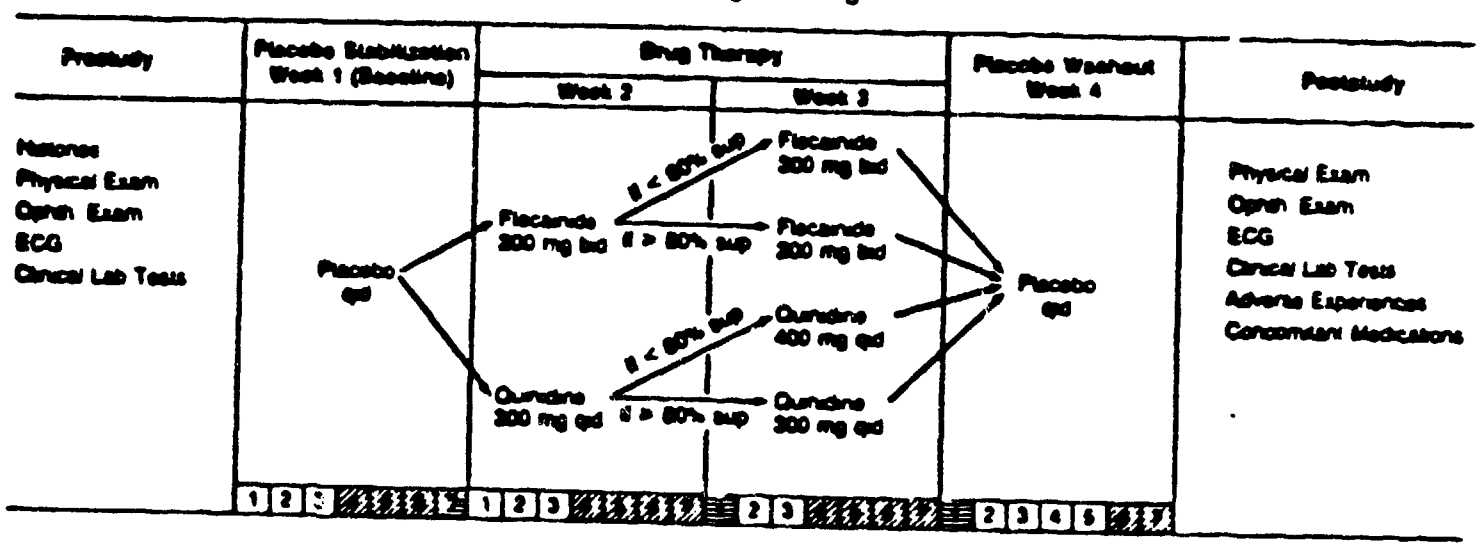
b) Flecainide-Quinidine Comparison Trial (Study 032)

STUDY DESIGN: Investigators at 16 sites participated in this study to determine the comparative safety and efficacy of multiple, oral dose administration of flecainide acetate and quinidine sulfate under double-blind conditions in patients with chronic premature contractions (PVCs), which included singled and paired premature beats and runs of ventricular tachycardia (V-tach).

This double-blind, parallel, randomized study included two weeks of active drug therapy, bounded before and after by placebo periods, each seven days long. (See Figure 12.)

Figure 12

Flecainide/Quinidine Comparison Study (032)
Study Design



■ Holter Monitoring — 48 consecutive hours during days 4 through 7 (weeks 1, 2 and 3) or days 6 and 7 (week 4)

■ Weekly Visit — Vital signs, ECG, adverse experiences, concomitant medications, clinical lab tests

Patients could be enrolled if they had ventricular arrhythmias that required antiarrhythmic therapy (greater than 30 PVCs/hr on placebo) and could be treated as outpatients. Patients were excluded from the study if they had digitalis intoxication arrhythmias, grade 2 or greater A-V block, bundle branch block combined with 1° A-V block, severe hemodynamically compromising arrhythmias, unstable angina, a recent myocardial infarction, Class III or IV CHF, a cardiac pacemaker, or a known idiosyncratic reaction or known serious toxicity to either quinidine or flecainide.

In the two-week, drug therapy period, each patient received either flecainide or quinidine. To maintain a double-blind design, each patient receiving flecainide took active drug twice a day (6 a.m. and 6 p.m.) alternating with placebo twice a day (noon and midnight) to create a qid dosage regimen. Each patient receiving quinidine took active drug four times a day (6 a.m., noon, 6 p.m. and midnight).

During the first week of drug treatment, patients received either flecainide 200 mg bid or quinidine 300 mg qid. Twenty-four hour Holter recordings obtained on the fifth or sixth day of active therapy were compared to baseline (placebo) results. The percentage of suppression of PVCs achieved determined the dose of drug each patient received during the next week of treatment. Unless precluded by limiting adverse experiences, a patient who experienced greater than or equal to 80% suppression of the baseline PVC frequency continued on the lower dose of drug. Conversely, if a patient experienced less than 80% suppression of baseline PVCs, with no limiting adverse experiences, the patient received a higher dose of active drug during the second week of treatment; either flecainide 300 mg bid or quinidine 400 mg qid. Additional Holter monitoring was performed during this week to evaluate suppression of PVCs.

A seven-day placebo washout period concluded the study. Final Holter monitoring determined the level of return of PVCs. Each patient who qualified for and participated in this study was subsequently allowed to receive long-term flecainide or quinidine therapy in an open fashion (Study 033).

RESULTS: The 16 study centers screened a total of 342 consenting patients of whom 280 qualified for the study. The main reasons for disqualification of 62 patients were: failure to show an average of 30 PVCs/hr at baseline (43/62 patients) and positive ANA titer at baseline (7/62) - both were protocol violations; miscellaneous reasons (12/62) included placebo intolerance, intercurrent illness, and logistical and technical problems.

The 280 qualifying patients included 198 males and 82 females with a mean age of 58.5 years. One hundred forty-one patients received flecainide and 139 received quinidine. Demographic characteristics were comparable between groups with the exception of race ($p = 0.049$); there were more whites in the quinidine group (127/139 or 91%) than the flecainide group (117/141 or 83%). There were no significant differences (p less than 0.05) in baseline arrhythmia profiles between drug groups. Baseline means (± one standard deviation) for qualifying patients by drug group were as follows:

Table 19
Baseline Arrhythmia Profiles
Flecainide-Quinidine Comparison Study (032)

	Flecainide	Quinidine
PVCs/hr	419 ± 448	429 ± 423
Paired beats/hr	27 ± 65	20 ± 46
V-tach beats/hr	7 ± 26	6 ± 19

Baseline cardiac diagnosis are in Table 20.

TABLE 20

FLECAINIDE-QUINIDINE COMPARISON TRIAL (STUDY 032)
BASELINE CARDIAC DIAGNOSES

	No. of Flecainide Patients[a] (%) (N=141)	No. of Quinidine Patients[a] (%) (N=139)
Atherosclerotic heart disease	73 (52%)	72 (52%)
Previous MI	42 (30%)	44 (32%)
Cardiomyopathy	16 (11%)	14 (10%)
Valvular disease	22 (16%)	30 (22%)
Hypertensive heart disease	50 (35%)	42 (30%)
Primary rhythm disorder	16 (11%)	19 (14%)

[a]Patients may have more than one cardiac diagnosis.

Of the qualifying patients, 233 completed the study. Of the 47 noncompleting patients, 40 discontinued because of adverse experiences (19 in the flecainide group and 21 in the quinidine group), including one flecainide patient without prior history of ventricular tachycardia who developed a new wide complex VT on the high dose and a second patient who had increased PVCs and new nonsustained VT. In addition four patients developed ECG changes leading to discontinuation (increased or new 1^0 AV block or widened QRS and PR intervals) and three developed junctional escape rhythms, in two cases with severe syncope due to sinus node dysfunction. Two patients developed worsened CHF, leading to discontinuation. Two quinidine patients developed ventricular tachycardia (both had prior history of VT) and one, CHF with increased PVCs. Four patients died, three of documented acute myocardial infarctions (all taking quinidine) and one suddenly out-of-hospital while taking placebo, 36 hours after taking flecainide for two weeks. The adverse experiences leading to withdrawal from flecainide were principally the cardiac experiences listed, as well as dizziness, blurred vision and nausea. Quinidine was discontinued principally because of diarrhea, nausea and vomiting. The discontinued patients and reasons for discontinuation are listed in Tables 20A and 20B. Other adverse experiences will be described in the safety section below.

The main basis for efficacy comparisons between flecainide and quinidine was the percent suppression of baseline PVCs which included 1) the total number of premature beats, 2) premature beats occurring in pairs (paired beats), and 3) premature beats occurring in runs of three or more (V-tach beats).

Forty-four percent (54/122) of the patients on quinidine who entered the second week of drug therapy required the higher dose compared to 18% (23/127) of the flecainide patients (p less than 0.0001).

The mean percent suppressions of PVCs by flecainide were 83.6% in the first week of therapy and 91.0% in the second week of therapy, versus 58.5% and 39.2% for quinidine, respectively. The median percent suppressions of PVCs by flecainide were 99.4% at week two and 99.5% at week three, versus 80.3% and 84.7% for quinidine at weeks two and three, respectively. The two-way analysis of variance on the ranks of percent suppression showed flecainide more effective than quinidine during both weeks two and three in suppressing PVCs (p less than 0.0001), paired beats (p less

TABLE 20A

QUALIFYING PATIENTS WHO DISCONTINUED WHILE TAKING FLECAINIDE (WEEKS 2 AND 3)

Center	Pt No.	Dose mg bid	Last Study Day	Reasons
02 Hodges	7	200	W3D2	Congestive heart failure
	23	200	W2D2	Severe syncope, fatigue, weakness, and junctional bradycardia.
03 Cook	7	200	W2D2	Grand mal seizure - vasovagal episode
04 Farnham	5	200	W3D3	Blurred vision, dizziness, first degree AV block worsened
	15	200	W2D7	First degree AV block, bradycardia
	20	200	W2D7	First degree AV block, dizziness
05 Hart	9	300	W3D5	Loss of equilibrium, dyspnea, fatigue
	10	200	W2D7	Severe weakness, diaphoresis, near syncope
06 Kalmanschn	10	200	W2D4	Palpitations and moderate dizziness
	14	200	W3D6	Severe fainting, nausea, dizziness, bradycardia, junctional rhythms
08 Lee	3	300	W3D7	Noncompliance
	6	300	W3D3	Ventricular tachycardia
	13	200	W2D4	Dizziness, peripheral blurring of vision, severe headache
10 Antlitz	3	200	W2D5	Congestive heart failure exacerbated
	4	200	W2D4	Dry mouth, nausea, numb hands and feet, disoriented
11 Marcus	2	200	W3D1	Widening of QRS and PR intervals
12 Morganroth	4	300	W3D2	Shortness of breath, nausea, junctional rhythm
	23	200	W2D3	Nervousness, dizziness, blurred vision, shortness of breath
13 Oshrain	19	200	W2D7	Blurred vision
17 Platt and Rosin	11	200	W3D1	Severe dizziness
	17	300	W3D6	Increase in PVCs, new, non-sustained V Tach

TABLE 20B

QUALIFYING PATIENTS WHO DISCONTINUED WHILE TAKING QUINIDINE (WEEKS 2 AND 3)

Center	Pt No.	Dose mg q'd	Last Study Day	Reasons
01 Beller	6	400	W3D3	Vomiting, nausea, cramps
02 Hodges	28	300	W2D2	Acute thrombosis - patient died
03 Cook	3	300	W2D3	Severe diarrhea
	5	300	W3D5	Fever, diarrhea, tinnitus, rash, backache
	9	400	W3D2	Nausea, shortness of breath, rapid heart beat
04 Farnham	1	300	W2D2	Acute myocardial infarction - patient died two days later
	8	300	W2D6	Personal - noncompliance
	9	300	W2D2	Diarrhea, nausea, "sick"
05 Hart	8	300	W2D7	Gastric disturbances, ankle edema, precipitated CHF, increase in PVCs
07 Laidlaw	3	300	W2D4	Severe shortness of breath and wheezing, diarrhea
	15	300	W2D4	Acute myocardial infarction - patient died
	22	300	W3D4	Severe diarrhea
08 Lee	1	300	W2D3	Nausea, diarrhea
	5	400	W3D5	Severe nausea, vomiting, diarrhea, headache
	18	300	W2D5	Severe nausea and diarrhea
11 Marcus	1	300	W2D2	Diarrhea
	4	300	W2D7	Swelling, red hands; fatigue; peripheral edema; increased stools
12 Morganroth	13	400	W3D5	Severe nausea and dizziness
13 Oshrain	5	300	W3D4	Rash; axillary adenopathy, abnormal LI
14 Reid	5	300	W2D2	Tremor, fever, diarrhea, headache
	9	300	W2D6	Ventricular tachycardia, ventricular fibrillation
	12	300	W3D5	Vomiting, diarrhea, soft stools, tinnitus, fever, thrombocytopenia
	13	300	W3D1	Ventricular tachycardia
	18	300	W2D7	Cramps, sinus tachycardia, diarrhea, dehydration
17 Platt and Resin	26	300	W2D7	Severe dizziness, nausea, vomiting, blurred vision

than 0.001) and V-tach beats (p less than 0.01). None of these analyses found significant differences between centers. Except for one center at week three, median percent suppression was greater for flecainide than quinidine in all 16 centers at both weeks two and three. In the one other instance, both drugs showed a median of 100% suppression.

At the end of the two week drug therapy period, a comparison between the flecainide and quinidine groups showed the following for percent suppression of PVCs, paired beats, and V-tach beats.

Table 21
Suppression of Arrhythmias In
Flecainide-Quinidine Trial

Percent Suppression	Flecainide Patients	Quinidine Patients	P-Value Between Drugs
PVCs			
100%	16%(19/118)	3%(3/110)	<0.001
≥95%	75%(88/118)	34%(37/110)	<0.0001
≥80%	85%(100/118)	57%(63/110)	<0.0001
Paired Beats			
100%	70%(73/105)	41%(41/99)	<0.0001
≥95%	85%(89/105)	60%(59/99)	<0.0001
V-tach Beats			
100%	79%(57/72)	55%(37/67)	<0.01
≥95%	86%(62/72)	66%(44/67)	<0.01

In addition to the above comparisons, 68% (80/118) of the flecainide patients had at least 80% suppression of PVCs plus complete (100%) suppression of paired beats and V-tach beats versus 33% (36/110) for quinidine (p less than 0.0001).

CONCLUSION: The doses of 200 mg to 300 mg bid of flecainide, and the doses of 300 mg to 400 mg qid of quinidine were equally tolerated in patients treated for chronic ventricular ectopy; discontinuations because of side effects were approximately equal, but quite common, (about 15%), and different in nature, quinidine causing

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intolerable diarrhea, nausea, and vomiting, flecainide causing more symptomatic bradycardia, A-V block, and one well-documented pro-arrhythmic event, a new VT in a patient with no prior VT history. At these doses, flecainide showed greater suppression (p less than 0.0001) of simple and complex PVCs and nonsustained ventricular tachycardia compared to quinidine.

c) Open-Label Study of Patients With Ventricular Tachycardia (Study 057 amended)

STUDY DESIGN: Investigators at 14 sites participated in this open-label study to evaluate the safety and efficacy of oral flecainide acetate in patients with refractory ventricular arrhythmias and significant coexisting cardiac disease. The study was modified from a trial (Study 057) of similar design with a more aggressive initial titration after early deaths were seen in that study (see below under 3b) and in the compassionate use Study 028.

In order to receive flecainide in this study, patients were required to have significant ventricular arrhythmias, especially VT (greater than or equal to six beats in a row at a rate of greater than or equal to 100 beats/min). If there was no history of VT, the patient was required to have more than 10 PVCs per hour and be refractory to previous therapy. Investigators were encouraged to enter patients who had associated cardiac disease (BBB or IVCD; Class III or IV CHF) in conjunction with their arrhythmia.

Patients were excluded from the study if they exhibited any of the following: digitalis intoxication arrhythmias, second or third degree heart block, atrial flutter or fibrillation without a ventricular arrhythmia QRS greater than 0.15 or PR greater than 0.28 sec, recent unstable MI, or pacemaker dependent rhythm. Patients were to be monitored for at least 7 days in-hospital.

Patients underwent baseline determinations after discontinuing all previous antiarrhythmic therapy for a minimum of four drug half-lives. Each patient was to complete 24 hours of baseline Holter monitoring. Patients with a history of VT had to have VT documented by rhythm strip, electrocardiogram (ECG), or Holter monitoring within two weeks prior to starting flecainide. Baseline radionuclide ejection fraction (RNEF) and 12-lead ECG with interpretation were obtained on each patient. The RNEF had to to be repeated at discharge if it was less than 30% initially. At the investigator's discretion, patients with conduction abnormalities underwent standard electrophysiologic testing.

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The initial starting dose was 100 mg bid. Upward dosage adjustments could be made if after four days efficacy was not achieved. Upward adjustments, however, were limited to 50 mg bid increments every four days to a maximum dose of 200 mg bid. These dosing requirements were lower than those most commonly used to treat similar patients in the compassionate-use protocols (200 mg bid initial dose, 300 mg bid maximum). Plasma flecainide trough levels were required on the fourth day of each dose level. The protocol did not specify an upper or lower plasma level limit, but the investigators tried to maintain trough plasma levels within the therapeutic range of 200 to 1,000 ng/ml.

The investigator's decision to discharge the patient from the hospital on flecainide was considered the best global assessment of effectiveness. This decision was based on one or more of the following: 1) Holter monitoring (required at baseline and at discharge), 2) telemetry, 3) PES testing (optional), 4) exercise stress testing (optional), and 5) the patient's history, symptoms, and response to previous therapy. The investigator performed interval evaluations for safety and efficacy on patients at the time of hospital discharge, one month and three months after initiating flecainide, and at quarterly intervals thereafter. In addition, the sponsor retrospectively established effectiveness criteria for patients released including (1) 100% suppression of VT by Holter, (2) 80% suppression of PVCs by Holter, and (3) non-inducibility of VT by PES or stress testing.

RESULTS: The first 96 patients (68 male, 28 female; mean age 61 years) enrolled into this ongoing study form the database for this summary.

Baseline demographic data (Table 22) were typical for these types of patients: 94 patients had a history of VT, 49 (51%) had a history of sustained VT and 45 (47%) had nonsustained VT; 2 patients (2%) were treated for PVCs; 43 (45%) patients had a history or evidence of CHF at baseline, and 30 (33%) had baseline RNEFs less than or equal to 30%; 49 patients had a history of conduction disturbances. The 96 patients had failed a mean of 4.4 previous antiarrhythmic agents prior to this study. There was a significant difference (p less than 0.05) in the mean number of previous antiarrhythmics between the sustained (4.9) and nonsustained (3.9) VT patient groups.

Table 23 summarizes efficacy results. In the judgement of the investigators, flecainide was effective in 73% (70/96) of patients during the initial in-hospital evaluation; these patients were discharged from the hospital on flecainide. Forty nine percent (47/96) of patients enrolled in the study remain ongoing for a mean of eight months (range 4.5 to 12 months). Of the 47 patients ongoing, 46 are free of symptomatic VT; one patient developed nonsustained VT associated with dizziness. The investigator chose to continue this patient on flecainide therapy due to marked decrease in frequency of his arrhythmia.

Of the patients with a history of sustained VT, 29/49 (59%) were discharged from the hospital on flecainide, and 22/49 (45%) are ongoing. Of the patients with a history of nonsustained VT, 39/45 (87%) were discharged from the hospital on flecainide, and 23/45 (51%) are ongoing.

Fifty patients had a baseline Holter tape and a Holter tape obtained prior to discharge. The median PVC suppression was 91.4%; 36/50 (72%) patients had at least 80% suppression of PVCs. Forty-three of the 50 patients had VT on baseline Holter tapes; 33/43 (77%) had complete suppression of VT; 10/43 (23%) patients had VT on their discharge Holter tape. No patient with zero VT beats at baseline had VT beats on their discharge Holter tape.

Twenty-three of the 96 patients had PES testing on oral flecainide. Flecainide provided complete suppression of VT on PES testing in 7/23 (30%) of these patients and five of seven remain ongoing. One of the suppressed patients died. Flecainide provided partial suppression in an additional 7/23 (30%) patients and three of these patients remain ongoing. Flecainide did not suppress VT during PES testing in 9/23 (39%) patients. Only one of these patients was discharged on flecainide; this patient remains ongoing.

Table 24 shows a listing of total daily doses received by all patients at discharge, and by ongoing patients at discharge and at their most recent visit.

A summary of the reasons for patient discontinuations is listed by frequency in Table 25A and the reasons for discontinuation for each patient are shown in Table 25B. Most patients who discontinued did so early in the study. Of the 49 discontinued patients, 26 (53%) discontinued flecainide prior to hospital discharge. These included eight patients whose arrhythmias worsened during initial hospitalization from one to 17 days after initiation (two increased frequency of VPCs and non-sustained VT; two had

VT that was more difficult to convert; one had more easily induced sustained VT; one had more easily induced non-sustained VT; one had inducible VT on PES that recurred the next day; and one developed new spontaneous VT different from baseline. Two later pro-arrhythmia episodes also occurred, one increased VPCs and non-sustained VT's and one arrhythmia that was more difficult to convert. In marked contrast to studies 028 and 057 (see below), however, there were no early deaths. Serious conduction disturbances including 3° A-V block were also seen in four patients after two, five, six and 100 days of therapy. All nine deaths and all five discontinuations due to noncardiac adverse experiences occurred after discharge.

Of the nine patients on flecainide who died in this study, three patients died in association with a documented acute MI; six died from sudden death experiences outside of the hospital, or en route to the hospital. Three of these patients had a previous history of sustained VT, three had non-sustained VT. No patients died of congestive heart failure, conduction disturbance, or in association with a documented proarrhythmic event.

The overall mean trough plasma levels for 31 discharged patients with analyzable samples, (mean daily dose, 260 mg) was 532 ng/ml. The overall mean plasma levels at discharge for sustained VT patients (556 ng/ml) and nonsustained VT patients (526 ng/ml) were not significantly different. The first 8 patients with pro-arrhythmic responses had mean daily doses of 325 mg and plasma levels of 622 ng/ml, only slightly higher than the mean dose and plasma levels for all discharged patients. Daily doses in seven patients with conduction disturbances were low, mean 271 mg. The one patient stopping therapy with worsened CHF was on 400 mg, with a plasma level of 620 ng/ml. Patients who died had a mean dose of 289 mg/day (9/9 patients) and a plasma level of 600 ng/ml (4/9 patients).

TABLE 22

Demographic Results

Total No. patients	96
No. males	68 (71%)
females	28 (29%)
Mean age (yrs)	61 (16-82)
Mean weight (kg)	74 (40-106)

Cardiac Diagnoses[a]	% of patients N = 96
Atherosclerotic heart disease	74%
Previous MI	57%
Cardiomyopathy	17%
Valvular disease	20%
Hypertensive heart disease	28%
Primary rhythm disorder	5%
History of CHF	45%
History of VT	98%
History of sustained VT	51%
History of nonsustained VT	47%
Mean number of previous antiarrhythmic agents	4.4

[a]Patients may have more than one cardiac diagnosis.

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TABLE 23
Efficacy Results

	All Patients	Sustained VT	Nonsustained VT	PVCs only
Enrolled	96	49	45	2
Discharged from the hospital on flecainide	70 (73%)	29 (59%)	39 (87%)	2 (100%)
Ongoing	47 (49%)*	22 (45%)	23 (51%)	2 (100%)
Free of symptomatic VT	46 (48%)	22 (45%)	22 (49%)	2 (100%)
All deaths	9 (9%)	5 (10%)	4 (9%)	0
Sudden Death	6 (6%)	3 (6%)	3 (7%)	0

*Mean duration of therapy 8.0 months (244 days)

TABLE 24

Flecainide Doses for Discharged and Ongoing Patients

Total daily doses (mg)	Dose at discharge for all pts (N=70)	Dose at discharge for ongoing pts (N=47)[a]	All patients (N=47)[a]	Dose for Ongoing Patients at Most Recent Visit[b] Patients sus. VT (N=22)	Patients nonsust.VT (N=23)
100	0	0	2 (4%)	1 (4%)	1 (4%)
150	2 (3%)	2 (4%)	3 (6%)	2 (9%)	1 (4%)
200	29 (42%)	21 (45%)	14 (30%)	5 (23%)	8 (35%)
250	1 (1%)	1 (2%)	0	0	0
300	31 (44%)	19 (40%)	20 (43%)	11 (50%)	8 (35%)
400	7 (10%)	4 (9%)	8 (17%)	3 (14%)	5 (22%)
Median dose		250 mg	300 mg	300 mg	300 mg
Mean dose		255 mg	269 mg	268 mg	272 mg

a Two patients had PVCs only.

b Mean duration of therapy for the 47 ongoing patients was 8.0 months.

TABLE 25A
Patient Discontinuations

Reason	No. of Patients N = 96		Discontinued in hospital	out
Inadequate response	12	(12.5%)	11	1
Worsened arrhythmia	10	(10.4%)	7	3
Death	9	(9.4%)	--	9
Non-cardiac adverse experiences	5	(5.2%)	--	5
Personal reason*	5	(5.2%)	2	3
Conduction disturbance	4	(4.2%)	3	1
Non-compliance	2	(2.1%)	--	2
Intercurrent disease	1	(1.0%)	--	1
Signs of CHF	1	(1.0%)	1	==
TOTAL	49	(51%)	24	25

*One patient moved to another city; the patient discontinued this study but enrolled in another flecainide study at the new location.

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Table 25B

Patient Discontinuations (DC)

Center	Pt. No.	No. Days on Oral Flecainide	Total Daily Dose (mg) at DC	Reason for Discontinuation
-01	101	77	400	Death
	102	13	300	Inadequate response-worsened arrhythmia
	103	14	300	Inadequate response
	105	1	200	Inadequate response - worsened arrhythmia
-02	301	3	200	Inadequate response
-06	101	86	350	Adverse experience - palpitations, malaise, blurred vision, anorexia
	104	15	300	Worsened arrhythmia
-07	101	69	300	Death
	103	12	200	Death
	104	6	300	Conduction disturbance - sinus pause
-10	101	7	300	Inadequate response
	102	201	400	Worsened arrhythmia
-11	101	3	200	Worsened arrhythmia
-12	101	2	100 oral + 80 IV	Inadequate response
	103	44	300	Inadequate response
	104	98	200	Adverse experience vertigo associated with blurred vision
	106	1	200	Personal reason - patient withdrew consent
	108	4	200	Inadequate response
	109	13	400	Inadequate response
	110	21	200	Death
	112	14	400	Signs of congestive heart failure
	113	5	200	Conduction disturbance - complete AV block
	115	2	200	Conduction disturbance - complete heart (AV) block
	119	100	200	Conduction disturbance - 2° AV block
-26	102	8	300	Inadequate response - worsened arrhythmia
	107	16	400	Inadequate response worsened arrhythmia

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Table 25B - continued

Patient Discontinuations (DC)

Center	Pt. No.	No. Days on Oral Flecainide	Total Daily Dose (mg) at DC	Reason for Discontinuation
-26	108	4	200	Inadequate response
	110	3	200	Inadequate response - other reason - wanted to increase dose before protocol would allow
	113	17	400	Inadequate response worsened arrhythmia
-31	102	83	300	Death
	103	41	200	Patient felt weak, short of breath
-34	104	12	300	Inadequate response
-63	101	16	500	Inadequate response - worsened arrhythmia
	102	10	600	Worsened arrhythmia
-65	101	5	200	Inadequate response
-72	101	14	200	Inadequate response
	105	58	150	Personal reason - discharged to nursing home

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CONCLUSION: In patients with VT, a baseline-controlled trial is the best that can be done, because prolonged outpatient placebo therapy is unacceptable and only an effective therapy can be maintained. This study demonstrated that administration of flecainide in lower initial doses (100 mg bid) with upward titration of dose to 200 mg bid as necessary (but most patients received 300 mg/day or less) to optimize efficacy and tolerance can result in effective treatment of refractory ventricular arrhythmias with marked reduction of VPBs. Symptomatic VT also seems to have been eliminated in many, although without a concurrent control this conclusion is not wholly secure. The frequency and severity of adverse experiences were more favorable than in trials with larger doses of drug (see report of study 057 and Safety section), supporting the recommendation of an initial dose of 100 mg bid with careful upward titration in patients with severe heart disease and associated ventricular tachycardia.

d) Flecainide-Disopyramide Trial (Study 060), Norway

STUDY DESIGN: Four Norwegian investigators participated in this multicenter study to evaluate and compare the efficacy and safety of flecainide acetate and disopyramide phosphate when given orally in the treatment of premature ventricular contractions (PVCs).

This was a randomized, double-blind, crossover comparison study of seven weeks duration. Following an initial seven-day placebo period, patients were randomly assigned to receive either flecainide 200 mg bid or disopyramide 150 mg qid for a period of 14 days. A second seven-day placebo washout period followed, after which patients were crossed over to alternative active treatment for a further 14 days. A third and final seven-day placebo period terminated the study. Following enrollment, each patient returned to the hospital for weekly safety and efficacy evaluations at days 7, 14, 21, 28, 35, 42, and 49.

Patients who met inclusion/exclusion criteria had various baseline evaluations performed including 24-hour Holter analysis. Patients qualified for treatment if they had more than 1,000 PVCs per 24 hours present during baseline monitoring plus 1) five or more isolated PVCs in any one minute of analysis, and/or 2) two or more consecutive PVCs recorded in any one minute of analysis. Patients were excluded if they 1) were not between 16 years and 75 years of age; 2) had NYHA Class III or IV CHF; 3) had digitalis intoxication arrhythmias; 4) had second degree or greater A-V block; 5) had bifascicular block or bundle branch block plus any A-V block; 6) had a history of myocardial infarction within six months; 7) had a history of ventricular tachycardia with syncope; or 8) required beta-blockers or other negative inotropic therapy.

RESULTS: A total of 32 patients with PVCs enrolled at four study centers. Twenty-six patients were male and six were female, with a mean age of 55.3 years. Cardiac diagnoses included ischemic heart disease, 16 patients; previous myocardial infarction(s), 14 patients; cardiomyopathy, eight patients; unknown etiology, six patients; and valvular heart disease, two patients. Baseline arrhythmia profiles (complexes per hour) are shown in Table 26.

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Table 26
Baseline Arrhythmia Profile
Flecainide-Disopyramide Trial (060)

	Mean ± SD
Total aberrant beats[a] (n = 25)	552.4 ± 835.7
Premature aberrant[b] beats (n = 25)	325.5 ± 609.8

[a]Total aberrant includes all forms of beats which differ from "normal" configuration as defined by the analyst on the Pathfinder System (Hertford Research).

[b]Premature aberrant beats most closely approximate PVCs counted on Cardiodata Systems which was utilized in U.S. studies.

Twenty-six of the 32 (81%) patients enrolled completed the study. Six patients discontinued during the study including two who died. One of the six dropped out on day one (placebo) for personal reasons; he also was not within the age requirement. Two patients discontinued while receiving disopyramide: one suffered acute pulmonary edema and severe, bloodstained diarrhea during the second day of drug, and the other patient presented with deep vein thrombosis and pulmonary embolism following one week of drug administration. One patient discontinued after one week of flecainide administration due to a possible myocardial infarction and ventricular fibrillation during the flecainide period.

Two patients died during the study. One died of cerebral thrombosis after the first week of disopyramide treatment; the second patient died suddenly while dancing following nearly two weeks of flecainide treatment.

Evaluation of the suppression of aberrant beats was performed in 25 of the 26 patients who completed the study; one patient was excluded due to an insufficient aberrant count throughout the placebo period. Disopyramide showed a median suppression of baseline total aberrant beats of 44% while flecainide showed a median suppression of 86%; the comparative difference was statistically significant (p = 0.007) using the paired t-test. For premature aberrant beats, disopyramide showed a 39% median suppression of baseline counts, and flecainide demonstrated a 92% median suppression; this difference was also statistically significant (p = 0.002).

The percentage of patients responding with greater than 50% suppression of total aberrant beats and 80% suppression of premature aberrant beats while on flecainide was significantly greater than on disopyramide. Flecainide showed a statistically significant greater suppression of multiform extrasystoles ($p = 0.005$) and couplets ($p = 0.048$). There was also some suggestion that flecainide was more effective in reducing episodes of salvos ($p = 0.079$) and bigeminy ($p = 0.155$), although these did not reach the level of statistical significance ($p = 0.05$).

Twenty-four of the 26 patients attained adequate therapeutic plasma levels of both study drugs. These were considered to be greater than 300 ng/ml flecainide and greater than 2.0 ug/ml disopyramide. One patient did not achieve a therapeutic plasma level of disopyramide which may account for the lack of efficacy observed. Another patient did not attain a therapeutic level of flecainide and tended toward the lower range during disopyramide administration; his compliance was questionable.

CONCLUSION: At a dose of 400 mg/day, flecainide was more effective than disopyramide 600 mg/day in the suppression of simple ventricular ectopic contractions and more complex arrhythmic events. Tolerance was generally good and no differences emerged between the two drugs in the incidence or severity of reported adverse effects. Two possible pro-arrhythmic events occurred during treatment with flecainide; one sudden death while dancing after two weeks of treatment; and one episode of VF following a possible AMI.

2. Chronic Safety and Efficacy Trials

a. Chronic Follow-up of Dose-Ranging Trial (Study 031)

OBJECTIVE: The purpose of this open-label study was to evaluate the long-term safety and continuing efficacy of flecainide in patients who successfully completed the 030 dose-ranging studies. The same three centers participated in this study.

RESULTS: A total of 30 patients were eligible for this study. Each had achieved greater than or equal to 80% suppression of baseline PVC frequency in the dose-ranging study. Patients returned to the study sites for interval visits at least every three months. The investigator determined the dosage regimen for each patient and made necessary changes to control or eliminate side effects, maintain efficacy, or determine the lowest effective maintenance dose. The maximum total daily dose allowed was 600 mg.

Twenty-nine patients elected to continue taking flecainide long-term. Twenty-four of 29 patients (83%) who entered the long-term study completed 12 months of treatment and 23 completed a second year of therapy (24 months). Five patients dropped out during the first year of the study. Only one patient discontinued because of adverse experiences; this patient wished to discontinue following month two because of blurred vision, dizziness, lightheadedness, and nervousness. A second patient withdrew from the study, without explanation, following month one and was lost to followup. The three remaining dropouts were judged to be therapeutic failures.

By the end of 24 months, 23 patients remained ongoing with one patient discontinuing during the second year due to loss of therapeutic effect (at month 21).

The following table shows the number of patients taking each of the various total daily doses at month 12 and month 24; 400 mg total daily dose remained the most common dose regimen in these patients.

Table 27
Summary of Total Daily Flecainide Dosing

Total Daily Dose of flecainide	Number of Patients at Month 12	Total Daily Dose Month 24
600 mg	2	2
500 mg	1	3
450 mg	0	1
400 mg	10	8
350 mg	0	2
300 mg	7	3
200 mg	4	4
Total Patients	24	23
Mean Daily Dose	358 mg	380 mg
Median Daily Dose	400 mg	400 mg

Sixteen patients were on a bid dose schedule at month 24, 4 patients were on a tid schedule, and 3 patients received flecainide in divided (unequal) doses either at 2 times per day (2 patients), or 3 times per day (1 patient).

The last Holter data available for 23 of the 24 patients who completed the first 12 months of therapy showed an average PVC suppression of 94% (range, 53% to 100%; median, 99%) and an average multiple PVC suppression of 98% (range, 86% to 100%; median, 100%). These results are comparable to the short-term dose-ranging study (030) results. Holter monitoring was infrequently performed during the second year of treatment and analysis of these Holter data was not done.

CONCLUSION: Flecainide efficacy data during the first year in ongoing patients was comparable to results in the earlier short-term study (030). Flecainide continued to be well-tolerated in this population through 24 months of therapy.

b. Chronic Followup of Flecainide-Quinidine Comparison Trial (033)

OBJECTIVE: Patients who participated in the short-term Flecainide-Quinidine Comparison Study (032) entered this long-term, chronic dosing study to receive either flecainide or quinidine therapy. Investigators and study sites were the same as those for Study 032.

RESULTS: A total of 211 patients entered the study. Those who received flecainide in the short-term study continued to take flecainide in this study. Patients who received quinidine in the short-term study could receive either quinidine or flecainide in the long-term study. Patients were permitted to cross over from quinidine to flecainide during the long-term study but not vice-versa (with one exception). Of the 211 patients, 194 received flecainide from the beginning of the long-term study while 17 started the study on quinidine. During the course of therapy, four patients crossed over from quinidine to flecainide while one switched from flecainide to quinidine. Therefore, a total of 198 patients have received flecainide, 103 having first received it as part of study 032, and 95 being switched from quinidine; 18 have taken quinidine. Because of the difference between the number of patients on each drug, only the data from those taking flecainide were analyzed.

The mean duration of therapy for ongoing flecainide patients was 12 months (6 to 24 months reported).

Eighty-one of 198 (41%) flecainide patients discontinued the study after a mean exposure of 3 months; 117 (59%) were still ongoing. Adverse experiences or adverse experiences accompanied by ECG changes, were the reason for the discontinuation of 23 patients (11.6%); 16 patients (8.1%) discontinued due to noncompliance or loss to followup; 12 patients (6.1%) died; 10 patients (5.1%) discontinued for personal reasons; 13 patients (6.6%) discontinued due to loss of therapeutic effect; and the remainder discontinued due to other reasons.

Adverse experiences were generally similar to those seen in study 032, perhaps surprising as doses were somewhat lower and half the patients had already completed their first exposure to the drug in the previous study. The main adverse experiences in the studies are shown below.

Adverse Experiences

	Study 032	Study 033
Dizziness	43/141 (30%)	49/194 (25%)
Abnormal vision	40/141 (28%)	63/194 (32%)
Nausea	13/141 (9%)	15/194 (8%)
Headache	12/141 (9%)	11/194 (6%)
Asthenia	7/141 (5%)	13/194 (7%)
Fatigue	7/141 (5%)	11/194 (6%)

There were 8 (4%) patients identified as having pro-arrhythmic responses to flecainide. Three patients, without a history of sustained VT, developed sustained VT on flecainide, in one case fatal (but that patient had recently begun another drug, aprindine) and in the other two cases sustained VT developed fairly shortly (7, 22 days) after starting flecainide. Three patients developed new supraventricular arrhythmias on flecainide, one new SVT, and the others sinus pause or arrest with symptomatic bradycardia and junctional escape rhythms. Two patients had increased rate of VPCs on flecainide, in one case with salvos of VT.

Six patients left the study early because of ECG changes, including 1° A-V block (four cases, with bundle branch block in two cases and sinus pauses in one), 2° block of Wenckebach type, and SVT. Eleven patients experienced new or worsened CHF on flecainide; one died of a cardiac arrest; six left the study (four because of CHF) and four remained in the study.

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Up to 24 months of therapy, 12 patients died. The causes of death include autopsy-proven acute myocardial infarction (one patient), CHF (one patient), in-hospital arrhythmic death (three patients), and out-of-hospital sudden death (seven patients). Of the in-hospital deaths, one was 5 days after flecainide was stopped; one occurred after 8 1/2 months of treatment during worsening CHF, and one involved the pro-arrhythmic event described above. Of the 7 out-of-hospital deaths, 4 were unobserved deaths after 2, 6, 15 1/2 and 16 months of therapy, and one was a "collapse" (10 months) not medically observed. One, however, occurred after just 4 days of treatment, with no prior history of VT and the VT seen in the ambulance was resistant to conversion. In the last case, asystole developed after 21 days of treatment.

Efficacy evaluations were based on 24-hour Holter monitoring (required every six months). For the 90 patients with Holter results at month 12, 72/90 (80%) patients achieved at least 80% suppression of their total baseline PVCs, and 61/90 (68%) achieved at least 95% suppression, with a median suppression of 98.9%.

An analysis of baseline multiple PVCs, which included premature paired beats (couplets) and V-tach beats (three or more consecutive beats) also showed excellent suppression. For 78 patients who had couplets at baseline analyzed at month 12, 65 (83%) had greater than 95% suppression and 57 (73%) showed total (100%) suppression. For 50 patients with V-tach beats at baseline, 47 (94%) had total suppression during the month 12 Holter analysis, another patient had greater than 80% suppression, and the two remaining patients showed less than 50% suppression at that visit.

Most flecainide dosage adjustments were made early in the patients' treatment program. Although the recommended starting dose was 200 mg bid (400 mg total daily dose), adjustments were made to achieve the lowest effective maintenance dose, to reduce side effects, or to increase the level of efficacy.

At month 12, the most common daily dose was 400 mg, followed by 300 mg and 200 mg, respectively, with a mean daily dose of 335 mg (median, 300 mg). Only 7 of 102 patients were on more than 400 mg.

CONCLUSION: Of the 198 flecainide patients who were enrolled, 117 (59%) remained on therapy after completing 6 to 24 months of long-term therapy with a mean treatment period exceeding one year. Flecainide continued to be effective in suppressing ventricular arrhythmias without limiting side effects in these ongoing patients. The effectiveness was not without cost, however, as there were serious side effects, including pro-arrhythmic events. During the study there were eight patients with possible pro-arrhythmic responses, including two with new VT. In addition, there were seven out-of-hospital sudden deaths, two of which occurred soon after the start of flecainide and may have represented pro-arrhythmic responses.

c. Chronic Controlled Trial/Ventricular Ectopy (Study 035), Netherlands

STUDY DESIGN: Investigators at four study centers in the Netherlands evaluated the long-term safety and efficacy of flecainide when administered to patients who successfully responded with at least 85% suppression of PVCs without intolerable side effects during short-term testing.

This open-label study included two treatment periods: stage 1 was an eight-day inpatient period followed by stage 2, a long-term outpatient period.

Patients were excluded from the study if they had 1) uncompensated heart failure; 2) digitalis intoxication arrhythmias; 3) atrial flutter or fibrillation; 4) grade 2 or greater atrio-ventricular (A-V) block; 5) a history of myocardial infarction within three months prior to study entrance; 6) bundle branch block combined with first degree A-V block; 7) unstable angina; 8) presence of a cardiac pacemaker; and/or 9) an enlarged heart. During stage 1, qualifying patients received four days of placebo treatment during which baseline evaluations, including 24-hour Holter monitoring, were performed. Patients qualified for flecainide treatment (days five through eight) if they had at least 500 PVCs during the 24-hour monitoring period plus five or more isolated PVCs in any one minute and/or two or more consecutive PVCs recorded at any time during monitoring. Qualifying patients received flecainide 200 mg bid beginning on day five. On day eight of stage 1, baseline procedures were repeated. If the patient experienced no toxicity during the three to four days of flecainide administration, and if the repeat Holter analysis showed at least 85% suppression of baseline PVCs, the patient entered the long-term phase (stage 2) of the study.

In stage 2 (outpatient therapy), the investigators could adjust a patient's dose and/or frequency of administration of flecainide based on monthly safety and efficacy evaluations. The maximum daily dose allowed was 500 mg. During stage 2, each patient returned to the hospital once for a flecainide withdrawal period after 3, 6, 9 or 12 months of therapy to determine the need for continued flecainide therapy. A return to flecainide treatment was appropriate if the off-drug Holter analysis showed that 1) the total number of PVCs exceeded the pre-withdrawal number by a factor of two or more; 2) the number of repetitive PVCs exceeded the number of pre-withdrawal episodes; and/or 3) the number of episodes of more than five isolated PVCs in any one minute of recording exceeded the pre-withdrawal numbers.

Safety evaluations were performed at each visit; ophthalmologic examinations were performed at yearly intervals, and each patient underwent Holter monitoring every two months to evaluate efficacy.

Each patient could continue to receive flecainide as long as it remained safe and effective for a minimum of one year. The investigator determined the dosage regimen for each patient and made necessary changes to control or eliminate side effects, maintain efficacy, or determine the lowest effective maintenance dose.

RESULTS: A total of 78 patients enrolled at four centers; 12 patients did not quality because of insufficient PVCs at baseline. Sixty-six patients qualified for study participation, including 48 males and 18 females with a mean age at enrollment of 53.1 years (range, 21 to 69 years).

Although the protocol required that patients were to have greater than or equal to 85% suppression of PVCs in part 1 to continue into part 2, investigators usually entered patients into part 2 if PVC suppression was considered adequate in the investigator's opinion.

Thirty-seven (56%) patients completed 12 to 28 months of therapy.

Forty-nine of 66 patients completed the flecainide one week washout period. Of these patients eight did not have the required number of PVCs return in order to continue therapy. Only one patient, however, was discontinued for lack of return of arrhythmia. The remaining seven patients

continued in the study; three continued because PVCs returned after the first week of washout and four continued because the investigator felt these patients required therapy.

During this study, 29 (44%) qualifying patients discontinued flecainide therapy. The reasons for the 29 discontinuations in decreasing order of frequency were: inadequate PVC suppression during short-term treatment (nine patients); death (seven patients); adverse experiences (three patients); inadequate suppression during long-term treatment (three patients); personal reasons (two patients); end of one year study participation (two patients); non-compliance (one patient); acute myocardial infarction (one patient); and no return of arrhythmia during washout (one patient). Two discontinuations are of interest; one patient developed a junctional bradycardia (50 bpm); a second had sinus pauses up to 1.65 seconds and a syncopal episode.

The cause of death for the seven patients who died in this study were cancer (one patient), in-hospital arrhythmic death (three patients), and out-of-hospital sudden death (three patients two of whom probably had AMIs). Two of the three in hospital deaths occurred early in the course of treatment, at 1 day and 4 days after initiation. One patient had a history of MI, CHF and recurrent sustained VT, poorly controlled by other agents, but developed VF on flecainide. A large left ventricular aneurysm was found at autopsy. The other, with a prior history of sustained VT developed non-resuscitable VT/VF after three days of flecainide therapy.

Twenty-four-hour Holter monitoring was performed every other month during long-term treatment on all ongoing patients through month 12; after month 12, Holter analysis was performed at the discretion of each investigator. The month 6 results on data from 49 patients showed that 43/49 (88%) of the patients achieved at least 80% suppression of baseline PVCs, and 35/49 (71%) of the patients achieved at least 95% suppression, with a median suppression at month 6 of 99.5%. Similarly, for data from 43 patients analyzed at month 12, 38/43 (88%) of the patients achieved at least 80% suppression of baseline PVCs, 33/43 (77%) achieved at least 95% suppression, and the median suppression was 99.5%.

Although the recommended starting dose for flecainide was 200 mg bid (400 mg total daily dose), the investigators made dosage adjustments to achieve the lowest effective maintenance dose, to reduce side effects, or to increase the level of efficacy. For 45 patients reporting at month 12, the most common total daily dose of flecainide was 300 mg (16 patients), followed by 400 mg (14 patients) and 200 mg (nine patients); the mean total daily dose was 308 mg (median, 300 mg).

CONCLUSION: Of the 66 patients who participated in this study, 37 (56%) remained on flecainide therapy at the time of this analysis, having completed 12 to 28 months of long-term therapy with a mean treatment period of approximately 17 months (median, 15 months).

Flecainide continued to be effective in suppressing ventricular arrhythmias without limiting side effects in these ongoing patients.

3. Compassionate-Use Trials

Trials 028 and 057 were similar in that both were designed to evaluate seriously ill patients with either very frequent VPCs or ventricular tachycardia/ventricular fibrillation. In fact, most patients enrolled in both trials had a history of VT/VF, often needing resuscitation, and often accompanied by CHF, a history of acute infarction and a low ejection fraction. The patients were clearly sicker and more at risk of dying than patients in the chronic VPC trials (030, 031, 032, 033, 035) and an increase in the number of deaths on flecainide was expected once these trials were begun. By late 1982, however, examples of cardiac arrests began to accumulate. These occurred early after the start of flecainide therapy accompanied by arrhythmias that were different from those seen previously and that were unusually difficult or impossible to reverse despite prompt resuscitative attempts in sophisticated medical environments. Sixteen such cases were found, 12 of which represented cases where deaths were early in the course of flecainide treatment and no other explanation for lack of successful resuscitation was apparent. These were discussed at an investigators meeting in December 1982. Enrollment of patients was suspended pending evaluation. The meeting concluded that while the patients were high risk patients (15/16 prior AMI, 11/16 prior arrests, 15/16 history of VT) the difficulty of resuscitation was unusual, suggesting a drug relationship; it was also noted that blood levels seemed high in these patients. Based on the meeting, the lower dose, slower titration, plasma level monitoring approach of study 057 amended was developed and studies 028 and 057 ceased further enrollment. In addition, the sponsor surveyed all investigators in early 1983 to review the history of all treated patients for instances of worsened arrhythmia.

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a. Study 028

STUDY DESIGN: Investigators at 45 sites participated in this open-label study to assess the safety and efficacy of oral flecainide when provided on a compassionate-use basis to patients with ventricular arrhythmias who were intolerant of marketed antiarrhythmic agents or whose arrhythmias were refractory to marketed anti-arrhythmic agents.

Arrhythmias were characterized by greater than 30 premature ventricular contractions (PVCs) per hour, uncomfortable or intolerable symptoms associated with PVCs, or ventricular tachycardia or fibrillation (VT or VF).

Patients with any of the following cardiac abnormalities were excluded from the study: 1) digitalis intoxication arrhythmias; 2) atrial flutter or fibrillation without a ventricular arrhythmia; 3) second degree or greater atrioventricular (A-V) block; 4) complete bundle branch block associated with first degree A-V block; 5) QRS interval greater than 0.15 seconds, PR interval greater than 0.28 seconds; 6) a recent clinically unstable myocardial infarction; 7) unstable angina; 8) pacemaker dependent rhythm; 9) a need to continue verapamil or disopyramide (excluded because of their negative inotropic effects), and 10) severe or uncompensated heart failure.

Patients were required to discontinue other antiarrhythmic therapy a minimum of two half-lives before starting flecainide, though in some cases patients were maintained on lidocaine until after flecainide had been started.

Throughout most of this study, the usual recommended starting dose of flecainide was 200 mg bid. During the study, accumulating experience indicated that lower doses were effective in many patients and perhaps provided a greater margin of safety, particularly in patients with more severe disease. Thus, during the course of the study, 100 mg bid also became a frequent starting dose. The study allowed for upward and downward alterations in dose levels and dosing schedule up to a maximum of 600 mg a day. Unlike the acute and chronic study of VT (Study 057 amended) there were no restrictions to the time interval between dosage adjustments.

Quantitative efficacy determinations, such as those obtained through 24-hour Holter monitoring were not required in this study, but were left to the discretion of the investigator. Determination of effective response was generally based on one or more of the following: a patient's arrhythmia symptoms, arrhythmia monitoring (24-hour Holter, telemetry or rhythm strip), programmed electrical stimulation (PES) and exercise stress testing.

RESULTS: A total of 228 patients received flecainide through this compassionate-use protocol. Individual periods of treatment ranged from one dose to 20.5 months (mean 5.5 months). For the ongoing patients, the mean time on flecainide was 13.5 months (median 13.3 months; range 7.1 to 20.5 months). The mean time on drug for discontinued patients was 2.3 months (range, one dose to 18.4 months).

Of the 228 patients who received flecainide, 200 were refractory to or intolerant of marketed antiarrhythmic agents and 28 transferred from other Riker sponsored studies. Baseline demographic data were available for 227 patients: the most frequently occurring cardiac diagnoses were atherosclerotic heart disease (61%), previous MI (51%), congestive heart failure (48%), hypertension (19%), cardiomyopathy (18%), and valvular disease (17%); 198 patients had a history of VT; 82 patients had a history of sustained VT. Forty patients were survivors of sudden death. Eighty-three patients had evidence of underlying conduction disturbances on baseline ECGs. The mean number of previous antiarrhythmics was 3.7 with some patients having received as many as ten marketed or investigational agents before receiving flecainide.

Of the 228 patients who received flecainide, 89 (39%) were ongoing as of September 1, 1983. Of the 198 patients with a history of VT, 70 (35%) were ongoing. Of the 82 patients who had a history of sustained VT, 21 (26%) were ongoing.

Although Holter monitoring was not required in this study, 32 ongoing patients had baseline and followup Holter recordings available for analysis. Based on the last Holter tape obtained during flecainide therapy for these patients, the median percent suppression of PVCs was 95.1%. Twenty-four of these patients had VT on their baseline Holter recordings; of these, 23 (96%) showed complete suppression of VT on their last Holter recording.

Programmed electrical stimulation (PES) was used by some investigators to determine efficacy in some patients. It is not known how many patients underwent electrophysiological testing on flecainide because investigators did not always provide these data. Fifteen patients who are known to have been tested electrophysiologically remain in the study and 25 patients who continued to be inducible by PES while on flecainide were discontinued as therapeutic failures.

Of the 228 patients who received flecainide, 139 (61%) discontinued this study. The most common single reasons for discontinuation given by the investigator were lack of response (45 patients, 25 of whom failed PES), adverse experience (41 patients), and death (27 patients). Most patients who discontinued flecainide tended to do so early in therapy in this study. Forty percent (56/139) of the patients who discontinued did so during the first week of therapy; and 65% (90/139) discontinued during the first month of therapy.

Non-cardiac adverse experiences were given as reasons for discontinuation in 26 patients (some had more than one). Most frequently reported as reasons for discontinuation were dizziness (11 patients); visual disturbances (10 patients); ataxia and nausea (four patients each); hypoesthesia, fatigue and tremor (three patients each); and nervousness, dyspnea, rash or dermatitis, paresthesia and headache (two patients each).

Cardiac side effects were given as reasons for discontinuation in 25 patients. These included: VT with increase in ectopy (12 patients); CHF (four patients); sinus node dysfunction (three patients); complete heart block (two patients); VT and CHF, VT and bundle branch block, and bundle branch block (one patient each). An additional patient was discontinued for widened intervals. These increases, as measured from study initiation to discontinuation, were: PR 0.19 to 0.32, QRS 0.10 to 0.15, and QT 0.38 to 0.54. Further evaluation identified additional patients who had apparent proarrhythmic events; some of those initially listed merely had their usual arrhythmia. Pro-arrhythmic effects, conduction disturbances, and CHF will be discussed in the Safety section below in detail. Briefly, of the 228 patients, 24 were felt to have had pro-arrhythmic events; one had an increased frequency of PVCs with short runs of VT, another bradycardia, and 22 new or worsened significant ventricular tachyarrhythmias. Of the 22 cases of sustained VT/VF, all had a prior history of VT, 16 had a history of heart failure, 19 had a history of old myocardial infarction and 12 had a documented prior arrest. Eight of the 22 patients died. All had prior MI and a history of VF and CHF. Seven of the eight had a prior arrest and the mean ejection fraction was 23.6%. The kinds of events considered pro-arrhythmic are shown in Table 27A.

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TABLE 27A

Prearrhythmic Events
Characterization of New or Worsened Ventricular Tachycarhythmias

Criteria	Patient ID	No. Patients Satisfying Primary Criterion
Occurrence of non-sustained VT[a] with no previous history.		0
Occurrence of sustained VT with no recent[b] history of same.	028-26-010 028-27-002 028-37-001	3
Occurrence of VT with a more "malignant" morphology or higher rate than recently observed.	028-13-001 028-26-011 028-44-105 028-87-101	4
Asymptomatic VT which becomes symptomatic	028-44-103 028-44-104	2
VT progresses to VF[a] where this has not occurred recently.	028-26-004 028-28-004	2
Cardioversion is required where it has not been required recently.	028-21-101	1
Resuscitation is more difficult (or impossible to accomplish) than previous resuscitation.	028-12-101[c] 028-14-132[c] 028-14-131[c] 028-33-103 028-34-101[c] 028-37-003 028-42-101[c] 028-43-003[c] 028-47-005[c] 028-72-101[c]	10
	Total	22

[a] VT = ventricular tachycardia.
VF = ventricular fibrillation.
[b] The definition of "recent" depends on the investigator's determination. "Recent" may be as short a period as a few weeks if there appeared to be a stable period prior to flecainide treatment.
[c] Patient died.

Thirty-two (15%) of the patients developed new or worsened CHF (not necessarily attributable to flecainide); 26 (29%) with pre-existing failure and six (5.1%) without prior CHF. Of the 32, 18 patients stayed on treatment, some with reduced dose, five discontinued treatment at least partly because of CHF, three discontinued for other reasons, and six patients died, four of those attributed to CHF/low output. A detailed discussion of CHF appears below in the Safety section.

ECG changes were seen in many patients, including episodes of 3° A-V block, bradycardia, sinus pauses, and bundle branch block. These too are discussed in the Safety section.

Twenty-seven (11.8%) patients who received flecainide died during the study, 12 in the first 10 days of treatment. These included: 11 cases of in hospital arrhythmic death (one of which occurred after just 5 days of treatment and could represent another pro-arrhythmic death), 5 cases of out of hospital sudden death, 5 cases of CHF/low cardiac output death, 3 cases of non-cardiac death, one case of acute myocardial infarction and two cases where the patients had incomplete information at the time of the report. Most patient deaths occurred early in therapy and most occurred in patients with severe pre-existing arrhythmias and underlying myocardial dysfunction. Deaths are discussed in more detail below. As noted earlier, some of the deaths were considered possibly or probably flecainide related.

The median total daily starting dose was 400 mg; in ongoing patients the median daily dose was 300 mg. This reduction in median total daily dose after a length of time on therapy has been observed in other studies where the recommended daily starting dose was 400 mg (Study 033).

Adverse experiences will be discussed in the Safety section below, but it is of interest that reports in this study were similar to those in other chronic studies despite the expected lesser rigor of a many - investigator "compassionate" protocol.

Adverse Experiences

ADR	% of patients long-term studies chronic ventricular arrhythmias n=280 (%)	% of patient 028 n=197 (%)
Dizziness	32	26
Abnormal vision	30	25
Headache	10	6
Nausea	10	6
Tremor	4	6
Asthenia	6	3
Palpitations	6	3
Fatigue	6	3
Dyspnea	5	4
Nervousness	5	2
Chest pain	4	2

CONCLUSIONS: Flecainide at a mean dose of 334 mg/day was an effective antiarrhythmic agent for some patients in this refractory population, providing successful therapy (evidenced by continued use by the physician) for 7 to 20 months (mean, 13.5 months) in 39% of patients enrolled. The drug did not appear to be associated with clinically significant physical, opthalmologic or laboratory abnormalities. Flecainide was, however, associated with some potentially serious cardiac side effects, notably worsening of arrhythmia, congestive heart failure, and to a lesser extent, conductio.. disturbances. The early pro-arrhythmic events led to the development of a more controlled protocol, the Acute and Chronic Study of Ventricular Tachycardia (057 amended), which investigated the safety and efficacy of lower doses of flecainide in a similar population of patients.

b. Study 057

STUDY DESIGN: Thirteen investigators participated in this open-label study to assess the safety and efficacy of chronic oral flecainide in treating patients with ventricular arrhythmias associated with significant cardiac disease.

The minimum criteria for entry into this study were greater than 10 PVCs per hour refractory to marketed antiarrhythmic therapy. (38/39 patients had significant VT; only one patient was treated for multifocal PVCs.) Investigators were encouraged to enroll patients with significant VT (greater than or equal to 6 beats in a row at a rate of greater than 100 beats/min), a conduction abnormality (BBB or IVCD), or Class III or Class IV CHF (New York Heart Association Classification). Patients were excluded from the study if they had digitalis intoxication arrhythmias, second or third degree A-V block, recent unstabilized MI, QRS greater than or equal to 0.15 or PR greater than 0.28 sec, or a pacemaker dependent rhythm. Other Class I antiarrhythmic agents, investigational drugs known to cause significant organ toxicity, calcium channel blocking drugs and any other medications that would affect myocardial contractility, with the exception of cardiac glycosides, were not permitted as concomitant medications. Beta-blocking agents and beta-stimulants were allowed for patients who required these because of conditions other than arrhythmia control.

Chest radiograph, a 12-lead electrocardiogram (ECG), laboratory studies, and a 24-hour Holter recording were required within one week prior to starting flecainide. All patients with Class III or IV CHF, or a CT ratio greater than 0.50 on their prestudy chest x-ray were required to undergo radionuclide ejection-fraction (RNEF) testing. The recommended starting dose of flecainide was 200 mg every 12 hours (bid). For patients with a history of either CHF or conduction abnormalities, an initial dose of 100 to 150 mg bid was suggested.

At approximately one week, one month, and three months after initiation of therapy, and at quarterly intervals thereafter, patients were required to return for follow-up evaluations.

Investigators were allowed to determine effective response to flecainide based on a patient's arrhythmia symptoms, arrhythmia monitoring (24-hour Holter and ECG rhythm strip) and occasionally by exercise stress testing or programmed electrical stimulation (PES).

Although not initially required, plasma flecainide samples were obtained in the majority of the patients.

RESULTS: Of the 39 patients who entered the study, 31 were male and eight were female. The majority of the patients had significant cardiac disease. Of the 39 patients, 29 (74%) had a history of atherosclerotic heart disease, 25 (66%) a history of congestive heart failure (CHF), and 12 (31%) a history of electrocardiographic conduction abnormalities. Thirty-eight (97%) of the 39 patients had a history of refractory ventricular tachycardia (VT) prior to starting flecainide, and one patient had multifocal premature ventricular contractions (PVCs). Although investigators were not required to characterize a patient's VT, 16 patients were reported by the investigators to have a history of sustained VT. Of the 16 patients with sustained VT, at least six were known to have a previous history of sudden death (ventricular fibrillation/cardiac arrest).

Thirty-nine patients enrolled in this study; 14 of 39 patients were ongoing for a mean length of time of 11.6 months (range ten to 12 months). Among the 25 patients who discontinued, nine were from one center where flecainide was evaluated with other investigational antiarrhythmics prior to choosing the most appropriate drug for chronic therapy and flecainide was discontinued due to side effects or "patient convenience." All nine patients enrolled at this site were discontinued after three or four days of flecainide therapy.

Efficacy in the ongoing patients was well maintained as evidenced by the frequency distributions of percent suppression of PVCs, paired beats, and VT beats. The median percent suppression of PVCs at the week one visit was 94.8% (18 patients); at all followup visits the median percent suppression was greater than 85%. The median percent suppression of paired beats was greater than 96% at all visits and the median percent suppression of VT beats was 100% (complete suppression). Overall, as of May 1, 1983, 7/17 ongoing study patients (41%) had not had any recurrence of their VT (mean length of flecainide therapy 4.8 months). In the other 10/17 ongoing patients, the investigators have considered the patients to be responders in that they have shown overall improvement of their VT.

Seven patients died. Of these seven patients, six were associated with unresuscitable ventricular arrhythmias. Four of the seven patients had a previous history of sustained VT, of which two had experienced at least one episode of "sudden death." According to the investigators, three of the deaths were possibly flecainide related, two were probably not related, one was definitely not related, and one was unknown. Four of the cases were among

"pro-arrhythmic" deaths considered at the December 1982 meeting of investigators. They occurred 10, 13, 24 and 60 days after flecainide was started.

Eight patients were discontinued as nonresponders. Seven patients discontinued because of adverse experiences, two because of adverse experiences and nonresponse, and one patient was discontinued because of personal reasons. One of the adverse experiences was a patient who developed difficult-to-convert VT/VF on exercise testing.

CONCLUSION: Flecainide was considered effective in 14 of 39 high risk patients with refractory ventricular arrhythmias for 10 to 12 months, but seven patients died, six with unresuscitable ventricular arrhythmias and several under conditions suggesting drug-relatedness.

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C. Safety

Apart from its cardiac effects, flecainide had few serious side effects, although there was a high rate of dizziness and visual disturbances.

Table 28 provides an overall summary of the incidence of adverse experiences listed by study and patient population. It is notable that the rates in chronic and short term studies are similar. The adverse effects of flecainide, both cardiac and non-cardiac were generally manifested early.

Table 28
Incidence of Adverse Experiences[a] Which Occurred in Greater than 3% of Patients in Any of the Studies Presented Below

Median Starting Dose Adverse Experiences	% Patients in Short-term V-Ectopy Study (032) 400 mg/day (N = 162)	% Patients in Chronic Studies (031,033,035) 400 mg/day (N = 290)	% Patients in Compassionate-Use Study (028) 400 mg/day (N = 197)	% Patients in VT Study (057 Amended) 200 mg/day (N = 92)
Non-Cardiac				
Dizziness	32%	34%	26%	9%
Visual Disturbances	28%	31%	25%	7%
Headache	8%	12%	6%	2%
Nausea	8%	11%	6%	2%
Dyspnea	6%	5%	4%	7%
Chest Pain	6%	6%	2%	1%
Asthenia	5%	6%	3%	4%
Fatigue	4%	8%	3%	3%
Nervousness	4%	5%	2%	1%
Palpitations	4%	8%	3%	3%
Tremor	4%	5%	6%	2%
Hypoesthesia	3%	3%	3%	1%
Paresthesia	3%	1%	0%	0%
Constipation	1%	3%	3%	0%
Syncope	1%	3%	3%	2%
Rash	0%	4%	3%	2%
Cardiac				
Pro-arrhythmic events[a]	2%	4%[b]	13%	8%
CHF[a]	4%	5%	15%	10%
Serious Conduction Defects	1%	2%	4%	2%

[a]Incidence of pro-arrhythmic events and CHF were assessed by direct questioning of investigators. All other adverse experiences were assessed by indirect questioning of patients.

[b]Study 035 was not surveyed for pro-arrhythmic events.

The discussion of safety will focus on eight major areas.

1. Non-cardiac Adverse Experiences - Dizziness and visual disturbances were the most frequent non-cardiac adverse experiences reported by patients taking flecainide. Non-cardiac adverse experiences lead to discontinuation of therapy in 5% to 12% of patients. These effects appear to be dose-related.

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2. Proarrhythmic Events - Approximately 6.8% of patients developed a worsening of arrhythmia while on flecainide. The risk of such a response is greatest in patients with serious arrhythmias but present in patients who have arrhythmias of lesser severity such as frequent VPCs. In the compassionate use studies about a dozen patients died from unresuscitable ventricular arrhythmias that may have been drug-related. All such patients had pre-existing congestive heart failure and were treated for ventricular tachycardia. Most had undergone previous resuscitations. While it is often difficult to distinguish an adverse drug effect from a failure of effectiveness as a cause of death, review of deaths indicate that flecainide poses life-threatening potential problems in such patients and requires close monitoring during early use.

3. Congestive Heart Failure (CHF) - Five percent of patients developed new or worsened CHF while taking flecainide. Patients with congestive heart failure prior to taking flecainide are at greatest risk of responding adversely to the drug. CHF developed rarely (1%) in patients who had no history of CHF.

4. Effects of Flecainide on the Scaler ECG and Conduction Disturbances - The majority of patients show significant increases in the PR interval and QRS intervals (each increase about 25%). These increases appear to be dose-related. First degree A-V block occurs in as many as 40% of patients. Other A-V conduction defects or effects on SA node function are less common but potentially serious. About 1% of patients have developed second or third degree A-V block and about 1.5% of patients developed evidence of sinus node dysfunction such as bradycardia or sinus pause. Occasional patients develop a time prolonged QT and one patient developed a torsade de pointes VT.

5. Effects of Flecainide on Vital Signs - Small increases in mean systolic and diastolic pressures have been seen in various patient populations studied with flecainide. Clinically significant changes, however, have rarely occurred (less than 1%). Drug related sinus bradycardia was reported in less than 1% of patients.

6. Effects of Flecainide on Routine Laboratory Measurements - Isolated elevation of alkaline phosphatase occurred in five patients studied at one center and isolated sustained SGPT elevations occurred in one patient in U.S. studies. In West German marketing experience, a small number of patients were found to have liver-related abnormalities while on flecainide. There is insufficient evidence at this time to determine whether flecainide can cause hepatic toxicity.

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7. Safety Experience with the Use of Flecainide with Other Antiarrhythmic Drugs and with Beta Blockers - The experience to date does not suggest an adverse interaction between flecainide and other antiarrhythmic drugs or other beta blockers.

8. Post Marketing Experience in United Kingdom and West Germany.

Safety Section Database: The database for this discussion includes the following trials:

Dose-Ranging Study (030) n=37; Flecainide/Quinidine Comparison Study (032) n=162; Chronic Studies/Ventricular Ectopy (031, 033, 035) n=290; Compassionate Use Studies (028, 057) n=266; Acute and Chronic Study/Ventricular Tachycardia (057 amended) n=96.

The Chronic Studies/Ventricular Ectopy group included patients followed long-term who had previously been in the Dose-Ranging Study and in the Flecainide/Quinidine Comparison Study, as well as a multicenter study of 66 patients in the Netherlands which was monitored by the U.S.-based sponsor.

Spontaneous adverse reaction reports from physicians treating patients in West Germany and the United Kingdom, where flecainide is presently marketed, are included. It is estimated that over 50,000 patients have been treated in these two countries.

The NDA contains safety information on an additional 201 patients who were treated in clinical studies overseas (United Kingdom, Germany, France and Norway). Sixty-nine of these patients were followed for one year or more. The adverse reactions reported in these studies were consistent with those reported in the U.S. studies and are not part of the database for these analyses.

1. Non-cardiac Adverse Experiences (NCAEs)

The incidence of non-cardiac adverse effects which occurred in at least 3% of patients taking either flecainide or quinidine in the pivotal Flecainide/Quinidine Comparison Study is presented in Table 29. The most frequent adverse experiences in patients taking flecainide were dizziness and visual disturbances. Dizziness included reports of lightheadedness and giddiness. Visual disturbances included reports of blurred vision, difficulty focusing, spots before eyes, etc. These visual disturbances were typically most apparent on lateral gaze and were usually transient.

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TABLE 29

Flecainide-Quinidine Trial

Median Daily Dose (mg) Adverse Effect	Percent of Patients Reporting Flecainide 400 (N=162)	 Quinidine 1200 (N=152)
Dizziness*	52	11
Visual Disturbances†	28	7
Headache	8	13
Nausea	8	18
Dyspnea	6	3
Chest Pain	6	1
Asthenia	5	4
Fatigue	4	5
Nervousness	4	<1
Palpitation	4	3
Tremor	4	1
Hypoesthesia	3	0
Paresthesia	3	0
Diarrhea	<1	39
Fever	0	5
Myalgia	1	4
Rash	0	5
Abdominal Pain	0	3
Vomiting	1	3

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

Animal studies have shown that flecainide possesses CNS effects which, at larger doses, are predominantly stimulant in nature. Effects of flecainide in mice and rats included ataxia and convulsions (by oral, intraperitoneal and intravenous routes) and in dogs included tremors, ataxia, emesis (by oral and intravenous routes), and clonic convulsions (by intravenous route only). Although flecainide was selected from a large series of closely related compounds primarily on the basis of reduced CNS effects, these stimulant signs, other than tremor, were prominent in animal toxicity studies when large doses were used.

Flecainide administration to humans also provokes CNS effects and the wide variety of neurological adverse experiences (dizziness, visual disturbances, tremor, hypoesthesia, parethesia, nervousness, ataxia and nystagmus) suggests effects on the central nervous system. These side effects, particularly dizziness and visual disturbances, commonly occur in the same patient, suggesting a central mechanism.

The incidence of noncardiac adverse experiences in the Flecainide-Quinidine Comparative Study (032) compared to that found in the Chronic Studies/Ventricular Ectopy (031, 033, 035), the Compassionate-Use Study (028), and the Acute and Chronic Study of Ventricular Tachycardia (057 amended) showed that experiences were quite similar in the different patient populations except that patients treated in 057 amended, the Acute and Chronic Study of Ventricular Tachycardia, had much lower incidences of adverse experiences, particularly dizziness and visual disturbances (see Table 28). These lower incidences appear to be associated with lower doses of flecainide (usually 200 to 300 mg/day) than those most commonly used in the other studies (400 to 600 mg/day).

Further evidence that noncardiac adverse experiences are dose-related is provided by intrapatient comparisons in the Dose Ranging Study (030) and the Flecainide-Quinidine Comparison Study (032). The following figure (Figure 13) shows the incidence of common noncardiac adverse experiences in patients who had the opportunity to receive two or more dosing regimens of flecainide. Lower daily doses were associated with fewer reports of noncardiac adverse experiences.

FIGURE 13

Relationship of Daily Dose to Common (Incidence ≥ 3%) NCAE's

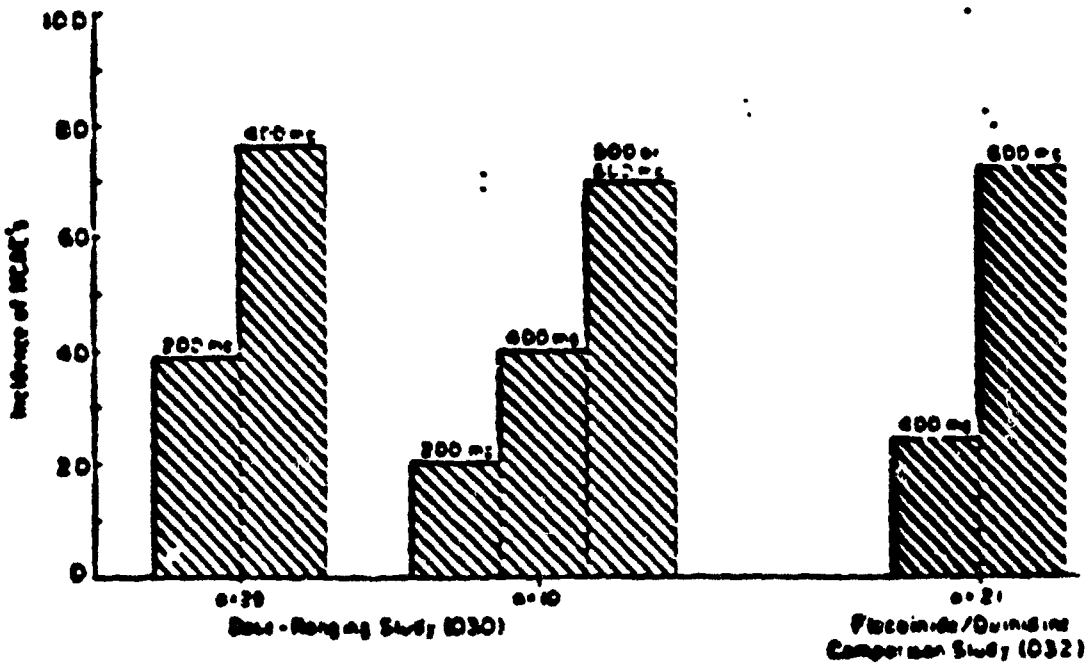

Table 30 shows the significant adverse experiences associated with flecainide therapy reported by 1% to 3% and by less than 1% of patients in all the major efficacy trials.

TABLE 30

Significant Adverse Experiences
Occurring in 1-3% and Less Than 1% of Patients
In All Major Efficacy Trials

	1% to 3%	Less Than 1%
Body as a Whole:	edema, malaise, fever	arthralgia, bronchospasm, myalgia, swollen lips, tongue and mouth
Cardiovascular:	tachycardia, sinus pause or arrest	angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension
Gastrointestinal:	vomiting, dyspepsia, anorexia, diarrhea	flatulence
Hepatic:		jaundice, elevation of transaminase levels and alkaline phosphatase levels,
Renal:		polyuria, urinary retention
Skin	rash	exfoliative dermatitis, urticaria pruritis
Visual	diplopia	eye pain or irritation, photophobia, nystagmus
Nervous system:	hypoesthesia paresthesia, paresis, ataxia, flushing, increased sweating, syncope, somnolence, tinnitus, vertigo	weakness, change in taste, twitching, dry mouth, convulsions, impotence, speech disorder, stupor
Psychiatric:	anxiety, insomnia, depression	amnesia, confusion, morbid dreams, apathy, decreased libido, depersonalization, euphoria

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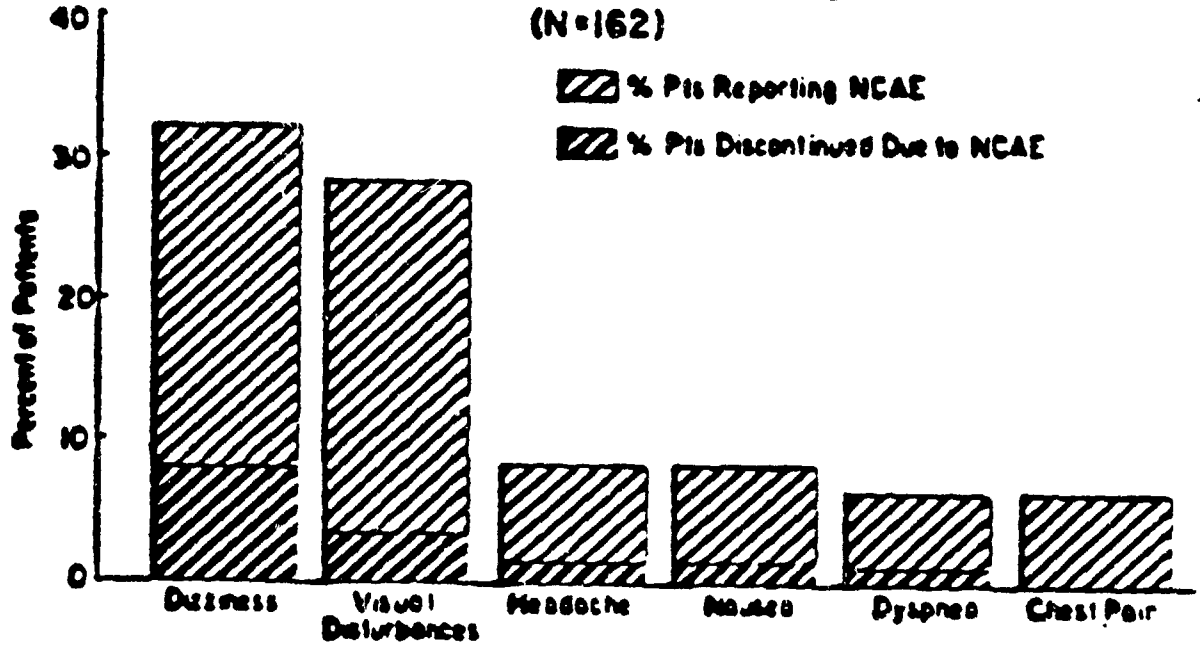
Noncardiac adverse experiences usually did not require discontinuation of flecainide. In the Flecainide-Quinidine Comparative study (032), 12% of patients discontinued because of noncardiac adverse experiences. It is possible, of course, that patients tolerated two weeks of symptoms that would not have proved acceptable in a longer-term study. Figure 14 below compares the incidence of reporting the six most common adverse experiences with the incidence of discontinuing flecainide because of each adverse experience in this trial. All patients treated in this study received doses of 400 to 600 mg/day and downward dosage adjustments to decrease side effects were not allowed in this protocol. In the Acute and Chronic Study of Ventricular Tachycardia (057 amended) which used lower doses (usually 200 to 300 mg/day), 5% of patients discontinued because of noncardiac adverse experiences.

FIGURE 14

Six Most Common NCAE's with Flecainide Therapy
Incidence of Reporting NCAE VS Discontinuing Due to NCAE
Flecainide/Quinidine Comparison Study (032)
(N=162)



In summary, dizziness and visual disturbances were the most frequent noncardiac adverse experiences. Noncardiac adverse experiences were usually well tolerated but led to discontinuation in 5% to 12% of patients. It appears that the incidence of noncardiac adverse experiences is dose-related, and the use of daily doses in the range of 200 to 300 mg/day is associated with a lower incidence of adverse experiences resulting in a much lower rate of discontinuation.

2. Proarrhythmic Events and Arrhythmic/Sudden Deaths

a. Early observation of pro-arrhythmic events - survey

As described previously, early experience in the 028 and 057 protocols showed that flecainide could have important pro-arrhythmic effects. An initial review was carried out because investigators were reporting examples of patients who sustained cardiac arrest in which resuscitation was unexpectedly difficult or impossible, even in good clinical circumstances. Sixteen patients with in-hospital deaths after an arrest, 12 within the first two weeks of flecainide therapy, were examined (four arrested outside the hospital, received CPR outside before reaching the hospital, but care may have been less than optimal). It was clear that they were members of a very sick population, six with mean EF of 25%, prior AMI in 15/16, a history of CHF in 15/16, prior cardiac arrest in 11/16, but some of the episodes seemed to represent drug-related worsening. No particular ECG or other lab finding marked these patients particularly, but plasma levels were higher than expected in the eight patients measured with 7/8 above 1000 ng/ml and 5/8 above 1900 ng/ml, compared with less than 1000 ng/ml in most patients in chronic studies. The possibility thus arose that the doses used were too high, at least for this population. Of the 12 who died within two weeks, 10/12 were receiving at least 400 mg/day.

The review of the 16 deaths led to a change in the protocol used for seriously ill patients (057 amended) and to a more detailed look at possible pro-arrhythmic events (fatal and nonfatal) in all treated patients. Because there had been no prospective definition of, or search for, pro-arrhythmic events the best available mechanism for receiving data up to that point was felt to be a survey of investigators, relying on their judgement to determine whether worsening of arrhythmia had occurred. While this is reasonable, it should be appreciated that this approach has numerous problems, some of them inherent in any open study of patients with serious arrhythmias, some in the survey methodology. The approach will, in general, not capture one class of pro-arrhythmic events at all, those being sudden deaths. These could represent pro-arrhythmic events but there is no way to know this in the absence of a control group. There is also a distinct possibility of overreporting in any study of this kind, as it is often impossible strictly to distinguish lack of effectiveness from a pro-arrhythmic event.

Fifty-five of 57 investigators responded to a questionnaire regarding proarrhythmic events and provided information on 588 of 592 patients surveyed. This survey included all patients studied in the major efficacy trials conducted in the U.S. with the exception of the Acute and Chronic Study of VT (057 amended). (In that study, designed after the pro-arrhythmia question had arisen, specific questions regarding proarrhythmic events were included in the case report forms.) Investigators were each allowed to use their own criteria to determine whether drug related worsening of arrhythmia had occurred. With three exceptions, two cases of QRS widening and one of second degree heart block (not an arrhythmia), the investigator's criteria were accepted.

b. Results of survey

Proarrhythmic events were reported in 47 (8%) patients; less the three doubtful cases, there were 44 such events in 588 patients (7.5%). Thirty of the events occurred among the 254 relatively ill patients from studies 028 and 057 (11.8%) while the remaining 14 took place in 334 other patients (4.2%). The rate in study 057 amended was 10/96 (10.4%).

Not all pro-arrhythmic events were equally worrisome. The sponsor classified them in three broad categories:

Category I - Increased PVC's compared to baseline (6 patients, no fatalities)

- One patient showed a tenfold increase compared to baseline Holter.

- Two patients showed a 3-4 fold increase compared to baseline Holter, one with new salvos of VT (that case should perhaps have been placed in category III).

- One patient showed a 50% increase compared to baseline Holter.

- Two patients showed more frequent VPCs on rhythm strip than had been seen on baseline Holter.

(Of these, only the 10-fold increase is really a persuasive pro-arrhythmic event, as spontaneous 50% to 3-4 fold changes are not uncommon.)

Category II - New supraventricular arrhythmias (5 patients, two fatalities)

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- One patient developed severe sinus bradycardia and could not be resuscitated

- One patient developed AF with a bizarre wide QRS complex and could not be resuscitated

- One patient developed new SVT

- Two patients developed sinus pauses with junctional escape rhythms

(The patient with AF was thought at post-mortem to have an evolving AMI.)

Category III - New or Worsened Ventricular Tachyarrhythmia (33 patients, 12 fatalities)

- 1 New non-sustained VT

- 8 Sustained VT without recent history of this,

- 4 Increased rate or more"malignant" morphology of VT

- 2 Asymptomatic VT became symptomatic,

- 3 VT progressed to VF with no recent history of this,

- 1 Cardioversion required with no recent history of this,

- 14 Resuscitation more difficult or impossible (12 died).

In three of these cases (one hypotensive VT needing repeated cardioversion, one new morphology VT requiring cardioversion and one sustained VT/VF with difficult resuscitation) the pro-arrhythmic event was observed during PES.

Among the 44 patients with pro-arrhythmic events, 18 had resuscitations that were prolonged, required unusual measures, or were unsuccessful, and 14 of these patients died. The clinical background for these patients is shown in Table 30A.

All of the patients who died, except one, were from studies 057 and 028. The only exception was a patient from study 033 that had a history of sustained VT on quinidine and procainamide and was always PES-inducible; death occurred after aprindine was begun. The patients were all clearly very ill, all 14 having histories of cardiac failure and

Table 30A
Patient Deaths

Study/Ptno	AGE	SEX	ASHD	OLD MI	HISTORY OF CHF	VT	CHF AND VT	DOCUMENTED PRIOR ARREST	LEFT VENTRICULAR EJECTION FRACTION (%)	CONCOMITANT MEDICATIONS	FLECAINIDE TOTAL DAILY DOSE (MG)	WEIGHT (KG)	PLASMA FLECAINIDE LEVELS (NG/ML)	DATE OF DEATH
028-12-101	44	M	+	+	+	+	+	+	17	Digoxin, Lasix, Coumadin, prednisone	600	64.4	6/10/82 553 ng/ml	6/12/82
028-14-112	75	M	+	+	+	+	+	+	30	Prazosin, Lasix, Isordil	200	[illegible]	none	8/06/82
028-14-132	61	M	+	+	+	+	+	+	25	Digoxin, Lasix, Minipress	400	89.4	none	10/22/82
028-14-133	55	M	+	+	+	+	+	+	12	Digoxin, Lasix, Isordil, hydralazine Coumadin	400	62.6	none	11/02/82
028-34-103	66	M	+	+	+	+	+	+	28	Digoxin, Lasix	400	69.4	10/30/82 471 ng/ml (4-1/2 hrs postdose)	10/30/82
028-42-101	61	M	+	+	+	+	+	-	15-18	Prednisone, Albuterol inhaler	500	67.1	none	9/24/82
028-43-003	55	M	+	+	+	+	+	+	30	Digoxin, Lasix, Isordil, allopurinol	400	90.7	6/28/82 1296 ng/ml	6/30/82
028-43-005	72	M	+	+	+	+	+	+	20	Digoxin, Lasix, Isordil	400*	81.7	none	7/14/82
028-72-103	73	M	+	+	+	+	+	+	35	Digoxin, Lasix	200	61.2	11/9/82 2238 ng/ml	11/05/82
033-14-006	22	M	-	-	+	+	+	+	16	Lasix, isosorbide, Coumadin, aprindine	300	79.8	10/12/81 1468 ng/ml 1/8/82 2594 ng/ml	1/11/82
057-02-204	80	M	+	+	+	+	+	-	46	Lanoxin, Lasix, nifedipine	400	84.8	10/7/82 595 ng/ml 10/11/82 2050 ng/ml	10/11/82
057-02-205	55	F	+	+	+	+	+	-	24	Digoxin, Lasix, Aldactone, nifedipine prazosin	250	68.0	11/3/82 1303 ng/ml 11/7/82 2001 ng/ml	11/07/82
057-21-003	66	M	+	+	+	+	+	+	28	Digoxin, Lasix, Coumadin	400	71.2	9/3/82 618 ng/ml	9/13/82
057-06-007	72	M	+	+	+	+	+	+	24	Digoxin, isosorbide, HCTZ, mexiletine	200	71.7	11/2/82 566 ng/ml	11/29/82

* Dose of flecainide had been increased from 200 BID to 300 BID, patient received one 300 mg dose.

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prior VT, 13/14 having a history of AMI, and 11/14 having been previously resuscitated; the mean EF was 24%. Nine of the 14 had plasma levels of flecainide within a few days of death, and, of these, five were outside the therapeutic range (upper limit 1000 ng/ml).

Proarrhythmic events were most likely to occur early in flecainide therapy; 43% in the survey occurred within the first four days of therapy and 57% within the first seven days. These events are also more likely to occur soon after a dosage change: 29% of proarrhythmic events in this survey occurred within four days of a dosage change. (It is possible, of course, that earliness of therapy or a recent dosage change were what led the investigator to identify an arrhythmic event as "pro-arrhythmic").

c. Comparison of pro-arrhythmia patients and other patients

The patients in whom pro-arrhythmia events developed were not distinct from the rest of the patients except with respect to the seriousness of their underlying disease. The mean daily dose was only slightly higher in the pro-arrhythmic patients (369 mg/day vs an average of 339 mg/day in all patients in chronic studies), not a likely source of the difference and perhaps simply a reflection of the initial dose in all studies being 400 mg and the early nature of most pro-arrhythmic events.

ECG interval changes were not helpful in predicting a pro-arrhythmic response. Interval changes were compared for 4 subsets of patients with pro-arrhythmic events (deaths, non-deaths, category I, II of arrhythmias, category III of arrhythmias) and two control groups, patients in studies 031 after one year of therapy and in 033 after six months of therapy. Data were available for 36 of the 44 pro-arrhythmia patients; in all cases the dose at the time of ECG was the same as that at the time of the pro-arrhythmic event. Results are shown for absolute interval change and percent change in Tables 30B and 30C. It can be seen that, in general, there are not major differences. QRS was significantly prolonged in the all pro-arrhythmia events, fatal PA events and Category III groups compared to study 033 but not study 031. There is perhaps a suggestion of a greater effect on JTc in the fatal and category III subgroups but it is a minimal difference at best. Patients with large interval changes (at least 50%) in PR, QRS, or QTc were no more common among the total or fatal pro-arrhythmia groups than in the patients in study 032 who experienced no pro-arrhythmic events.

The pro-arrhythmia patients did differ from the others in cardiovascular diagnoses and histories.

	Percentage of Patients with Diagnosis/History of:				
	ASHD	MI	VT	CHF	VT and CHF
Patients with PA-events	73	68	80	57	52
Other Patients	50	38	44	28	19
Ratio PA/Other	1.5	1.8	1.8	2.0	2.7

TABLE 30B

Mean Absolute Increase from Baseline ± 1 Standard Error (Seconds)

ECG Interval	Patients with PA[a] Events (n=36)	PA Deaths (n=12)	PA Non-Deaths (n=24)	PA Patients Categories I & II (n=11)	PA Patients Category III (n=25)	Chronic Patients on Flecainide 031-Month 12 (n=23)	Chronic Patients on Flecainide 033-Month 6 (n=95)
PR	0.040 ± 0.008	0.044 ± 0.013	0.038 ± 0.009	0.030 ± 0.014	0.045 ± 0.009	0.042 ± 0.006	0.032 ± 0.002
QRS	0.023 ± 0.004	0.030 ± 0.009	0.020 ± 0.005	0.015 ± 0.006	0.026 ± 0.006	0.025 ± 0.003	0.015 ± 0.002
QTc	0.029 ± 0.011	0.056 ± 0.023	0.015 ± 0.010	0.010 ± 0.012	0.037 ± 0.014	0.020 ± 0.010	0.023 ± 0.005
JTc	0.006 ± 0.010	0.018 ± 0.019	0.000 ± 0.011	-0.003 ± 0.015	0.018 ± 0.012	-0.004 ± 0.009	0.005 ± 0.008

TABLE 30C

Mean Percent Increase from Baseline ± 1 Standard Error (Seconds)

ECG Interval	Patients with PA Events (n=36)	PA Deaths (n=12)	PA Non-Deaths (n=24)	PA Patients Categories I & II (n=11)	PA Patients Category III (n=23)	Chronic Patients on Flecainide 031-Month 12 (n=23)	Chronic Patients on Flecainide 033-Month 6 (n=95)
PR	23 ± 4	23 ± 7	23 ± 5	20 ± 7	25 ± 4	26 ± 4	20 ± 2
QRS	24 ± 5	29 ± 10	22 ± 6	15 ± 6	28 ± 7	32 ± 5	18 ± 2
QTc	7 ± 3	14 ± 6	4 ± 2	3 ± 3	9 ± 4	5 ± 5	6 ± 1
JTc	0.0 ± 0.03	0.1 ± 0.05	0.0 ± 0.03	0.0 ± 0.05	0.0 ± 0.04	-0.4 ± 3	3 ± 2

[a]PA = Proarrhythmic.

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Although the risk of a pro-arrhythmic event is clearly greater in the patients with a prior history of ASHD, AMI, CHF and post VT, and was greater in the studies of patients with serious arrhythmias and a higher likelihood of such risk factors, patients with lesser degrees of illness and, in particular, no prior history of sustained VT, are also at risk for a serious arrhythmic event as the following cases illustrate:

Category I

1. 033-05-16

2. 033-17-025

Category III

3. 032-08-006

4. 032-17-017

5. 033-13-015

6. 033-14-006

7. 033-17-012

8. 057-02-204

9. 028-WD-101

Cases 033-05-16 and 032-17-017 represent apparent induction of new non-sustained VT; cases 028-WD-101, 032-08-006, 033-13-015, 033-17-012, and 057-02-204 represent new sustained VT in patients without prior history of more than short non-sustained VT. Because these cases emerged in open studies, it is not possible to say whether these event rates were more, less or just as frequent as they would have been with other, or no, antiarrhythmic therapy, but they were considered by investigators to represent possible flecainide-caused events and the case histories support this possibility.

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818-033-05-16

This 53-year-old male had a history of ASHD and hypertension treated with nadolol. A month prior to flecainide therapy a Holter showed 158 PVCs/hour. Flecainide was started on 10/22/81 at 200 mg BID. This was stopped due to complaints of dizziness, fatigue, weakness and staggering on 10/24 and restarted three days later at 150 mg BID. Two weeks later a Holter showed 709 PVCs/hour and salvos of VT. Flecainide was discontinued on 11/12. There were no significant changes in PR, QRS or Q^T intervals.

818-033-17-025

This 66-year-old male had a history of old anterior myocardial infarction with angina and class I congestive heart failure. A mitral insufficiency murmur and an S3 gallop were heard prior to therapy with flecainide. At baseline patient had an average of 133 PVCs/hour with bigeminy and R on T phenomenon. Prior antiarrhythmic therapy included quinidine, Pronestyl and tocainide. On 11/5/81 flecainide 200 mg BID was started and his PVCs increased to 178 per hour. The dose was increased to 300 mg BID which caused dizziness, blurred vision and headache. On 11/25 he entered the 033 study on flecainide 50 mg BID which reduced PVCs to 25 per hour. On 1/7/82 the dose was increased to 50 mg TID. In February, the patient had approximately 60 PVCs per hour. This increased to 575 PVCs per hour in June. On 8/9 flecainide was increased to 100 mg TID, the Holter on 8/19 showed 1651 PVCs per hour. Flecainide was discontinued on 9/8. PR interval prior to flecainide therapy was 0.28, QRS was 0.10, QT was 0.46. On therapy in August 1982, PR interval was 0.20, QRS was 0 09 and QT was 0.52.

818-032-08-006

This 55-year-old male had a history of old inferior myocardial infarction and coronary bypass surgery. He was being treated with Isordil for angina and Coumadin for recurrent deep vein thrombophlebitis. Prior antiarrhythmic therapy, for frequent PVCs, included quinidine, disopyramide and acebutolol. The patient was started on flecainide at 200 mg BID on 6/19/81 for an average of 128 PVCs/hour. The dose was increased to 300 mg BID on 6/26 because he had achieved only 52% suppression of PVCs. "On 6/28 the patient reported to the ER with palpitations and lightheadedness, the evaluation revealed wide complex tachycardia which did not respond to usual conservative measures such as Valsalva and Tensilon. He did respond to a 50 watt sec. cardioversion and converted to relatively

regular rhythm. He was admitted to CCU and continued on flecainide 300 mg BID. Approximately 1-1/2 hours after the next dose, he again developed wide complex arrhythmia. All further medications were held, except the nitrates, and over the next 12 hours, he converted back to his normal ECG. A prophylactic pacer was inserted at the time he had the wide complex tac dia because of possible periods of complete heart block. The patient did well and was subsequently discharged on alternate antiarrhythmic therapy. The PR interval prior to flecainide was 0.16, QRS 0.08 and QT 0.44. On the 25th of June at 200 mg BID the PR interval was 0.17, QRS 0.07 and QT 0.37. Within hours after cardioversion, the PR was 0.22, QRS was 0.18 and QT was 0.48.

818-032-17-017

This 63-year-old male had a history of hypertensive cardiovascular disease treated with Catapres. Holter monitor showed 70 PVCs per hour with couplets. Flecainide therapy was started at 200 mg BID on 10/8/81. A week after starting flecainide, his Holter showed 245 PVCs per hour and non-sustained ventricular tachycardia which had not occurred before. The PR interval prior to flecainide was 0.19, QRS 0.09 and QT 0.36. On flecainide the PR interval was 0.23, QRS 0.13 and QT 0.44.

818-033-13-015

This 64-year-old diabetic male had a history of an old inferior MI and multifocal PVCs with couplets. Previous therapy included procainamide, tocainide and quinidine. He completed the 032 study on quinidine. The patient entered the 033 study and started flecainide on 8/17/81 at 200 mg BID. This was stopped on 8/24 due to malaise. "Holter on 8/24 demonstrated ventricular tachycardia starting at 18:46 and continuing to end of tape at 21:12. Ventricular tachycardia was still present at exam on 8/26. He was admitted to the hospital and cardioverted. Patient had stopped taking flecainide himself and prior to this was taking flecainide irregularly. He was in CHF at this time (probably percipitated by VT). Patient had sino-atrial conduction time abnormality at EP study after cardioversion." PR interval prior to therapy was 0.14, QRS was 0.13, QT was 0.42. On 8/24 the PR interval was 0.20, QRS was 0.14, QT was 0.40.

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818-033-14-006

This 22-year-old male had a history of severe congestive cardiomyopathy felt likely secondary to excessive alcohol intake. He had easy fatigability, extertional dyspnea, orthopnea and PND. He was found to have cardiomegaly, hepatomegaly and a pleural effusion with an ejection fraction of 16%. He was treated with digoxin, Lasix and isosorbide dinitrate. Holter monitoring showed 7,500 PVCs over a two-day period, with episodes of nonsustained ventricular tachycardia. He was placed on quinidine; six days later he had an episode of ventricular tachycardia and fibrillation from which he was successfully resuscitated. Following successful EP study on 10/5/71, he was started that day on flecainide, 200 mg BID, however he developed syncope on 12/31/81. He later underwent repeat EP study which showed nonsustained ventricular tachycardia could be readily induced. The decision was made to discontinue flecainide. On 1/9/82 the dose was reduced from 250 mg BID, to 150 mg BID at which time aprindine was begun. Two days later he abruptly went into sustained ventricular tachycardia, which degenerated into ventricular fibrillation. Cardioversion resulted in asystole and he could not be resuscitated. According to the investigator, "while flecainide initially proved 95% suppression of his ventricular ectopy, and completely controlled his ventricular tachycardia, the episode on 12/31/81 (syncope), in retrospect, was likely ventricular tachycardia. A subsequent electrophysiology was 'different' from the one done on 10/31/81, and indicated that yet another antiarrhythmic medication should be tried. His death was an arrhythmic death." Prior to therapy the PR interval was 0.18, QRS 0.14 and QT 0.44. On flecainide, the PR interval was 0.20, QRS 0.12 and QT 0.52.

818-033-17-012

This 68-year-old male had a history of cardiomyopathy and hypertension treated with captopril. A S3 gallop was heard prior to therapy with flecainide. On 8/20/81, flecainide therapy at 200 mg BID was instituted for PVCs with couplets, bigeminy and ventricular tachycardia "3 beats in a row." Patient achieved 99% suppression of baseline PVCs (1,200 PVCs/hour) in the 032 study. On 9/10 he entered the 033 study on the same dose of flecainide, 200 mg BID. Two days later he entered the hospital with ventricular tachycardia requiring CPR, bretylium, magnesium sulfate, lidocaine, dopamine, propranolol and IV digoxin being given before he maintained normal sinus rhythm. The investigator noted that the patient had had a similar event while on

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therapy with Pronestyl. Prior to therapy his PR interval was 0.18, QRS was 0.09, QT was 0.42. On therapy the PR interval was 0.24, QRS was 0.12, QT was 0.54.

818-057-02-204

This 80-year-old male had a history of recurrent subendocardial myocardial infarctions, and class III congestive heart failure with an ejection fraction of 46% (higher than expected because of mitral regurgitation). He had symptoms of dyspnea, orthopnea, PND, edema, fatigue and palpitations. He had chronic atrial fibrillation and was treated with Lanoxin, nifedipine, Lasix and hydralazine. Previous antiarrhythmic therapy for multifocal PVCs included quinidine and procainamide, which were discontinued due to side effects, and disopyramide, discontinued because of increasing heart failure. The patient was begun on 100 mg flecainide BID on 10/2/82. Over the next 10 days he was gradually increased to 200 mg BID because of lack of therapeutic effect. On 10/11 "patient came to ER complaining of increased shortness of breath and fatigue." ECG showed wide, irregular QRS complex tachycardia without P waves. This rhythm was unresponsive to cardioversion and continued until death. This patient had no prior history of sustained ventricular tachyarrhythmias before beginning flecainide. The patient had severe left ventricular dysfunction. Post mortem exam showed recent posterior infarction. QRS prior to flecainide therapy was 0.116, QT was 0.329. Four days before his death, the QRS was 0.132, QT was 0.379.

818-028-WD-101

This 58-year-old male had a history of cardiomyopathy and cerebral embolus secondary to atrial fibrillation. He was being treated with flecainide for chronic atrial fibrillation by an investigator (W.D.) using a separate IND application for this purpose. Concomitant medications included digitoxin and Coumadin. On 10/23/82 flecainide 100 mg BID was started and increased on 11/1 to 200 mg TID with conversion to normal sinus rhythm. On 12/18 the dosage was changed to 300 mg q12 hours. The patient went in and out of atrial fibrillation, and on January 25, 1983, the Holter showed recurrent ventricular tachycardia alternating with sinus rhythm. The patient was hospitalized and flecainide was withdrawn. Atrial fibrillation returned with only occasional PVCs thereafter noted. Patient's digitoxin level was normal at the time of his ventricular tachycardia. The ECG intervals on 10/19/82, prior to flecainide were QRS 0.12, QT 0.40, on 1/3/83 the PR was 0.24, QRS 0.12 and QT 0.46.

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d. Arrhythmic Deaths and Sudden Death

Through October 15, 1983, 65 of 770 patients receiving oral flecainide had died. Six of these were non-cardiac deaths; 3 were deaths associated with an autopsy-proven acute myocardial infarction; 8 were deaths attributed to congestive heart failure and low-output states (see discussion of CHF below). The remaining 44 deaths were caused by documented arrhythmias or were sudden deaths; these are summarized in two tables, 30D and 30E, showing in-hospital documented arrhythmic deaths (21 of the 44) and out-of-hospital sudden or unobserved deaths (23 of the 44), respectively. The tables include the investigator's opinion of the relation to flecainide; but note that this changed in some cases when a "no-relation" case was included as a possible pro-arrhythmic event in the survey. Of course, sudden death experiences, some undoubtedly resulting from an undocumented AMI, in this population are to be expected and cannot, in most cases, be attributed to flecainide. As discussed earlier, however, some did seem to represent pro-arrhythmic events and have been included in the survey, and a number of others, not in the survey, but occurring early after therapy could potentially represent pro-arrhythmic events. With respect to the latter, the following cases are of interest because there was no prior history of sustained VT and because they occurred relatively soon after starting flecainide.

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1. 033-02-007

2. 033-17-005

3. 028-59-101

R-818-033-02-007

This 63-year-old male with ASHD received flecainide for three weeks with good suppression of his chronic ectopy until he suddenly collapsed at home after breakfast. Upon arrival of the paramedics, he was found to be in asystole. During treatment he developed a supraventricular rhythm which degenerated into VT and VF, and he could not be resuscitated in the ambulance or emergency room. Cause of death was listed as "either ventricular tachyarrhythmias or ventricular asystole." The investigator felt that the patient's death was possibly related to flecainide. Although this patient's data was presented at the Flecainide Investigators' Meeting in December 1982, the investigator chose later not to consider this patient's death as a proarrhythmic event in that survey.

R-818-033-17-005

This 50-year-old male with ASHD, a previous MI and congestive failure received flecainide for four days for ventricular ectopy when he collapsed while attending a picnic. Monitoring by paramedics demonstrated ventricular tachycardia which was extremely resistant to therapy in the ambulance and the hospital room. The patient could not be resuscitated. The cause of death was listed by the investigator as "ventricular fibrillation, with severe atherosclerotic heart disease, severe CHF." The investigator felt that the patient's death was probably not related to flecainide.

R-818-028-59-101

This 64-year-old male received flecainide for frequent PVCs unresponsive to conventional drugs. After three days of monitoring, his arrhythmia appeared to be well controlled, but while playing tennis the following day he collapsed, and cardiopulmonary resuscitation was unsuccessful. He was dead on arrival at the local hospital. The cause of death was listed as "ventricular fibrillation." The investigator felt a relationship of the death to flecainide was possible.

SUMMARY OF 1 .IENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

TABLE 30D

Patients Who Developed Arrhythmias In-Hospital Leading to Death

R-818 Study No.- Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
0*020-12-101	44	M	♦	♦	♦	VT	♦	♦	600	6 days	VT	No
0*020-14-112	75	M	♦	♦		VT	♦	♦	200	5 days	Cardiac arrest	No
020-14-114	76	F	♦	♦	♦	VT	♦	♦	250	6 mos	VT/VF as a result of ischemic heart disease and S-A dissociation	No
020-14-123	61	M	♦	♦		VT	♦	♦	500	5 days	VT	No
0*020-14-132	63	M	♦	♦	♦	VT	♦	No CHF EF 13%	400	3 days	Cardiac arrest as consequence of VT	Probably
0*020-14-133	55	M	♦	♦	♦	VT/VF	♦	♦	400	2 days	VT/VF	Probably
0*020-34-103	66	M	♦	♦		VT/VF	♦	♦	400	11 days	Incessant VT	Probably
*020-42-101	61	M	♦	♦	♦	VT		♦	500	2 days	Acute coronary insufficiency with subsequent exacerbation of ventricular dysrhythmias	Probably not
0*020-43-003	55	M	♦	♦		VT/VF	♦	♦	400	5 days	Ref.V-arrhythmia, low cardiac output ➔ acidosis	Possible
0*020-43-005	71	M	♦	♦		VT	♦	♦	600	4 days	Refractory VT	Unknown
0*020-72-103	73	M	♦	♦		VT	♦	♦	300	5 days	Cardiac arrest	Possible

* Patients discussed at Investigator's Meeting, December 10, 1982.
@ Deaths related to proarrhythmic events in survey, February, 1983.

SUMMARY OF PATIENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

TABLE 30D (Concluded)

Patients Who Developed Arrhythmias In-Hospital Leading to Death

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
033-06-005	74	M	♦			PVCs		♦	400 (off F 5 days)	30 days	Terminal VF	No
033-06-018	75	M	♦	♦		PVCs			400	8-1/2 mos	Cardiac arrest (VT/VF)	Probably not
0*033-14-006	22	M			♦	VT/VF	♦	♦	300	3-1/2 mos	VT/VF asystole	No
0*057-02-204	80	M	♦	♦		PVCs		♦	400	9 days	VT resulting in cardiogenic shock & death	Possible
*057-03-003	66	M	♦		♦	VT/VF	♦	♦	200	3 days	Incessant VT	Possible
*057-06-007	72	M	♦	♦		VT	♦	♦	200	2 mos	Recurrent VT	Probably not
057-08-005	54	M			♦	VT	♦	♦	500	12 days	Intractable VT	Probably not
(035)-MM-03-203	39	M			♦	VT		♦	400	4 days	VF	Probably not
(035)-MM-03-016	53	M	♦	♦		VT		♦	400	1 day	VF	Possible
(035)-MM-03-006	31	M				VT			400	8 mos	VT - asystole	Probably not

* Patients discussed at Investigator's Meeting, December 10, 1982
0* Deaths related to proarrhythmic events in survey February, 1983.

SUMMARY PATIENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

TABLE 30E

Patients Who Died Following Out-of-Hospital Sudden Death Experiences or Unobserved Deaths

B-010 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhythmia	Previous Resuscitation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
020-02-104	76	M	+	+		VT/VF	+	+	200	13 1/2 mos	Probable cardiac arrest due to ischemic heart disease	Probably not
020-07-105	62	M	+	+		PVCs			300	7 mos	Possible CVA	Probably not
020-14-130	61	M	+		+	VT			200	2 mos	Probable cardiac arrest and sudden death	Probably not
020-55-001	71	M	+	+		VT		+	400	1 1/2 mos	Cardiac arrhythmia	Unknown
020-59-101	64	M	+	+		PVCs		+	400	4 days	V-fib	Possible
020-74-102	52	M	+			VT			350	5 mos	AMI, Cardiac arrest?	No
*031-03-009	63	M	+	+		VT			400	25 mos	VF	Possible
032-06-004	71	M	+	+		PVCs		+	600	14 days	Possible acute arrhythmia	Probably not
033-02-001	66	M				PVCs			400	16 mos	Probable arrhythmia either with or without MI	Probably not
*033-02-007	63	M	+	+		PVCs		+	200	21 days	Either VF or V-asystole	Possible
033-06-007	76	M	+	+		PVCs		+	400	6 mos	Cardiac arrest & arrhythmia. ? 2° to AMI	No

* Patients discussed at Investigator's Meeting, December 10, 1982.

SUMMARY OF PATIENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

TABLE 30E

Patients Who Died Following Out-of-Hospital Sudden Death Experiences
or Unobserved Deaths

R-818 Study No. Patient No.	Age	Sex	AMHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
833-11-002	69	M	♦		♦	VT		♦	200	15 1/2 mos	Cardiac arrhyth-mia probable VF	No
833-13-008	71	M	♦			VT			400	2 mos	Sudden death ? MI ? arrhythmia	No
833-14-14	61	M	♦	♦		VT			400	10 mos	Probable MI, cardiac arrest	Probably not
*833-17-005	58	M	♦	♦		PVCs		♦	400	4 days	VF with severe AMHD, severe CHF	Probably not
857-01-101	51	M	♦	♦		VT	♦		400	2 1/2 mos	VT/VF sudden death	Possible
@*857-02-205	55	F	♦	♦		VT		♦	250	24 days	Arrhythmia ?type ? cause	Possible
857-02-206	75	M			♦	VT/VF	♦	♦	200	7 mos	Sudden death, either AMI or arrhythmia	Unknown
857-07-101	71	M	♦	♦	♦	VT,VF	♦	♦	300	70 days	Arrhythmia-either primary or secon-dary to ischemic event	Probably not
857-07-103	67	M	♦	♦	♦	VT		♦	200	13 days	Ischemia causing pulmonary edema (inferred)	Probably not

* Patient discussed at Investigator's Meeting, December 1982.
@ Deaths related to proarrhythmic events in survey February, 1981.

SUMMARY O IENTS WHO DIED WHILE
RECEIVING Fl...AINIDE THERAPY

TABLE 30E (Concluded)

Patients Who Died Following Out-of-Hospital Sudden Death Experiences
or Unobserved Deaths

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
(036)-[illegible]-03-209	55	M	♦	♦		PVCs			300	14 mos	Cardiac arrest	No
(036)-[illegible]-03-105	66	M	♦	♦		PVCs			400	1 mo	Sudden death, Probable VF	No
(036)-[illegible]-03-034	67	F	♦	♦		VT		♦	400	6 days	Myocardial infarction	Probably not

Of the 44 patients, 38 (86%) had ASHD, 32 (73%) had a prior AMI, 14 (32%) had cardiomyopathy, 18 (41%) had a prior cardiac arrest requiring resuscitation, 32 (73%) had histories of VT and/or VF while 12 (27%) were being treated for chronic VPCs, and 31 (70%) had prior histories of CHF.

Sixteen of the 44 (36%) died within the first 10 days of flecainide therapy; 24 (55%), within the first month. The mean dose was 365 mg/day.

The following tables summarize all of the cardiac deaths in flecainide-treated patients by study through October 15, 1983, including four with incomplete information.

Study	n	Proven AMI	CHF	In-Hospital Arrhythmia	Out-Hospital Arrhythmia or SD
030	35				
031	29				1
032	141				1
033	198	1	1	4	7
035	66			3	3
037	10	1	1		
057	39		1	4	6
028	228	1	1	11	8
060	31				1

e. Study 057 amended

The use of the lower dosing regimen in the 057 amended study only slightly lowered the incidence of proarrhythmic events. However, the severity of these experiences was decreased compared to studies of similar patients treated with higher doses in the compassionate-use studies. Although nine deaths occurred in the 057 amended study (six out-of-hospital sudden deaths, three MIs) no deaths were thought by the investigator to be related to proarrhythmic events. Table 30F lists these nine patients and includes cardiac history and total daily dose at time of event.

Table 30?

Patient Deaths

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
057-01-101	51	M	+	+		VT_s	+		400	77 Days	VT/VF sudden death.	Probably not
057-06-110	30	M	+	+		VT_{ns}		+	400	107 Days	Cardiac arrest secondary to acute MI - suspected. No autopsy.	No
057-06-113	70	M	+	+		VT_s		+	200	163 Days	Acute ischemic episode - MI on autopsy.	No
057-07-101	71	M	+	+		VT_s	+	+	300	70 Days	Arrhythmia-either primary or secondary to ischemic event.	Probably not
057-07-103	67	M	+	+		VT_{ns}		+	200	12 Days	Ischemia causing pulmonary edema (inferred).	Probably not
057-12-110	69	M			+	VT_{ns}		+	200	21 Days	Cardiac arrest. Precipitating factors unknown.	Unknown
057-26-105	57	M	+	+		VT_{ns}			400	242 Days	Cardiac arrhythmia. Sudden collapse while dancing.	Probably Not
057-31-102	74	M	+	+		VT_s	+	+	300	83 Days	Hospitalized for MI. No autopsy.	No
057-12-110	72	F	+	+		VT_s		+	200	153 Days	Cardiac arrhythmia. Collapsed in hallway.	No

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f. Conclusion

Like other antiarrhythmic drugs, flecainide can worsen pre-existing arrhythmias or create new ones. As most long term data on flecainide comes from open studies it is not possible to compare its pro-arrhythmic potential with other drugs. Podrid, Lown, and co-workers had described pro-arrhythmia frequencies of 10% or greater for a variety of drugs, indeed, for virtually all antiarrhythmic drugs, [Velebit, et al: Circulation 65:886-894, 1982] but those authors' vigorous exercise testing and repeated Holter measurements may have represented a more vigorous search than occurred in flecainide patients. Winkle, Mason and co-workers [Am Heart J 102:857-864, 1981] have described dramatic worsening of arrhythmias in 11% of 90 patients with prior VT/VF given encainide, a close relative of flecainide, and of the development of VT needing resuscitation in one of 47 patients with frequent VPCs and non-sustained salvos. Other studies have shown worsening of arrhythmias in some patients receiving amiodarone.

For the patients with serious prior arrhythmias, the pro-arrhythmic potential of flecainide seems within a range that is similar to other drugs. What is less clear, on the basis of short-term controlled data and longer term open, uncontrolled studies, is what the risk of flecainide is in patients with relatively benign arrhythmias such as frequent VPCs. That flecainide can induce life-threatening arrhythmias in these patients, at least on occasion, seems clear. Complete assessment of this risk will require further data in these populations, preferably longer term controlled data. Part of the difficulty in evaluating this risk, of course, is the absence of evidence that antiarrhythmic agents are of life-prolonging value in patients with less serious arrhythmias.

It is important to note that most pro-arrhythmic events have occurred early during treatment, both in the older studies and in 057 amended. In the latter study, slower dose-titration and close observation have been associated with an outcome of no fatal pro-arrhythmic events although non-fatal events have continued to occur. Starting flecainide in-hospital with close observation is clearly prudent for patients with sustained ventricular tachycardia, symptomatic congestive heart failure, sinus node dysfunction, or ejection fractions less than 30%.

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3. Congestive Heart Failure

Animal and human clinical pharmacologic data show a negative inotropic effect of flecainide. In all of the major studies cases of CHF were identified on the basis of the physician's diagnosis or the presence of symptoms, e.g., shortness of breath, that suggested CHF. This initial screen was then referred by further review to eliminate cases in which the diagnosis of CHF or of a relationship to flecainide was unlikely.

Table 31A shows the incidence of new or worsened CHF in three groups of patients: those patients treated primarily for chronic ventricular ectopy (030, 031, 032, 033, 035); those patients treated in the Compassionate-Use Studies (028, 057); and those patients in the Acute and Chronic Study of Ventricular Tachycardia (057, amended); both the initial screen and reviewed values are given. Tables 31B and 31C show the clinical characteristics of the patients and the sponsors view of drug-relatedness. Many of the episodes, especially those considered drug-related occurred early in treatment with flecainide.

The overall incidence of developing possibly flecainide-related new CHF in patients without a previous history of CHF is thus low, about 1%, regardless of the population studied. The incidence of developing worsened CHF in patients with pre-existing heart failure was 9% in the ventricular ectopy studies and 19% in the compassionate use experience in which patients with more severe heart disease were treated. In the Acute and Chronic Study of VT which used lower initial doses to treat patients with severe cardiac disease, the incidence was the same as that in the ventricular ectopy studies, 9%. In this last study, five of the six patients who developed new or worsened CHF continued on flecainide in spite of developing CHF. All six were successfully treated by adjusting diuretics.

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TABLE 31A

Incidence of Flecainide-Associated CHF

	New CHF		Worsened CHF	
	Initial Screen	Reviewed	Initial Screen	Reviewed
Acute & Chronic Studies/ Ventricular Ectopy (030, 031, 032, 033, 035)	2% (6/306)	0.7% (2/306)	15% (10/67)	9% (6/67)
Compassionate Use Studies (028, 057)	5% (6/131)	0.8% (1/131)	2% (32/115)	19% (22/115)
Acute and Chronic Study/VT 9% (4/43) (057 Amended)		6% (3/53)	4% (2/53)	12% (5/43)
All Studies	3.1% (15/490)	1% (5/490)	20.9% (47/225)	14% (32/225)

New and Worsened CHF

	Initial Screen	Reviewed
All Studies	8.7% (62/715)	5% (37/715)

TABLE 31B

Summary of Patients Who Developed CHF While on Flecainide Therapy

Patient No.	Age	Sex	History of CHF	Cardiomegaly	On Dig/Diuretics at Study Start	Symptoms at Study Start	Coronary Artery Disease	Old MI	Cardiomyopathy	Valvular Heart Disease	Hypertensive Heart Disease	Exposure to Flecainide at Time of CHF (Months)	Dose at Time of CHF (mg bid)	Flecainide Discontinued?	Flecainide Restarted (mg bid)	In Biker's Opinion, Was This a Patient with Flecainide-Related CHF?
035-02 (0101)	57	M	+	+	+	+	+	+	-	-	-	2	200	Yes	200	Yes
												11	100 tid	No	---	---
030/031-03 (0002)	43	F	+	-	Dc'd	+	-	-	+	-	-	3-4	100 tid	No	---	No
032/033-02 (0006)	62	M	-	-	-	-	+	-	-	-	-	1 1/2	200	Yes	No	Yes
032/033-02 (0007)	63	M	+	+	+	-	+	+	-	-	+	8 days	200	Yes	100	Yes
032/033-05 (0008)	72	F	+	+	+	+	-	-	-	+	-	1 day	200	Yes	No	No
032/033-06 (0013)	73	M	-	-	-	-	+	+	-	-	+	1 dose	100	Yes	No	No
032/033-07 (0003)	70	M	+	+	+	+	+	+	-	-	-	2 1/2	200	No	---	Yes
032/033-07 (0020)	65	M	-	+	-	-	+	+	-	-	+	7 days	200	Yes	No	Yes
032-10 (0003)	63	F	+	+	+	+	+	+	-	-	+	1 day	200	Yes	No	Yes
032/033-11 (0002)	48	M	+	+	+	+	-	-	+	-	+	9	100	Yes	100	No
032/033-11 (0008)	47	M	+	+	+	+	-	-	+	-	-	1 1/2	100	No	---	Yes
												6	100	Yes	50	---
032/033-12 (0012)	62	M	+	+	+	+	+	-	-	-	+	7	150	Yes	No	Yes
032/033-13 (0007)	67	M	-	+	-	+	+	+	-	-	-	3	200	No	---	No
032/033-13 (0015)	64	M	-	+	-	-	+	+	-	-	-	7 days	200	Yes	No	No
032/033-17 (0014)	77	M	-	+/-	-	+	+	+	-	+	+	15	300 QD	No	---	No
032/033-17 (0026)	72	F	+	+	+	+	+	-	+	+	-	5	50 tid	No	---	No

TABLE 31C

Congestive Heart Failure - Summary of
Patients who Developed New Or Worsened CHF During Flecainide Therapy

Patient I.D	BNHF (1)	Age	Sex	History CHF	Cardiomegaly	Cm Dig at Baseline	Symptoms/Findings at Baseline	Coronary Artery Disease	Old MI	Valvular Heart Disease	Hypertensive Heart Disease	Exposure to Flecainide at Time of CHF	Dose at Time of CHF	Outcome (d/c = flecainide discontinued)		In Other's opinion was this a Patient with Flecainide-related CHF?
020-02-102		51	M	-	-	-	-	+	+	-	-	46 Days	200 BID	ongoing, dose ↓ to 150 BID		
-103		69	M	+	+	+	+	+	+	+	+	13 Days	200 BID	d/c, restart 100 BID		
-07-101		76	M	+	+	+	+	+	+	+	+	3 Days	300 BID	died (CHF related death)		
-107		50	M	+	+	+	+	+	+	+	+	14 Days	150 BID	d/c		
-08-112		62	M	+	-	-	-	+	+	-	+	1 Day	200 BID	ongoing, dose ↑ to 300 BID		
-11-104		61	M	+	-	-	-	+	+	-	+	23 Days	300 TID	pt. trans. to another flec. study, dose ↑ to 100 BID		
-14-101		53	M	-	-	-	-	+	+	-	+	100 Days	150 BID	ongoing		
-115		35	F	+	-	-	-	+	+	+	-	36 Days	100 BID	ongoing		
-131		64	M	+	+	+	+	-	-	-	-	10 Days	300 BID	died (CHF related death)		
-133		55	M	+	+	+	+	+	+	+	+	2 Days	300 BID	died (arrhythmic death)		
-19-101		75	F	+	-	+	+	+	+	-	-	6 Days	200 BID	d/c		
-26-002		72	M	+	-	+	+	+	+	-	-	37 Days	150 QAM	ongoing ↑ 100 BID		
-003		67	M	+	+	+	+	-	-	-	-	75 Days	300 BID	ongoing, dose ↓ 200 BID		
-27-011		78	M	+	-	-	+	+	+	-	-	75 Days	150 BID	continued fo 6 more weeks then d/c for other reasons		
-28-003		76	F	+	+	+	+	+	+	-	-	65 Days	100 QAM	continued for 1 more month then d/c for other reasons		
-006		67	M	+	+	+	+	-	-	-	-	3 Days	100 TID	d/c		
-007		59	M	+	-	+	-	+	+	-	-	70 Days	200 QAM	ongoing		
-012		61	M	-	+	-	-	-	-	-	+	71 Days	300 QAM	ongoing		
-34-101		55	M	+	+	+	+	-	-	-	-	10 Days	150 QAM	died (CHF related death)		
-102		56	M	+	+	+	+	+	+	-	-	26 Days	200 BID	continued for 6 more months, then d/c for other reasons		
-008		84	M	+	+	+	-	+	+	-	-	1 Years	100 BID	ongoing		
-37-003	10	59	M	-	-	-	-	+	+	-	-	9 Days	200 BID	d/c		
-51-102		64	M	+	+	+	-	+	+	-	+	12 Days	200 BID	d/c		
-103		69	M	-	-	-	-	-	-	-	+	80 Days	200 BID	ongoing		
-60-101	26	75	M	+	+	+	+	-	-	-	-	101 Days	100 BID	ongoing		
-61-101		57	M	+	+	+	+	+	+	-	+	11 Days	250 BID	died (acute MI)		
-103	26	63	M	+	-	+	+	+	+	-	+	95 Days	300 BID	died (CHF related death)		
-65-101		68	F	+	+	-	+	+	+	-	+	11 Days	200 BID	ongoing		
-68-102	110	61	M	+	+	-	+	+	+	-	-	2 Days	200 BID	d/c		
-70-101		68	M	+	+	-	-	+	+	+	-	10 Days	200 BID	ongoing		
-87-101		29	F	+	+	+	+	-	-	+	-	1 Day	200 BID	d/c		
-90-101		84	M	+	-	+	+	+	-	-	-	30 Days	100 BID	dose ↓, then pt. d/c due to intercurrent disease		
057-03-201*	25	79	M	+	+	+	+	+	+	-	+	1000 Days	100 BID	ongoing		
-06-003	11	62	M	+	+	-	+	+	+	-	+	14 Days	150 BID	ongoing		
-06-006	11	68	M	+	+	+	-	-	+	-	-	68 Days	300 BID	ongoing, changed schedule to 200 TID		
-06-007	26	72	M	+	+	+	+	+	+	-	+	98 Days	150 TID	died (cardiac arrest)		
-10-007	20	71	M	+	+	+	+	-	-	-	-	2 Days	300 BID	d/c		
-11-003	80	64	F	+	+	-	+	-	-	+	-	1 Day	150 BID	ongoing, dose ↑ to 100 BID		

* Baseline value of 444 spuriously high because patient's CHF status was unstable at this time than several months earlier when BNHF was 240.

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Figure 15 shows the outcome of the 37 patients who developed new or worsened CHF likely to have been related to flecainide. One-half of these patients continued on flecainide despite the occurrence of new or worsened CHF. Most of these continued flecainide at the same dose, with the investigator adjusting digitalis, diuretics, or both. The others continued flecainide at a reduced dose. One-half of the 37 patients (2.5% of patients taking flecainide) discontinued flecainide because of CHF. Four of these patients died of CHF related deaths; three of these four were receiving flecainide at the time of death and one died two days after discontinuing flecainide. All four were in the Compassionate-Use studies. Seven (22%) of the 37 patients who developed new or worsened CHF did so during the first four days of therapy; two-thirds during the first month of therapy. There were four other patients who died of low output states or CHF not likely to have been related to flecainide.

FIGURE 15

37
Patients Developed CHF
on Flecainide
(All Studies)

51% (19/37) Continued on Flecainide		49% (18/37) Discontinued Flecainide
35% (13/37) Continued at the <u>SAME</u> Dose	16% (6/37) Continued at a <u>REDUCED DOSE</u>	11% (4/37) Died

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In summary, the risk of a patient developing new congestive heart failure while on flecainide therapy was small (about 1%) when the patient had no history of congestive heart failure. In patients with pre-existing heart failure 9% to 19% of patients develop worsening of CHF at some time during the studies. In the majority of these cases, congestive failure was easily treated following adjustments in digitalis and/or diuretics, reducing the dose of flecainide, or discontinuing flecainide, but a few patients died at least partly due to worsened failure. Most patients who developed new or worsened CHF did so during the first month of therapy.

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4. Effects of Flecainide on the Scaler ECG/Conduction Disturbances

Changes in ECG intervals are an expected pharmacological effect of flecainide. There is a positive relationship between dose and degree of interval lengthening during the initial flecainide titration period (Table 31D) and the ECG interval changes seen after initial therapy tend to remain stable with chronic therapy. Table 31E shows this for studies 032 (acute) and 033 (chronic) and other acute/chronic comparisons.

PR intervals increase commonly by 25% (0.04 seconds) and as much as 118% in some patients. First degree A-V block (PR greater than 0.20 seconds) occurred in up to 40% of patients. To date, four patients have developed third degree A-V block and two patients have developed second degree A-V block (Wenckebach type) while on flecainide.

QRS intervals increase commonly by 25% and as much as 150% in some patients usually without producing detrimental clinical effects. Many patients with unifascicular bundle branch block and five patients with bifascicular block have received flecainide; some of these patients progressed to higher degrees of block. In the Compassionate-Use study 4% of patients developed new bundle branch block. There were two occurrences in all studies of new bifascicular block.

QT interval changes are usually minimal (8%) with most of the change due to increases in the QRS interval rather than the JT interval (QT minus QRS). This is expected from the known preferential electrophysiologic effects of flecainide on depolarization rather than repolarization. There have, however, been occasional patients with true QT prolongation. This effect predisposes to a Torsade de Pointe type VT and one such event has occurred in a patient with QT prolongation.

In all studies, 11 patients showed signs of sinus node dysfunction while receiving flecainide, resulting in sinus bradycardia, sinus pause or sinus arrest with junctional escape rhythms.

ECG changes led to a total of 28 discontinuations, sometimes because the investigator became uncomfortable with the large changes seen but more often because they were dangerous or symptomatic. Table 31F shows these discontinuations.

TABLE 31D

Absolute and Percent Changes for ECG Intervals
after Three Days of Therapy in R-818-030 Dose-Ranging Study

	Mean Percent Increase From Baseline			Mean Absolute Increase From Baseline (sec)		
	Dose (mg Bid)			Dose (mg Bid)		
	100	200	250/300	100	200	250/300
PR	9.0%	18.9%	24.1%	0.015	0.031	0.038
QRS	11.7%	20.7%	26.5%	0.009	0.016	0.021
QT	6.2%	7.5%	6.3%	0.022	0.027	0.023
JT*	4.8%	3.9%	0.7%	0.013	0.011	0.002

*JT = QT minus QRS

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TABLE 31E

Acute Dose and Chronic Therapy Comparison:
Absolute Increase in ECG Intervals

	Patients from Studies 030 and 031		Patients from Studies 032 and 033			Patients from Study 035	
	030 Day 14	031 Mo. 12	032 Wk 2	032 Wk 3	033 Mo. 6	035 Stage 1 Day 8	035 Stage 2 Mo. 12
PR	0.036	0.042	0.042	0.039	0.032	0.024	0.026
QRS	0.022	0.025	0.020	0.017	0.015	0.008	0.010
QT	0.033	0.032	0.024	0.028	0.026	0.009	0.014
JT	0.013	0.008	0.004	0.011	0.012	0.001	0.004

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Table 31F

Discontinued Patients - ECG Changes

Study	Center	Pt No.	Flecainide Dose (mg bid)	Duration	Reasons	Interval Changes (seconds)
032	04	005	200	10 days	1° AV block, worsened, blurred vision, dizziness	PR: 0.24 to 0.32
		015	200	7 days	1° AV block, bradycardia	PR: 0.18 to 0.23
		020	200	7 days	1° AV block, dizziness	PR: 0.16 to 0.28
	11	002	200	8 days	Widening of PR and QRS	PR: 0.21 to 0.26 QRS: 0.08 to 0.12
		007	200	4 days	Widened QRS non-qualifying patient	QRS: 0.10 to 0.16
	17	021	200	2 days	Widened PR non-qualifying patient	PR: 0.17 to 0.22
033	01	002	200	3 months	Sick sinus syndrome 1° AV block	PR: 0.28 to atrial fibrillation
	03	003	200	6 days	1° AV block, complete RBBB with marked right axis deviation	PR: 0.18 to 0.22 QRS: 0.09 to 0.14
		008	200	6 days	1° AV block LBBB, severe dizziness	PR: 0.16 to 0.24
	04	009	150	3 days	NSR with sinus pauses, junctional escape beats, 1° AV block, PACs	PR: 0.16 to 0.22
	12	024	300	31 days	Lack of therapeutic response, 2° AV block (Wenckebach), blurred vision, light-headedness, constipation	PR: 0.20 to 0.26

Table 31F - continued

Discontinued Patients - ECG Changes

Study	Center	Pt No.	Flecainide Dose (mg/) at DC	Duration	Reasons	Interval Changes (seconds)
028	04	101	50 TID		Widened QRS	QRS: 0.14 to 0.24
	11	102	200 BID	3 days	Sinus pause	PR: 0.19 to 0.20
			100 TID	3 days	resolved with decreased dose; D/C due to lack of efficacy.	QRS: 0.08 to 0.10 QT: 0.36 to 0.42
	13	001	200 BID	3 months	Widened intervals Proarrhythmic events.	PR: 0.19 to 0.32 QRS: 0.10 to 0.15
	14	102	200 BID	3 days	Bradycardia Sinus exit block	Baseline: PR: 0.24 QRS: 0.12 QT: 0.38 Followup: Not available
	14	112	100 BID	5 days	Severe bradycardia Hypotension Died	Baseline: PR: 0.18 QRS: 0.10 QT: 0.52
	14	129	200 BID	1 day	3° AV Block Bradycardia Dizziness, Nausea	Baseline: PR: 0.12 QRS: 0.08 QT: 0.34 Followup: Not available
	14	130	200 BID	4 days	Bundle branch block Widened intervals. Increased VT on holter	PR: Not avail. QRS: 0.10 to 0.20 QT: 0.40 to 0.43

Table 31F - continued

Discontinued Patients - ECG Changes

Study	Center	Pt No.	Flecainide Dose (mg/) at DC	Duration	Reasons	Interval Changes (seconds)
028	20	102	200 BID	1 dose	Widened PR, QRS, QT	Baseline: PR: 0.26 QRS: 0.12 QT: 0.40 Followup: Not available
	20	103	200 BID	1 day	Sinus pauses LBBB	PR: 0.20 to 0.20 QRS: 0.08 to 0.14 QT: 0.44 to 0.48
	26	010	200 BID	14 days	Widened intervals proarrhythmic event	PR: 0.16 to 0.18 QRS: 0.08 to 0.16 (ADV. EXP.) QT: 0.42 to 0.52
	28	014	200 BID 100 BID	1 day 2 days	Sinus pause	Baseline: PR: 0.14 QRS: 0.08 QT: 0.44 Followup: Not available
	44	104	200 BID	2 days	Widened intervals Proarrhythmic event	PR: 0.18 to 0.22 QRS: 0.08 to 0.10 QT: 0.44 to 0.46
	54	102	200 BID	2 days	3^{o} AV block, Hypotension, Polyuria	Baseline: PR: 0.176 QRS: 0.101 QT: 0.341
057	10	002	100/150	2 days	2^{o} AV Block	Baseline: PR: 0.18 QRS: 0.12 QT: 0.34 Followup: Not available
		008	300	4 days	IVCD Blurred vision	Baseline: PR: Not avail.

Table 31F - continued

Discontinued Patients - ECG Changes

Study	Center	Pt No.	Flecainide Dose (mg/) at DC	Duration	Reasons	Interval Changes (seconds)
057, amended	12	113	100 BID	5 days	3° AV block	Baseline: PR: 0.20 QRS: 0.06 QT: 0.48
	12	115	100 BID	2 days	3° AV block	Baseline: PR: 0.24 QRS: 0.12 QT: 0.40

The incidence of sudden deaths, proarrhythmic events or second or third degree AV block was not higher in 352 patients who developed 25% or more increases in PR or QRS intervals while receiving flecainide than in 95 patients who did not develop such increases (studies 030, 031, 032, 035, 057 and 057 amended).

Figure 15(A) shows an estimate of the probability for QRS changes greater than or equal to a 25% increase over baseline as a function of plasma level in 32 patients studied by Hodges in the 030, 031, 032 and 033 studies. The figure also shows estimates of the probability of achieving 80% suppression of PVCs and the probability of developing cardiac adverse experiences ("Therapeutic Window" analysis to be discussed further in Safety Section 6.) While the probability of all three events (80% suppression of PVCs, developing 25% increase in QRS, and cardiac adverse effects) appear to be related to plasma level, there does not appear to be a direct relationship between widening of QRS and either 80% suppression of PVCs or development of cardiac adverse experiences. The cardiac adverse experiences in these studies, it should be noted, include principally bundle branch block and bradycardia, not pro-arrhythmic events.

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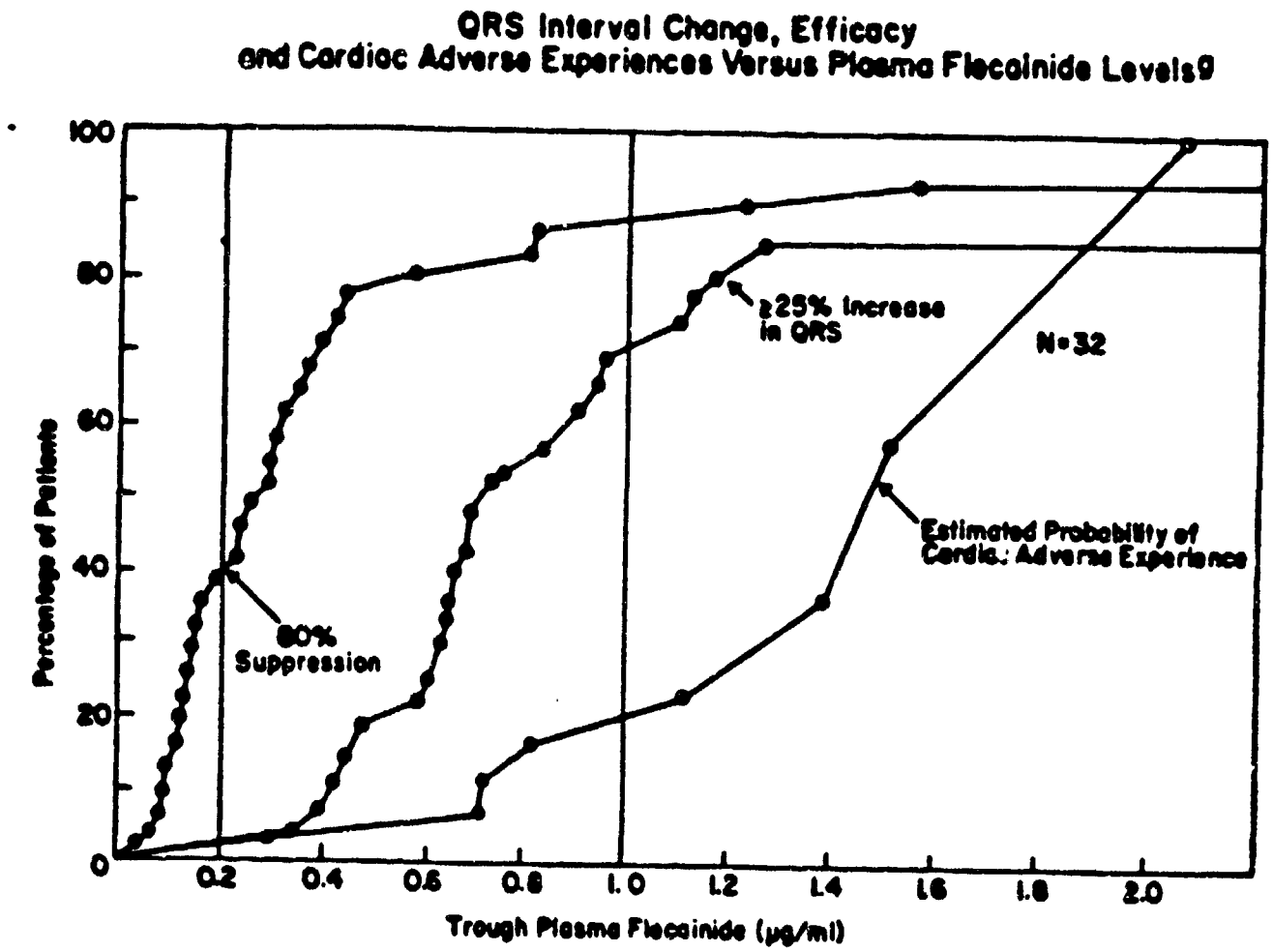
Figure 15A



*Hodges - Dose Ranging Study (030), Chronic Followup (031)
Quinidine Comparison Study (032), Chronic Followup (033)

5. Vital Signs

The sponsor reviewed mean changes in blood pressure, heart rate, and respiratory rate taken at each visit in patients treated in the Acute and Chronic Ventricular Ectopy Studies (033, 031, 032, 033, 035). In addition, all reports of adverse reactions related to vital sign changes were reviewed from all trials.

Blood pressure showed an average increase of about 5mm in systolic pressure and about 3mm in diastolic pressure compared to baseline. The changes did not increase with time. Two patients were reported as developing hypertension while receiving flecainide.

Mean heart rate showed no consistent trend; there were six reports of sinus bradycardia. In five of these six patients, however, bradycardia was either present to the same degree prior to flecainide, or the bradycardia was noted only once and did not recur with continued flecainide therapy.

Mean respiratory rate usually fell in these studies. These changes, however, were insignificant (about 1 breath per minute), and no patient was found to have clinically significant changes in respiratory rate.

6. Routine Laboratory Measurements

In U.S. monitored studies two questions were raised regarding possible effects of flecainide on routine laboratory measurements.

a. In the Dose-Ranging Trial (030) five patients developed new persistent elevations of alkaline phosphatase. All patients showing this abnormality were studied at one center. The elevations were less than twice the normal range and were not associated with elevations of bilirubin, SGOT, SGPT, leucine aminopeptidase (LAP), 5' nucleotidase, calcium, phosphorus, or urinary hydroxyproline. Four of the five patients continue to receive flecainide for over two years with elevations persisting but not increasing. One patient discontinued at three months for unrelated reasons; moved away and no follow-up data is available.

No persistent alkaline phosphatase elevations were found in 198 patients taking flecainide in the chronic followup of patients in the Flecainide-Quinidine Comparative study and there were no reports of persistent elevations in other studies.

b. In the chronic followup of patients studied in the Flecainide-Quinidine Comparative study, one patient developed small (2 x normal) rises in SGPT after 15 months of flecainide therapy. These changes persisted during six additional months of flecainide therapy. Flecainide was discontinued and within two months SGPT had returned to normal. The investigator refused to rechallenge the patient.

In West Germany flecainide has been marketed since August 1982. In December 1983, after 15 months of marketing experience, the sponsor estimated that at least 30,000 patients had received flecainide in West Germany. Reports of adverse experiences have been consistent with the results of U.S. studies with one addition: 18 patients have been reported who developed liver-related abnormalities including increased hepatic enzymes and "cholestatic jaundice." Of these patients:

- Two patients' abnormalities resolved while remaining on flecainide. (One patient developed acute "typical" hepatitis, the second patient had a single elevated SGPT value.)

- Four patients had either pre-existing liver disease or elevated hepatic enzymes prior to initiating flecainide.

- Three patients had elevations which were less than twice the normal range.

- Five patients had significant elevations in bilirubin and/or transaminases though no consistent pattern was present. The only biopsy in this group was read as "viral hepatitis."

- Four patients had virtually no information provided despite attempts by the sponsor to obtain further details.

Several of these 18 patients were on multiple drugs while taking flecainide. Where information is available, all abnormalities in these patients were either improving or had resolved as of the most recent information.

The reports to date are not sufficient to conclude whether flecainide can cause hepatic toxicity. No patient was rechallenged, which would provide the truest test of drug effect. The incidence may be low enough to reflect the spontaneous occurrence of such abnormalities in a presumed population of 30,000. Although no cause and effect relationship has been established, it is advisable to discontinue flecainide in patients who develop unexplained jaundice or signs of hepatic dysfunction in order to eliminate flecainide as the possible causative agent. The package insert states that reports of elevated transaminase levels and jaundice have occurred in patients taking flecainide.

7. Safety Experience With the Use of Flecainide with Other Antiarrhythmic Drugs and With Beta Blockers

Adverse experiences were reviewed in 226 patients taking other antiarrhythmic drugs either concomitantly with flecainide, or shortly before or after flecainide therapy.

In US studies, 81 patients received one or more of nine other antiarrhythmic drugs during treatment with flecainide. Five deaths were reported in these patients; four were arrhythmic deaths and one patient died of "pump failure." All five patients had pre-existing CHF and previous resuscitations. Other adverse experiences were consistent with known side effects of flecainide or the other antiarrhythmic drug. Thirty-one of these 81 patients received lidocaine, usually during the first few days of flecainide therapy. One of the five deaths occurred in these 31 patients. Other side effects in patients taking lidocaine with flecainide were: sinus pause (1), syncope (1), bundle branch block (1), chest pain (1) and loss of appetite (1). The other 4 deaths occurred in patients receiving amiodarone, procainamide, aprindine and bretylium.

Seventy-five patients received flecainide within one day after stopping another antiarrhythmic drug (during washout of the previous antiarrhythmic). Three of these patients developed 3° AV block. Otherwise adverse experiences which occurred during the subsequent two days of flecainide therapy were consistent with those reported for flecainide or the other antiarrhythmic drug.

Seventy patients received another antiarrhythmic drug within three days after discontinuing flecainide (during flecainide washout). The adverse experiences were consistent with those reported for flecainide or the other antiarrhythmic drugs.

Adverse experiences were reviewed for 94 patients who for periods up to 35 months received beta blockers while taking flecainide. The most commonly used beta-blockers included propranolol (42 patients), metoprolol (23 patients), nadolol (14 patients) and atenolol (11 patients). The incidences of both non-cardiac and cardiac adverse experiences in these patients were similar to those reported for all patients taking flecainide. The incidence of fatigue (an adverse experience common to both beta blockers and flecainide) was somewhat higher in patients taking beta blockers (8%) than in all patients taking flecainide (usually 3-4%). Forty-two percent of the 94 patients experienced no adverse experiences.

8. Post Marketing Experience

a. United Kingdom

Tambocor[R] (flecainide acetate) has been marketed in the United Kingdom (UK) since September 1983. By the end of January 1985, over 1.4 million tablets had been sold. Based on an average dose of 300 mg (3 tablets) per day, it is estimated that approximately 3,000 patients have been treated with 1,300 patient-year exposure. An additional 10,000 ampuls (150 mg/ampul) have been sold for intravenous use.

The Committee On Safety of Medicine (CSM) has received a total of 44 adverse reaction reports (yellow cards) during the 17 month period from September 1983 to February 1984, when the product was commercially available. Four of these were cases that resulted in death (two from "cardiac arrest," one from "arrhythmia" and one from "myocardial infarction"). Table 32(A) is the list of adverse reactions provided by the CSM in February 1985. All reported adverse effects are consistent with US data submitted in the NDA.

b. West Germany

Tambocor[R] (flecainide acetate) has been marketed in West Germany since September 1982. By the end of January 1985, 60 million tablets had been sold with an average of 2.4 million tablets sold per month during the most recent three months. Marketing surveys suggest an average dose of 250 mg/day (2.5 tablets). This suggests an exposure of 65,000 patient-years in 50,000 to 100,000 patients.

Adverse drug reactions are usually reported by physicians directly to the pharmaceutical company, and occasionally to the Drug Commission of the German Medical Association. Table 32(B) lists the adverse experiences reported in West Germany from September 1982 through November 1984. A total of 336 adverse reactions were reported.

TABLE 32A

Post Marketing Adverse Reactions Reported in the United Kingdom (9/83 through 1/85)

Reaction Name	Reports	Deaths
Skin and Appendages		
rash	1	0
rash maculo-papular	2	0
urticaria	1	0
Central Nervous System		
headache	1	0
migraine	1	0
myoclonus	1	0
neuropathy	1	0
paresthesia	1	0
tremor	1	0
Autonomic Nervous System		
accommodation abnormal	2	0
palpitation	1	0
Visual Disorders		
teichopsia	1	0
vision abnormal	1	0
Gastro-Intestinal Disorders		
dispepsia	1	0
flatulence	1	0
stomatitis ulcerative	1	0
vomiting	2	0
Hepatic Disorders		
hepatic function abnormal	1	0
hepatitis	1	0
Metabolic and Nutritional		
weight increase	1	0
Cardiovascular Disorders		
cardiac failure	1	0
cardiac failure left	2	0
ECG abnormal	1	0
Intra-Cardiac Disorders		
angina pectoris aggravated	1	0
myocardial infarction	1	1
Arrhythmias		
arrhythmia	1	1
AV block	2	0
cardiac arrest	3	2
fibrillation ventricular	1	0
Peripheral Vascular Disorders		
thrombophlebitis	3	0
thrombophlebitis arm superficial	1	0
Respiratory Disorders		
pulmonary edema	1	0
Application Site Disorders		
injection site reaction	3	0

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TABLE 32B

Post Marketing Adverse Reactions Reported in
West Germany (9/82 through 11/84)

Reaction Name	Reports
Skin and Appendages	
rash	4
alopecia	2
pruritis	2
sweating	1
photosensitivity reaction	1
allergic skin reactions	1
Muscle Skeletal Disorders	
pain in extremities	2
Collagen Disorders	
lupus erythematous (physician later determined not related to drug)	1
Central and Peripheral Nervous System	
headache	7
dizziness	6
hypoaesthesia	2
paresthesia	1
polyneuropathy	1
tremor	1
Hearing and Vestibular Disorders	
tinnitus	1
temporary loss of hearing	1
Visual Disorders	
vision abnormal	11
eye pain	2
photopsia	1
diplopia	1
conjunctivitis	1
Psychiatric Disorders	
confusion	6
impotence	3
sleep disorder	2
paranoid reaction	1
paroniria	1
agitation	1
psychosis	1
hallucination	1
euphoria	1
loss of artistic activity	1
Gastro-Intestinal Disorders	
nausea	8
diarrhea	4
constipation	3
vomiting	2
dysphagia	1

TABLE 32B (continued)

Post Marketing Adverse Reactions Reported in West Germany (9/82 through 11/84)

Reaction Name	Reports
Liver and Biliary System (see Effects of Flecainide on Routine Laboratory Measurements page 96)	
increase in liver function tests	
no information	8
cholestasis	4
(1 with pre-existing alcoholic cirrhosis)	2
hepatitis	
chronic aggressive hepatitis	1
viral hepatitis (non A, non B)	1
jaundice and increase in liver function tests	1
Metabolic and Nutritional Disorders	1
hyperglycemia	
hyperkalemia	1
hypokalemia	1
weight increase	1
Endocrine Disorders	1
gynecomastia	
breast enlargement	4
Blood Disorders (*these were reported in detail, Safety Update 10/84)	1
*leukopenia	
(1 later determined to be secondary to acute myelomonocytic leukemia)	3
*thrombocytopenia	
(later determined to be present prior to flecainide)	1
*pancytopenia	
(later determined secondary to "pre-leukemia")	1
*agranulocytosis	
(physician retracted report without explanation, no details)	1
leukopenia	
(physicians refuse to provide details)	2
increased prothrombir time	2
Vascular Disorders	
thrombophlebitis	1
phlebitis	1
Respiratory System Disorders	
bronchospasm	1
hyperventilation	1
Urinary System Disorders	1
urinary retention	1
Body as a Whole - General Disorders	
muscular weakness	
(1 in arms and legs)	2

TABLE 32B (continued)
Post Marketing Adverse Reactions Reported in
West Germany (9/82 through 11/84)

Reaction Name	Reports
Cardiac Side Effects	
Cardiovascular Disorders General	
cardiac insufficiency	12
circulatory collapse	6
edema	5
pulmonary edema	4
negative inotropic effect	2
hypotension	1
cardiac asthma	1
cardiogenic shock	1
ECG changes	1
stroke	1
low output syndrome	1
Myocardial, Endocardial, Pericardial and Valve Disorder	
angina pectoris	4
myocardial infarct	1
Heart Rate and Rhythm Disorders	
QRS widening	22
bradycardia	19
BB block (with edema and QT prolongation, 1 case after exercise)	18
AV block	13
ventricular tachycardia	10
ventricular fibrillation	10
cardiac arrest or asystole or syncope (1 case after iv injection)	7
proarrhythmic effect	6
QT prolongation	5
AV block or bundle branch block (unspecified)	5
SA block	4
ventricular flutter	4
atrial fibrillation	2
Adams-Stokes	2
pacemaker exit block	1
extrasystoles	1
ventricular extrasystoles	1
QT widening	1
AV dissociation	1
reentry syndrome	1
repolarization disturbance	1
atrial flutter	1
sinus dysfunction	1
Deaths	
cardiac arrest	5
myocardial infarction (1 probable)	3
left cardiac insufficiency	3
ventricular tachycardia	1
cause unspecified	19

D. Dosing Rationale and Plasma Level Monitoring

The recommended starting dose of flecainide is 100 mg every 12 hours. This should be increased in increments of 50 mg bid every four days until efficacy is achieved. The maximum recommended dose is 200 mg every 12 hours for patients with sustained ventricular tachycardia. For patients with nonsustained ventricular tachycardia and PVCs, if the symptoms are not controlled at 400 mg/day and plasma level is below 0.6 µg/mL, the dosage may be cautiously increased to 600 mg/day. The four day interval allows for the attainment of steady-state plasma levels. For patients with congestive heart failure, myocardial dysfunction, or renal impairment the dose should be kept as low as possible but again the maximum dose should not exceed 200 mg every 12 hours. This section will address the following topics:

1. Starting Dose
2. Maximum Dose
3. Dose Interval
4. No Loading Dose
5. Evidence to Support a Low Starting Dose with Upward Titration
6. Therapeutic Range
7. "Therapeutic Window" (plasma level vs. effect/adverse effects)

1. Starting Dose

The initial dose of 100 mg every 12 hours was tested in the Dose-Ranging Study (030). Twenty-six percent of patients achieved greater than 80% suppression of PVCs at that dose. In the Acute and Chronic Study of Ventricular Tachycardia (057 amended), 30% of patients who entered the trial were effectively treated with 100 mg bid and discharged from the hospital on that dose.

2. Maximum Dose

Studies of VPC suppression suggested some added response to doses as high as 600 mg per day. In the Dose-Ranging Study (030) 14% of the patients required 300 mg twice-a-day in order to achieve efficacy of 80% suppression. In the Flecainide-Quinidine Comparison Study (032), 18% of patients required 300 mg twice a day, the highest dosage studied. Of the patients in the chronic studies of ventricular ectopy, after one year of therapy, 4% of patients were taking 600 mg/day, and 21% were taking 200 mg/day or less. During this year patients could be titrated upward or downward to optimize efficacy and tolerance. Therefore, it appears unlikely that higher doses would be required by a significant percentage of patients. In study

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057 amended the dose was limited to 400 mg per day and most patients received 300 mg or less with favorable effects compared to studies using larger doses. There is no documented reason to use doses above 400 mg in patients with serious arrhythmias.

3. Dose Interval

Hour-by-hour Holter monitoring data were available for 31 patients in the Dose-Ranging Study (030). During the third day of dosing, at the dose determined to be efficacious for each patient, the median percent suppression of PVCs, at each hour, remained greater than 90%; that is, there was no evidence of decreased suppression at the end of each 12-hour dosing period.

In the Dose-Ranging Study (030) after three days of receiving an efficacious dose, patients underwent a placebo washout of flecainide. Holter monitoring during the first 24 hours of washout showed that patients who were treated successfully with 100 mg bid or 200 mg bid did not show less than 80% suppression of PVCs at any hour during the 24-hour washout. Patients requiring the higher dose, 300 mg bid, began to show breakthrough of arrhythmia at about 13 hours after the last dose. These data support the use of a bid-dosing regimen.

4. Loading Dose Not Recommended

In the Package Insert the sponsor notes that a loading dose is not recommended because of the increased likelihood of adverse effects. The bases for this conclusion are:

a. Single dose Study (024) which shows that the most pronounced negative inotropic effects of flecainide occurred when plasma levels were rising most rapidly rather than when levels were highest.

b. Three of eight patients developed CHF after one to six doses of flecainide in Study 056 which used a loading dose of 200 mg every eight hours.

c. A higher incidence of cardiac adverse effects or death occurred during the first four days of therapy in patients who received an initial dose of 200 mg bid (approximately a loading dose regimen) in the Compassionate-Use Studies compared to a similar patient population in the 057 amended study who received an initial dose of 100 mg bid (10.8% versus 1%).

d. The nonloading regimen, with hospitalization and careful upward titration, proved to be practical and effective as shown by the safety and efficacy data presented for the Acute and Chronic Study of Ventricular Tachycardia (057 amended). In this study over half the patients were treated for refractory sustained ventricular tachycardia; the group of patients who might be expected to benefit most from a loading dose regimen.

5. Evidence to Support a Low Starting Dose with Upward Titration

Two study populations, the compassionate-use studies (028,057) and the Acute and Chronic Study of VT (057 amended), had similar demographic characteristics. The only discernible difference in the treatment of these two populations was the recommended flecainide dosing schedule.

In the compassionate-use studies, the recommended starting dose was 400 mg/day (200 mg bid), with upward and downward adjustments allowed at the discretion of each investigator with no time restrictions for adjustments; the maximum allowable dose was 300 mg bid.

In the Acute and Chronic Study of VT, the recommended starting dose was 200 mg/day (100 mg bid), with upward and downward adjustments allowed, but upward adjustments were made no more frequently than every 4 days; the maximum allowable dose was 400 mg/day (200 mg bid).

There is evidence that adverse experiences were more frequent when the higher dosage regimen was used. In the compassionate-use studies, the incidence of new or worsened CHF was 19%, compared with 9% in the Acute and Chronic Study of VT. Patient discontinuations due to cardiac adverse effects or sudden death within the first four days of treatment were 10.8% in the compassionate-use studies compared with 1% in the Acute and Chronic Study of VT. The incidences of the most common non-cardiac adverse experiences, dizziness and visual disturbances, were also higher in the compassionate-use studies, 23% and 25%, respectively, compared with 9% and 7% in the Acute and Chronic VT study (p less than 0.05).

6. Therapeutic Range

During the washout phase of the Dose-Ranging trial (030) the plasma level associated with the return of PVCs (to less than 80% suppression) was determined for each patient. Figure 16 displays the data from that trial showing that plasma levels ranged from a low of 0.12 ug/ml to a high of just over 1.0 ug/ml at the time that PVCs returned.

FIGURE 16

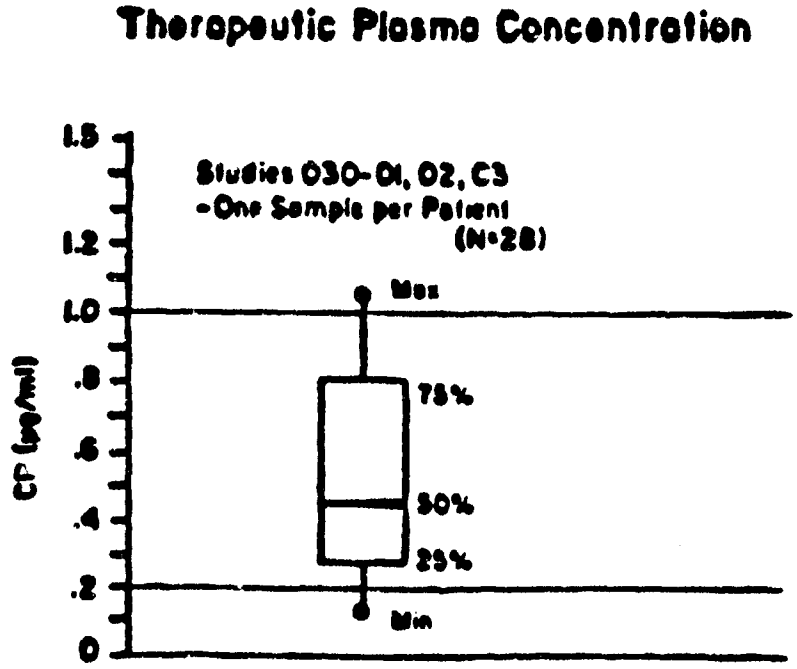
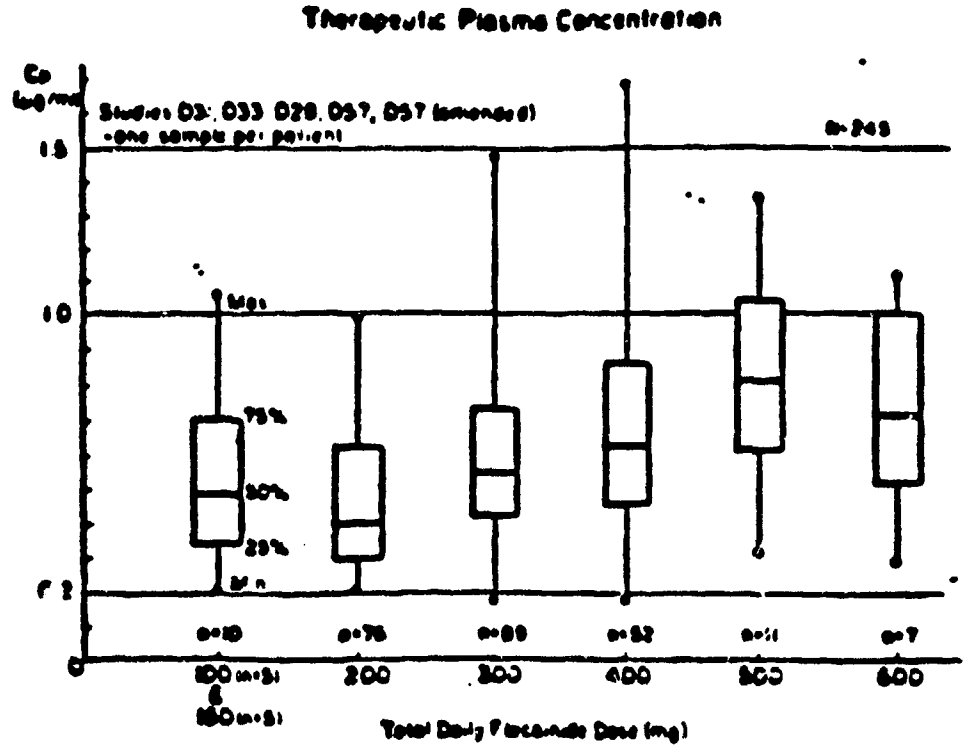


Figure 17 shows the most recent trough plasma levels obtained in 245 patients in chronic followup studies including patients with chronic stable PVCs and those with more serious heart disease and ventricular tachycardia. At each dosage level are displayed the maximum and minimum plasma levels for that group of patients. The boxes represent the 25th, 50th, and 75th percentile. Ninety percent of samples fall within the range of plasma levels of 0.2 to 1.0 ug/ml, the proposed therapeutic range. A few patients were doing well with plasma levels higher than the therapeutic range.

FIGURE 17



7. <u>"Therapeutic Window" (plasma level versus effect/adverse effects)</u>

In one institution an attempt was made to correlate plasma levels with effectiveness at suppression of PVCs and cardiac adverse experiences. Figure 18 shows data from 32 patients at one center from a variety of flecainide studies who had plasma level data available to evaluate the levels associated with suppression of PVCs ar the levels associated with cardiac adverse experiences. The two lines represent the probability of achieving 80% suppression of PVCs and the probability of developing cardiac adverse experiences, respectively, as a function of plasma level. The probability of achieving 80% suppression of PVCs rises rapidly with plasma levels in the therapeutic range, but after 1.0 ug/ml there is little increased efficacy. The probability of developing cardiac adverse experiences is low until one reaches the upper end of the therapeutic range. Above 1.0 ug/ml the probability of cardiac adverse experiences increases sharply. Therefore, it is recommended that a therapeutic plasma concentration for flecainide be considered to be between 0.2 and 1.0 ug/ml. The relevance

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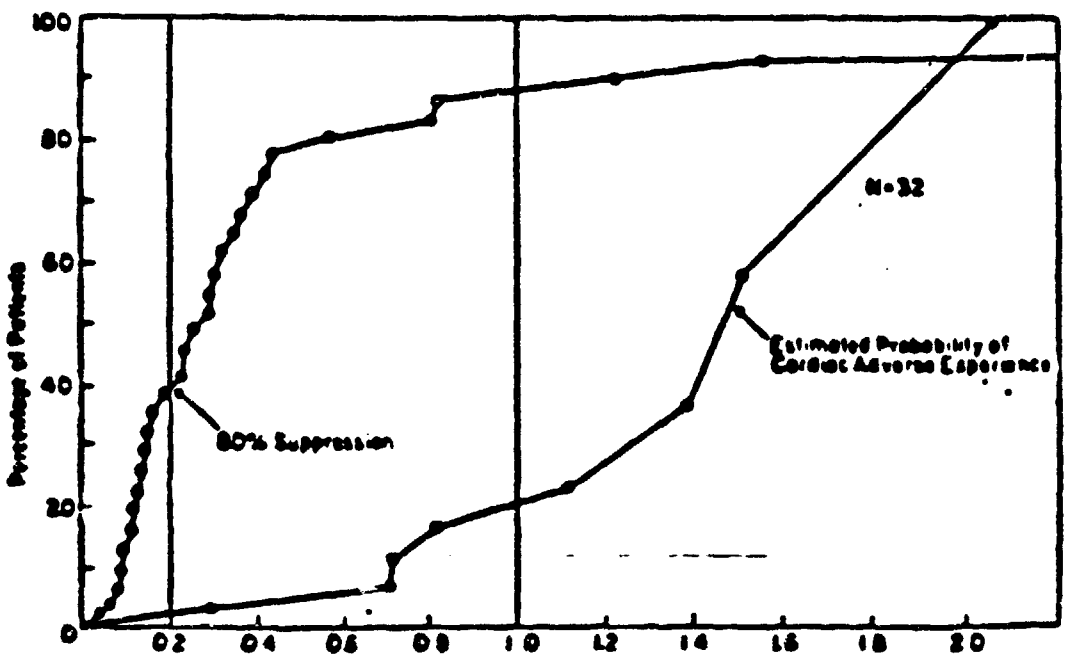
of this analysis to the recurrent VT/VF population is uncertain. It is clear, however, that the lower doses used in 057 amended were often effective; mean trough plasma levels in 31 discharged patients was 532 ng/ml suggesting that the plasma level response curve of these arrhythmias may not be greatly different from VPCs.

FIGURE 18

Efficacy and Cardiac Adverse Experiences Versus Plasma Flecainide Levels[1]



[1] Pooled - Dose Ranging Study (030), Chronic Follow-up (031)
Blinded Comparison Study (032), Chronic Follow-up (033)

VI. Pertinent Advisory Committee Minutes

On June 21, 1984, the Cardiovascular and Renal Drugs Advisory Committee reviewed flecainide and recommended approval. The committee agreed that there was sufficient evidence that flecainide was effective in suppressing PVCs, nonsustained and sustained VT.

The Committee felt that the cautionary statement regarding hepatic dysfunction related to flecainide treatment in the proposed package insert was adequate. The sponsor and FDA should monitor reports of such occurrence post-marketing and change the labeling if necessary.

The committee unanimously agreed that there was sufficient evidence regarding the hemodynamic effects of flecainide such that reasonable labeling could be written now, but requested that additional data be collected after approval in a patient population (to be defined by the FDA and sponsor) to better define the hemodynamic effects.

Since the sponsor had time to only briefly summarize concomitant medication data that were in the NDA, the committee suggested that the FDA and sponsor work out the labeling according to data available.

The committee urged the FDA to revise the indication for all antiarrhythmic drugs suggesting that they should be used only in symptomatic arrhythmias until the benefit of treating asymptomatic arrhythmias was proven.

VII. Safety Update

A. Cardiac Adverse Events

In September of 1985, the sponsor performed a cross-study analysis of several key safety issues.

A total of 1,330 patients was examined. This number includes 746 patients enrolled in studies previously discussed in the NDA, including the dose ranging study and chronic followup (030 and 031); the flecainide/quinidine comparative study and followup (032 and 033); the Rotterdam chronic efficacy and safety study (035); the compassionate use studies (028 and 057); and the acute and chronic study of ventricular tachycardia (057 amended). An additional 584 patients were enrolled in a postmyocardial infarction study (037, 10 patients); an open-label safety and efficacy study (067, 86 patients); a post marketing surveillance study (UK, 155 patients); and 333 additional patients enrolled in the 057 amended study.

Mean ± S.D. followup on all 1,330 patients was 292 ± 393 days (range, 1-1843 days; median 104 days). Mean ± SD followup on 573 ongoing patients was 506 days ± 464 days (range, 1-1843 days; median, 365 days). Followup was greater than six months for 580 patients, greater than one year for 369 patients, greater than two years for 188 patients and greater than three years for 118 patients.

Patients were first classified according to the severity of their underlying arrhythmia including 1) premature ventricular complexes only, 2) non-sustained ventricular tachycardia, and 3) sustained ventricular tachycadia. They were then further categorized by the presence or absence of structural heart disease, exposure to various dosage levels of flecainide, and in/out patient initiation of therapy. Patients were then analyzed for 1) possible or probable proarrhythmic events, 2) new or worsened congestive heart failure resulting in death or discontinuation, 3) serious conduction disturbances and 4) deaths due to cardiac and non-cardiac causes.

Table 33 shows the number of patients in each of the various categories and subgroups. Of the 1,330 patients, 470 had premature ventricular complexes only, 469 had nonsustained ventricular tachycardia and 391 patients had sustained ventricular tachycardia.

TABLE 33

PATIENTS IN DATABASE STRATIFIED FOR VARIOUS BASELINE CHARACTERISTICS AND DOSE(S) RECEIVED

	PVC ONLY	NONSUSTAINED VT	SUSTAINED VT	TOTAL
STRUCTURAL HEART DISEASE				
NO	132	64	28	224
YES	338	405	363	1,106
TOTAL	470	469	391	1,330
TOTAL DAILY DOSE[a]				
200	260	347	301	908
300	142	250	195	587
400	324	218	160	702
600	44	50	25	119
STUDY				
028/057	59	118	100	277
057, AMENDED	27	204	198	429
OUTPATIENT INITIATION OF THERAPY	273	88	15	376

[a] Patients were included more than once if exposed to multiple flecainide dosages.

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Proarrhythmic events were classified into one of three categories:

1. Those arrhythmic events that resulted in death.

2. Those events that were considered serious but nonlethal, defined as worsened ventricular arrhythmias that required immediate termination with drugs, overdrive pacing or cardioversion. If the proarrhythmic event was associated with hypotensive symptoms, it was also considered serious but nonlethal.

3. Other proarrhythmic events as judged by the investigator included those with an increase in premature ventricular complexes (using previously published criteria), new or increased frequency of nonsustained ventricular tachycardia or new ventricular arrhythmias characterized by a change in configuration or rate (of ventricular tachycardia) but which did not result in worsening of symptoms as compared with baseline.

Proarrhythmic events occurred in 6.8% of the 1,330 patients in the database. These events were serious in 2.3% of patients and lethal in 1.0%. Serious nonlethal events occurred in 6.6% of patients with sustained ventricular tachycardia, in 0.9% with nonsustained ventricular tachycardia and 0% in those with premature ventricular complexes only. Proarrhythmic death occurred in 3.1% of patients with sustained ventricular tachycardia, in 0.2% with nonsustained ventricular tachycardia, and 0% with premature ventricular complexes. Serious nonlethal proarrhythmia occurred in 2.6% of patients with underlying structural heart disease as compared to 0.4% in patients in whom this finding was absent, and death occurred in 1.2% versus 0%, respectively.

New or worsened congestive heart failure leading to study discontinuation occurred in 1.4% of the 1,330 patients, and all had underlying organic heart disease. Six (0.5%) patients died of congestive failure; all had significant myocardial dysfunction prior to flecainide initiation. Although heart failure was related to underlying organic heart disease, there was no clear relationship to dose or type of arrhythmia.

Symptomatic conduction disturbances occurred in 29 (2.2%) of the 1,330 patients. Nineteen of these 29 patients had pre-existing conduction disturbances, 20 discontinued flecainide and nine continued taking the drug, eight of whom received permanent pacemakers. The incidence of significant conduction disturbances was not related to the presence or absence of structural heart disease, severity of underlying arrhythmia, or dose of flecainide.

As previously discussed, evidence from this analysis indicated that the incidence of proarrhythmic events is related to both the presence of underlying structural heart disease and type of ventricular arrhythmia. Further, patients with sustained ventricular tachycardia in the high initial dose compassionate studies (028, 057) had twice the incidence of proarrhythmic events (26%) compared with the patients in the low initial dose study (057 amended) of ventricular tachycardia (13.1%)

Another significant finding from this analysis concerns length of time on flecainide prior to the event. It is notable that 12 of the 13 proarrhythmic deaths occurred within 14 days of flecainide initiation. Also, 23 of 30 patients (77%) who had serious nonlethal proarrhythmic events, three of six deaths due to congestive heart failure, and three of four who developed syncope due to a conduction disturbance had these events within 14 days of starting flecainide treatment.

The fact that these adverse reactions usually occur early in treatment supports the recommendation that flecainide therapy be initiated in-hospital for patients with sustained ventricular tachycardia, serious compromised left ventricular function (particularly with symptomatic congestive heart failure), sick sinus syndrome and other unstable cardiac status, such as unstable ischemia and electrolyte imbalance (particularly hypokalemia). This analysis also supports the recommendation that patients start flecainide therapy at a low dose (100 mg BID) with careful upward titration (50 mg BID) at intervals no more frequent than every four days with appropriate monitoring of efficacy and flecainide plasma levels.

B. Non-cardiac Adverse Experiences

By July 1, 1985, 429 patients had enrolled in the 057 amended study (enrollment was initiated January 1983). The incidence of reported noncardiac adverse experiences was evaluated for all 429 patients, regardless of dose, and further evaluated by dose received during upward titration (Table 34). The pattern of these adverse experiences is consistent with that previously reported.

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Table 34
Most Common Adverse Effects in Patients Treated With TAMBOCOR
in the Acute and Chronic Study of Ventricular Tachycardia

Adverse Effect	Incidence in All 429 Patients at Any Dose	Incidence by Dose During Upward Titration 200 mg/Day (N=426)	300 mg/Day (N=293	400 mg/Day (N=100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance+	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

* Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.

\+ Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

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VIII. Flecainide is an effective anti-arrhythmic agent. In studies of VPC suppression it was superior to quinidine and disopyramide, achieving 95% suppression of VPCs in 3/4 of patients in the largest study (flecainide vs quinidine, 032) and 100% suppression of paired beats and VTach beats in 70% and 79% respectively. In patients with documented VT, about half with sustained VT, who had been refractory to 3-4 other antiarrhythmic agents, flecainide was effective enough to allow hospital discharge in 73% including 59% of patients with sustained VT, with 48% free of symptomatic VT and still on drug after a mean follow-up of eight months. In 30-40% of patients with PES-inducible VT, flecainide provided complete suppression of inducibility.

Non cardiac side effects are reasonably well tolerated with dizziness and visual disturbances being the main problems each occurring in about 1/6 to 1/3 of patients. Flecainide has a negative inotropic effect, and about 14% of patients with CHF developed worse CHF; only 1% of patients developed new CHF. Flecainide caused 2^{o} or 3^{o} AV block in 10 patients (about 1%) and sinus node dysfunction/ bradycardia in 19 patients (about 1.5%). Both problems occur early in treatment, in general, and can be monitored. The pro-arrhythmic effects of flecainide, described above, are well-documented and serious and are present for patients with severe heart disease and serious arrhythmias (16.4%) and those with only PVCs (7.7%) and nonsustained VT (2.8%). While lower doses in study 057 amended seem to have reduced fatalities, an 8-10% rate for pro-arrhythmic events was still present.

Despite its pro-arrhythmic, negative inotropic and conduction-inhibiting effects, flecainide has a role in the treatment of patients with life threatening arrhythmias. With the recommended slow titration and hospital monitoring, it can be used to manage some patients not treatable with other agents with risks probably no worse than the other agents.

Although flecainide is very effective in VPC suppression, it can be recommended for this use at present only if the benefit of symptomatic relief outweighs the risks of proarrhythmia and other adverse effects, since there is no evidence that treatment of these lesser arrhythmias has a favorable effect on mortality or sudden death.

IX. Approved Package Insert:

A copy of the package insert is attached.

TAMBOCOR®
(flecainide acetate)
Tablets

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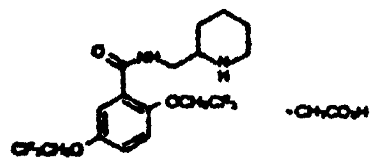
DESCRIPTION:

TAMBOCOR™ (flecainide acetate) is an antiarrhythmic drug available in tablets of 100 or 200 mg for oral administration.

Flecainide acetate is benzamide, N-(2-piperidinylmethyl)-2,5-bis (2,2,2-trifluoroethoxy)- monoacetate. The structural formula is given below.



Flecainide acetate is a white crystalline substance with a pK_a of 9.3. It has an aqueous solubility of 48.4 mg/ml at 37°C.

CLINICAL PHARMACOLOGY:

TAMBOCOR has local anesthetic activity and belongs to the membrane stabilizing (Class I) group of antiarrhythmic agents; it has electrophysiologic effects characteristic of the IC class of antiarrhythmics.

Electrophysiology. In man, TAMBOCOR produces a dose-related decrease in intracardiac conduction in all parts of the heart with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods were observed only in the ventricle. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction (see Warnings).

TAMBOCOR causes a dose-related and plasma-level-related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful 30-40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 μg/ml may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 μg/ml. Plasma levels above 0.7-1.0 μg/ml are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally.

In animals and isolated myocardium, a negative inotropic effect of flecainide has been demonstrated. Decreases in ejection fraction, consistent with a negative inotropic effect, have been observed after single administration of 200 to 250 mg of the drug in man; both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses (see Warnings).

Metabolism in Humans. Following oral administration, the absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range, 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life with steady-state levels approached in 3 to 5 days; once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one-fifth as potent) and the meta-O-dealkylated lactam of flecainide (non-active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found in urine; only 5% of an oral dose is excreted in feces. In patients, free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 μg/ml).

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. (See Dosage and Administration.)

In patients with congestive heart failure (NYHA class III), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 14 hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar. (See Dosage and Administration.)

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 μg/ml. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs (see Precautions, Drug Interactions).

INDICATIONS AND USAGE:

TAMBOCOR is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

TAMBOCOR is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of TAMBOCOR, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, TAMBOCOR, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients depending on their cardiac status and underlying cardiac disease (see Dosage and Administration).

The effects of TAMBOCOR in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including TAMBOCOR, has been shown to have a favorable effect on mortality or sudden death.

CONTRAINDICATIONS:

TAMBOCOR is contraindicated in patients with pre-existing second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Proarrhythmic Effects.

TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias.

In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. Their frequency appears to be related to dose and to the underlying cardiac disease.

Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule (see Dosage and Administration).

Patients with less serious arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal.

The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).

Heart Failure.

TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of preexisting CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg bid (see Dosage and Administration) and patients should be monitored carefully. Close attention must be given to maintenance of cardiac function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics, others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/ml.

Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose-related increases in PR, QRS, and QT intervals. PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one-third of patients may develop new first-degree AV heart block (PR interval ≥0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study, 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur, and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythmia associated with Tambocor induced QT prolongation and bradycardia.

Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block, or right bundle branch block associated with a left hemiblock occur, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes, and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally threshold changes are within the range of multiprogrammable pacemakers and, when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture.

Electrolyte Disturbances. Hypokalemia or hypomagnesemia may alter the effects of Class I antiarrhythmic agents, increasing the likelihood of proarrhythmia. These abnormalities should be corrected before administration of TAMBOCOR.

PRECAUTIONS:

Drug Interactions. TAMBOCOR has been administered to patients receiving digoxin, preparations of beta-adrenergic blocking agents without adverse effects. During administration of flecainide and closely related TAMBOCOR to healthy subjects steady-state digoxin a maintenance dose of digoxin a 13% ± 18% increase in plasma digoxin levels occurred in two weeks post-dose. In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, steady-state flecainide levels were increased about 20% and propranolol levels were increased about 22% compared to control values. In this normal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects when the drugs were administered together. No effects were detected. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive in TAMBOCOR clinical trials. Patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.

Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction.

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgment of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with relaxants or digitalis to recommend concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

Pregnancy. Pregnancy Category C. Flecainide has been shown to have teratogenic effects (cleft palate, sternebrae and vertebrae abnormalities, slide rib with cervical vertebrae fusion) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day, respectively. However, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the progress of labor, affects the duration of labor or delivery or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. It is not known whether flecainide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse effects in infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 16 years of age have not been established.

Use in Patients with Hepatic Impairment. Studies to determine the effect of hepatic impairment upon the elimination of TAMBOCOR have not yet been completed. Because the drug undergoes extensive biotransformation (most likely in the liver), patients with significant hepatic impairment should not receive TAMBOCOR unless the potential benefits clearly outweigh the risks.

ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR (described in detail in Warnings section) were new or exacerbated ventricular arrhythmias which occurred in 7% of patients and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unexplainable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest, about 1.2% all together (see Warnings). The frequency of most of these serious adverse events generally increases with higher trough plasma levels, especially when these trough levels exceed 1.0 µg/ml.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no tissue and direct relationship with TAMBOCOR has been established. In foreign post-marketing surveillance studies, there have been rare reports of hepatic obstruction, microvasculitis and hepatic failure and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects are based on a multicenter efficacy study utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this study 5.4% of patients discontinued due to non-cardiac adverse effects.

Table I

Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 429 Patients at Any Dose	Incidence by Dose During Upward Titration 200 mg/Day (N=426)	300 mg/Day (N=293)	400 mg/Day (N=100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance†	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400–600 mg/day, the incidence of these adverse experiences was similar except for dizziness (32%) and visual disturbances (28%).

The following abdominal adverse experiences, possibly related to TAMBOCOR therapy and occurring at 1% to less than 3% of patients, have been reported in acute and chronic treatment: *Body as a Whole* – malaise, fever. *Cardiovascular* – tachycardia, sinus pause or arrest. *Gastrointestinal* – vomiting, diarrhea, dysphagia, anorexia. *Skin* – rash. *Visual* – diplopia. *Nervous System* – hypokinesia, paralgesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, spontaneous tinnitus. *Psychiatric* – anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients: *Body as a Whole* – sweating, loss tongue and mouth, laryngitis, bronchospasm, laryngitis. *Cardiovascular* – angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension. *Gastrointestinal* – flatulence. *Urinary System* – polyuria, urinary retention. *Hematologic* – leukopenia, thrombocytopenia. *Skin* – urticaria, exfoliative dermatitis, pruritus. *Visual* – eye pain or irritation, photophobia, nystagmus. *Nervous System* – tinnitus, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor. *Psychiatric* – amnesia, confusion, decreased libido, depersonalization, euphoria, marked dreams, anxiety.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval; increase in the QRS duration, QT interval and amplitude of the T-wave; a reduction in myocardial rate and contractility; conduction disturbances; hypotension; and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol; mechanically assisted respiration; circulatory assists such as intra-aortic balloon pumping; and transvenous pacing in the event of conduction block. Because of the long plasma half-life of flecainide (12 to 27 hours in patients receiving usual doses), and the possibility of markedly non-linear elimination kinetics at very high doses, these supportive treatments may need to be continued for extended periods of time. Hemodialysis is not an effective means of removing flecainide from the body.

DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels in patients with normal renal and hepatic function may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, increases in dosage should be made no more frequently than once every four days, since during the first 2 to 3 days of therapy the maximal effect of a given dose may not be achieved.

For sustained ventricular tachycardia patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day, and the plasma level is below 0.6 µg/ml, the dosage may be cautiously increased to a maximum of 600 mg/day.

Use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and congestive heart failure, particularly during the first few days of dosing (see Warnings). Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients, efficacy at the lower dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction (see Warnings). The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg bid every four days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

In patients with renal impairment, the initial dosage should be 100 mg every 12 hours. Dosage increases should be made cautiously at intervals greater than 4 days, observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change. It is recommended that plasma level monitoring be used to guide dosage adjustments (see below).

Based on theoretical considerations, rather than experimental data, the following suggestion is made when transferring patients from another antiarrhythmic drug to TAMBOCOR: allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting TAMBOCOR (if at the usual dosage). In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalization for several

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 µg/ml. The probability of adverse experiences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 µg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Because elimination of flecainide from plasma may be slower in patients with severe chronic renal failure or severe congestive heart failure, plasma level monitoring may be especially helpful in these patients.

HOW SUPPLIED:

TAMBOCOR is supplied as white, round, scored tablets containing either 100 or 200 mg of flecainide acetate and embossed with RIKER on one side and TR 100 or TR 200 on the other side.

Tambocor, 100 mg/tablet, is available in:
- Bottles of 100 — NDC #0089-0307-10
- Bottles of 500 — NDC #0089-0307-50 and
- Bottles of 1000 — NDC #0089-0307-80

Tambocor, 200 mg/tablet, is available in:
- Bottles of 100 — NDC #0089-0317-10
- Bottles of 500 — NDC #0089-0317-50 and
- Bottles of 1000 — NDC #0089-0317-80

Store at controlled room temperature 15°-30°C (59°-86°F) in a tight, light-resistant container.

TR-1 OCTOBER 1985

Manufactured by
Riker Laboratories, Inc./3M
St. Paul, Minnesota 55144

NDA 18-830 TOMBOCOR (flecainide acetate) Tablets
(R-818)

Tables and Figures of Medical Review

TABLE 2: SPECIAL STUDIES

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818V-001	Drug safety & pharmacokinetics in normals	D. Hunninghake	Open	8 subjects	Single iv dose 2 @ 0.5 mg/kg over 5 min 2 @ 1.0 mg/kg over 5 min 2 @ 1.5 mg/kg over 5 min 2 @ 2.0 mg/kg over 5 min
				1 subject	1 @ 5,7.5,10,12.5 mg at 2 hour intervals

Conclusions:
The single, intravenous doses (up to 2.0 mg/kg) were well tolerated by all subjects in the study.

The relatively long plasma half-life of flecainide (mean 11 hours, range 7.3 to 14 hours) indicates that plasma drug levels will be maintained for prolonged periods; thus, flecainide is likely to provide sustained therapeutic activity and should be suitable for twice daily oral dosage during chronic treatment of cardiac arrhythmias.

R-818V-003	Safety & effect of flecainide on cardiodynamics	P. Miller	Open	12 patients	Single iv dose 4 @ 0.5 mg/kg over 5-10 min 2 @ 0.75 mg/kg over 5-10 min 3 @ 1.0 mg/kg over 5-10 min 3 @ 1.5 mg/kg over 5-10 min

Conclusions:
A sustained reduction in cardiac output and an increase in peripheral resistance was observed after flecainide administration. Because of the small number of patients, insufficient duration of hemodynamic observations and lack of appropriate baseline measurements, no further conclusions can be drawn about the extent of cardiodynamic effects produced by the drug in this study.

The only side effects reported by the investigator were difficulty voiding urine and hypotension. The investigator was uncertain whether these side effects were related to flecainide administration.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818V-005	Determine rate & extent of absorption of flecainide. Obtain pharmacokinetic data, assess safety & tolerance.	G. Lewis	Open	16 subjects	Single oral & iv doses 4 @ 60 mg oral, 7 days later 60 mg iv 4 @ 120 mg oral, 7 days later 120 mg iv 4 @ 180 mg oral, 6 weeks later 200 mg oral 4 @ 240 mg oral only

Conclusions:
The plasma level data indicate that flecainide is promptly and extensively absorbed from the capsule formulation and that the drug does not undergo extensive biotransformation in man during absorption or on the first pass through the liver after absorption. The plasma half-life data confirm that flecainide disappearance from plasma is relatively slow in man. From a pharmacokinetic viewpoint, these oral absorption and plasma elimination properties of flecainide demonstrate that the drug is well suited for oral, chronic, treatment of cardiac arrhythmias with twice daily dosage.

The single, oral doses (up to 240 mg or 3.53 mg/kg) and the single, intravenous doses (up to 120 mg or 1.70 mg/kg) were well tolerated by all subjects in the study.

R-818V-015	Effect of flecainide on intracardiac conduction system & sinus node function when administered as a single intravenous dose	R. Helfant	Open	15 patients	Single iv doses of 1.0 mg/kg administered over 5-10 min

Conclusions:
Flecainide administration lengthened the conduction intervals (PA, A-H, and H-V), but only demonstrated a statistically significant increase in the H-V and A-H intervals at 20 minutes postdosing. Flecainide had no significant effect on sinus node function.

TABLE 2 : SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-018	Determine plasma levels of flecainide during seven days of oral dosing. Assess multiple-dose pharmacokinetics of flecainide. Determine safety & tolerance of multiple oral doses of flecainide in subjects	G. Lewis	Open	16 subjects	Seven days of therapy 4 @ 80 mg bid 4 @ 120 mg bid 4 @ 150 mg bid 4 @ 180 mg bid

Conclusions:
The plasma level data during multiple oral dosage directly confirm that (consistent with its relatively long plasma half-life) flecainide predictably accumulates in plasma to steady-state levels within a few days; these data confirm that flecainide, from a pharmacokinetic viewpoint, is well suited for twice daily oral dosage for the chronic treatment of cardiac arrhythmias.

The plasma half-life data (for the first and final doses) indicate that multiple oral dosing (up to 180 mg bid) for seven days has no consistent or substantial influence on the rate of flecainide elimination from human plasma (no apparent induction or inhibition of drug elimination processes). The plasma pharmacokinetics of flecainide appear to be independent of dose and to be reasonably linear over a range in multiple oral dosage regimens of 1.1 to 2.8 mg/kg bid. The plasma half-life data are in agreement with previous data for male subjects. This further confirms the relatively long half-life of flecainide in man.

Flecainide was well tolerated by all subjects after single oral doses and during multiple oral dosing regimens (up to 180 mg bid) for seven days. Minor increases in the PR interval were the only electrocardiographic changes observed during the study. Side effects were minor and transient.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818V-022	Determine the effect of intravenous flecainide on right and left ventricular performance using radionuclide angiography in patients with suspected or diagnosed heart disease	R. Helfant M. Bodenheimer	Open	20 patients	Single iv dose 4 @ 1.0 mg/kg over 5-13 min 5 @ 1.5 mg/kg over 5-13 min 10 @ 2.0 mg/kg over 5-13 min 1 @ 0.7 mg/kg over 5-13 min

Conclusions:
The investigator made the following conclusion in his report. "These data support the conclusion that at doses of 1.0 and 1.5 mg/kilogram, flecainide administered intravenously has a minimal effect on normal right and normal left ventricular function. However, if a baseline abnormality is present, there is a tendency for deterioration, particularly in the abnormal segment to occur. After the administration of 2.0 mgs/kilo approximately one half the patients including those with initially normal right or left ventricular function showed deterioration in both global and regional contraction. Thus, there is the potential for an adverse effect on both regional and left ventricular function if higher doses, that is 2.0 mgs/kilogram of flecainide is required. However, while deterioration in left and right ventricular function was detected, there was no apparent adverse effect on systemic pressure, i.e. systolic or diastolic blood pressure or heart rate."

The sponsor concurs, and adds that these data support previous findings of some negative inotropic effect of flecainide. It is difficult to characterize the magnitude of this effect because it varies from patient to patient. In most patients who received the highest dose (2.0 mg/kg), flecainide produced less than a 10% decrease in left ventricular ejection fraction. However, a few patients may experience larger decrements in myocardial performance; therefore, flecainide should be administered cautiously in patients with a history suggesting borderline or compromised myocardial status.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818V-023	To compare the effects of flecainide & vehicle on left ventricular function using catheter tip sensors in patients with suspected or diagnosed left ventricular disease.	M. Hodges	Double-blind, vehicle-controlled, parallel study	2 patients	Single iv dose 2.0 mg/kg over 5 min

Conclusions:
Study terminated because of difficulties in recruiting patients. Because only one patient received flecainide in this study, no conclusions can be drawn about the effects of intravenous flecainide on left ventricular function. No adverse experiences were reported in this patient.

R-818-024	Compare the effects of oral flecainide and placebo on left ventricular function using non-invasive techniques.	M. Hodges	Double-blind, placebo-controlled, two-period, crossover	10 subjects 20 patients	Single oral dose 250 mg

Conclusions:
Flecainide depresses myocardial contractility to a slight degree, but overall left ventricular pump function is maintained.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-026	Compare relative rate & extent of flecainide absorption between a tablet & capsule formulation.	G. Lewis	Open, randomized two-period crossover	17 subjects entered 16 subjects completed	Single dose 200 mg of each formulation

Conclusions:
The plasma level data indicate that flecainide absorption from the wet granulation tablet is essentially complete and that absorption is prompt and reasonably comparable in rate to the capsule. From a drug absorption point of view, this tablet appears acceptable for clinical use.

The plasma half-life data are in good agreement with previous data for male subjects and further confirm the relatively long half-life of flecainide in man.

The 200 mg doses of flecainide (both tablets and capsules) were well tolerated by all subjects in the study.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-038	Determine effect of chronic renal impairment on flecainide elimination. Assess influence of hemodialysis on flecainide elimination. Determine if dosage adjustments are necessary in this patient population.	R. Cutler	Open	10 patients with varying degrees of chronic moderate renal failure. 10 patients with end stage renal disease	Single oral dose 200 mg

Conclusions:
Flecainide absorption (rate and extent) in renal patients appears to be comparable to that in healthy subjects and is reasonably prompt and essentially complete. However, the rate of flecainide elimination from plasma may be slower in some patients with more severe impairment of renal function and the extent of excretion in urine and the renal clearance of unchanged flecainide are both markedly lower in patients with end stage renal disease. For these reasons and because metabolites of flecainide may possibly accumulate in plasma of these patients with multiple dosage, an adjustment downward in drug dosage should be made for renal patients with creatinine clearances, conservatively, of 20 ml/min/m^2 or less; initial dosage regimens should be decreased by 25% to 50% and patients should be closely monitored for tolerance.

Hemodialysis does not appear to be an effective means for removal of flecainide from the body.

The single, 200 mg oral dose of flecainide was well tolerated by all patients. No drug-related side effects were reported.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-039	Pharmacokinetics & cardiodynamics of flecainide in healthy subjects & in patients with congestive heart failure.	J. Franciosa	Open	9 subjects 10 patients	Single oral dose 200 mg

Conclusions:
No detrimental effects on cardiac function or exercise performance were noted following a single, 200 mg oral dose of flecainide in either patients with congestive heart failure or in age- and weight-matched subjects free of cardiac disease. No major effects on mean arterial blood pressure or systemic vascular resistance, resting or exercising, were produced in either group. Small, but statistically significant, effects on ECG intervals were produced by the drug.

Congestive heart failure did not appear to alter either the rate or extent of flecainide absorption. However, the rate of flecainide elimination from plasma was somewhat slower in CHF patients than in subjects. No relationship existed between cardiac index (baseline resting) and either plasma half-life or plasma clearance. The extent of urinary excretion of unchanged flecainide was equivalent in CHF patients and aged-matched subjects. Although mean renal drug clearance was lower in patients than subjects, the difference was not statistically significant; renal clearance accounted for the same proportion of total body (plasma) clearance in both groups.

Based on cardiodynamic and pharmacokinetic data from this single dose study, only modest downward adjustments, if any, in initial flecainide dosage regimens for patients with CHF appear to be indicated. Such results, however, may not be predictive of those from continuous administration of flecainide, and downward adjustments in dose may be required in patients with left ventricular dysfunction as dictated in individual cases.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-039	Pharmacokinetics & cardiodynamics of flecainide in healthy subjects & in patients with congestive heart failure.	J. Franciosa	Open	9 subjects 10 patients	Single oral dose 200 mg

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TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-041	Effects of oral flecainide & propranolol administered alone & concurrently on cardiac function in healthy male subjects.	J. Holtzman	Open	10 subjects	Total of nine days of flecainide 200 mg bid; Total of twelve days of propranolol, 80 mg q8h

Conclusions:
Individually, both propranolol and flecainide demonstrated mild negative inotropic effects which were frequently additive when the drugs were coadministered; none of the interactions were synergistic even though plasma levels for each drug were slightly increased.

R-818-045	Effects of flecainide on plasma digoxin levels when given concurrently to subjects.	G. Lewis	Open	17 subjects entered 15 subjects completed	Five days of flecainide, 200 mg bid; Twenty-two days of digoxin, 0.25 mg

Conclusions:
During coadministration of flecainide to healthy, adult male subjects stabilized on a maintenance dose of digoxin, only a small, but at some times statistically significant, increase in plasma digoxin levels occurred. The magnitude of these changes in digoxin levels with flecainide is markedly less than that found for quinidine and, for flecainide, should be of no clinical significance for patients receiving chronic digoxin therapy.

Plasma flecainide levels were found to be within the range associated with suppression of PVCs. No significant changes were observed between prestudy and poststudy clinical evaluations. Transient changes in ECGs were noted; these were characteristic of those produced previously by flecainide (increased PR intervals) or digoxin alone ("digitalis effect"; ie, increased PR, sloping of the ST segment). No safety problems were encountered in this study due either to digoxin alone or to digoxin-flecainide coadministration.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-049	Comparative oral absorption of three flecainide dosage formulations & the effect of food on drug absorption.	A. Cohen	Open, randomized three-period crossover plus 4th period with food	25 subjects entered 18 subjects completed	Single oral dose 200 mg of each formulation; 200 mg as tablet with food

Conclusions:
The relative bioavailability of flecainide from the final tablet formulation was comparable to that from a reference solution; no statistically significant difference was seen in either the rate or extent of absorption.

The capsule formulation showed a comparable extent of flecainide absorption relat that from the solution (and tablet), but demonstrated a significantly slower rate flecainide absorption. The difference in the absorption rate between tablet and capsule should be of no clinical consequence. Similar mean steady-state plasma levels would be expected for both formulations, because they both deliver the same amount of drug to the systemic circulation. A slightly lower peak-trough fluctuation in plasma levels would be predicted for the capsule based on its slower rate of absorption.

Absorption of flecainide from the capsule formulation was compared previously to an intravenous dose in study R-818V-005-01. The capsule was shown to provide nearly complete absorption. Thus, it can be concluded from the similarity of the AUC values in the present study that the extents of flecainide absorption from the tablet and solution were also nearly complete.

When the tablet was administered with a meal, both the rate and extent of flecainide absorption were essentially equivalent to those seen under fasting conditions.

No significant changes were observed between prestudy and poststudy clinical evaluations. No safety problems were encountered in this study due to flecainide administration witn any of the three dosage formulations.

TABLE 2: **SPECIAL STUDIES (Continued)**

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-049	Comparative oral absorption of three flecainide dosage formulations & the effect of food on drug absorption.	A. Cohen	Open, randomized three-period crossover plus 4th period with food	25 subjects entered 18 subjects completed	Single oral dose 200 mg of each formulation; 200 mg as tablet with food

Conclusions:
The relative bioavailability of flecainide from the final tablet formulation was comparable to that from a reference solution; no statistically significant difference was seen in either the rate or extent of absorption.

The capsule formulation showed a comparable extent of flecainide absorption relative to that from the solution (and tablet), but demonstrated a significantly slower rate of flecainide absorption. The difference in the absorption rate between tablet and capsule should be of no clinical consequence. Similar mean steady-state plasma levels would be expected for both formulations, because they both deliver the same amount of drug to the systemic circulation. A slightly lower peak-trough fluctuation in plasma levels would be predicted for the capsule based on its slower rate of absorption.

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When the tablet was administered with a meal, both the rate and extent of flecainide absorption were essentially equivalent to those seen under fasting conditions.

No significant changes were observed between prestudy and poststudy clinical evaluations. No safety problems were encountered in this study due to flecainide administration with any of the three dosage formulations.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-050-03	Metabolic disposition of carbon-14 labeled flecainide.	A. Cohen	Open	4 subjects	Single oral dose 200 mg ^{14}C-labeled flecainide

Conclusions:
Flecainide absorption is prompt and essentially complete following oral dosage. Flecainide and its metabolites are extensively eliminated in urine (about 85% of the dose); only about 5% of the dose is accounted for in feces. On the average, about half of the carbon-14 excreted in urine is accounted for as unchanged flecainide. Much of the remainder of the carbon-14 in urine is accounted for by two major metabolites, one of which is meta-O-dealkylated flecainide; the other metabolite has been identified as 5-hydroxy-N-[2-(6-oxopiperidylmethyl)]-2-(2',2',2'-trifluoroethoxy)-benzamide. Meta-O-dealkylated flecainide exists in urine in both the free and conjugated forms, but is found primarily as the conjugate. On the average, total meta-O-dealkylated flecainide (free and conjugated) in urine accounts for about 14% of the dose. Based upon the previously reported TLC analyses, the other major urinary metabolite represents about the same fraction of the dose as meta-O-dealkylated flecainide and is also found primarily in its conjugated form.

Thus, flecainide undergoes extensive biotransformation in humans and both unchanged flecainide and its metabolites are primarily excreted in urine. In addition, flecainide does not undergo extensive biliary excretion in humans, unless reabsorption occurs after biliary elimination. Also, metabolites of flecainide are present in human plasma and the rate of elimination of total metabolites from plasma is only somewhat slower than that for unchanged drug.

The single, 200 mg oral dose of flecainide was well tolerated by all subjects.

TABLE 2 : SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-054-01	Effects of iv flecainide on left ventricular function (invasive).	B. Singh	Double-blind, randomized, vehicle-controlled, parallel study	18 patients	Single iv dose 6 @ 1.0 mg/kg over 5 min 6 @ 2.0 mg/kg over 5 min 6 on vehicle over 5 min

Conclusions:
Flecainide administered intravenously in doses up to 2.0 mg/kg over five minutes produces a mild transient negative inotropic effect.

R-818-054-02	Effects of iv flecainide on left ventricular function (invasive).	P. Troup	Double-blind, randomized, vehicle-controlled parallel study	2 patients	Single iv dose 1 @ 1.9 mg/kg over 5 min

Conclusions:
Because only one patient received flecainide in this study, no conclusions can be drawn about the effects of intravenous flecainide on left ventricular function. No adverse experiences were reported for either patient.

TABLE 3: PIVOTAL STUDIES
(R-818-030 and R-818-032)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients	Average Age	Duration of Flecainide Therapy & Dose(s)	Results
030-01	Dose ranging & safety & efficacy in treating chronic PVCs	J. Anderson	Single-Blind Dose Ranging followed by open efficacy/ safety study	14 entered[a] 12 qualified 9 completed	55	Dose Ranging with pre & post placebo washout periods: 3 days/dose (doses 100, 200, 250 mg bid). Efficacy: 2 weeks at effective dose	Dose Ranging - Median effective dose - 200 mg bid. Efficacy on average greater than 90% suppression during outpatient therapy.
030-02	Dose ranging & safety & efficacy in treating chronic PVCs	M. Hodges	Single-Blind Dose Ranging followed by open efficacy/ safety study	12 entered 12 qualified 10 completed	56	Dose Ranging with pre & post placebo washout periods: 3 days/dose (doses 100, 200, 300 mg bid). Efficacy: 2 weeks at effective dose	Dose Ranging - Median effective dose - 200 mg bid. Efficacy on average greater than 90% suppression during outpatient therapy.
030-03	Dose ranging & safety & efficacy in treating chronic PVCs	R. Woosley	Single-Blind Dose Ranging followed by open efficacy/ safety study	11 entered 11 qualified 11 completed	51	Dose Ranging with pre & post placebo washout periods: 3 days/dose (doses 100, 200, 250 mg bid). Efficacy: 2 weeks at effective dose	Dose Ranging - Median effective dose - 200 mg bid. Efficacy on average greater than 90% suppression during outpatient therapy.

Conclusions: Over all three centers, the mean percent suppression of baseline PVCs was 96.1% at the effective dose during dose ranging. The mean suppression during the outpatient phase was greater than 94%. For multiple PVCs (PVCs that occur in pairs, triplets, or runs of four or more), the mean suppression was 98.2% at effective dose during dose ranging and was greater than 96% during the outpatient phase. The most frequently reported adverse experiences were lightheadedness, constipation, blurred vision, sleepiness, itchiness, dizziness and nervousness.

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[a] On this table the word "entered" refers to patients who received at least one dose of active therapy.

TABLE 3: PIVOTAL STUDIES (Continued)

Protocol	Study Purpose	Study Design	Reference Drug	Patients: Flecainide N	Flecainide Average Age	Patients: Quinidine N	Quinidine Average Age	Duration of Therapy	Results: Median Percent Suppression of PVCs: Flecainide	Results: Median Percent Suppression of PVCs: Quinidine
032-01 B. Beller	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	10 entered[a] 10 qualified 10 completed	61	9 entered 9 qualified 8 completed	53	Two weeks. 200 mg bid F or 300 mg qid Q 1st week; same in 2nd week if effective in first week; otherwise 300 mg bid F or 400 mg qid Q	99.1	86.0
032-02 M. Hodges	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	12 entered 11 qualified 9 completed	63	14 entered 11 qualified 10 completed	66	Two weeks. 200 mg bid F or 300 mg qid Q 1st week; same in 2nd week if effective in first week; otherwise 300 mg bid F or 400 mg qid Q	98.5	79.2
032-03 W. Cook	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	4 entered 2 qualified 1 completed	69	4 entered 4 qualified 1 completed	64	Two weeks. 200 mg bid F or 300 mg qid Q 1st week; same in 2nd week if effective in first week; otherwise 300 mg bid F or 400 mg qid Q	100	100
032-04 J. Farnham J. Morledge	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	10 entered 7 qualified 4 completed	49	10 entered 7 qualified 4 completed	61	Two weeks. 200 mg bid F or 300 mg qid Q 1st week; same in 2nd week if effective in first week; otherwise 300 mg bid F or 400 mg qid Q	99.9	79.6

[a] On this table the word "entered" refers to patients who received at least one dose of active therapy.

TABLE 3: PIVOTAL STUDIES (Continued)

Protocol	Study Purpose	Study Design	Reference Drug	Patients: Flecainide N	Flecainide Average Age	Patients: Quinidine N	Quinidine Average Age	Duration of Therapy	Results: Median Percent Suppression of PVCs: Flecainide	Results: Median Percent Suppression of PVCs: Quinidine
032-05 W. Hart	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	13 entered[a] 12 qualified 10 completed	64	12 entered 11 qualified 10 completed	60	Two weeks. 200 mg bid F or 300 mg qid Q 1st week; same in 2nd week if effective in first week; otherwise 300 mg bid F or 400 mg qid Q	99.9	83.8
032-06 R. Kalmonsohn	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	9 entered 8 qualified 5 completed	70	6 entered 5 qualified 5 completed	69	Two weeks. 200 mg bid F or 300 mg qid Q 1st week; 200 mg week 2 if effective in first week; otherwise 300 mg bid F or 400 mg qid Q	99.5	76.6
032-07 J. Laidlaw	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	14 entered 11 qualified 11 completed	63	13 entered 12 qualified 9 completed	69	Two weeks. 200 mg bid F or 300 mg qid Q 1st week; 200 mg week 2 if effective in first week; otherwise 300 mg bid F or 400 mg qid Q	98.2	97.4
032-08 G. Lee R. Low	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	14 entered 13 qualified 10 completed	47	13 entered 12 qualified 9 completed	56	Tow weeks. 200 mg bid F or 300 mg qid Q 1st week; 200 mg week 2 if effective in first week; otherwise 300 mg bid F or 400 mg qid Q	100	80.6

[a] On this table the word "entered" refers to patients who received at least one dose of active therapy.

TABLE 3: PIVOTAL STUDIES (Continued)

Protocol	Study Purpose	Study Design	Reference Drug	Patients: Flecainide [a]	Flecainide Average Age	Patients: Quinidine	Quinidine Average Age	Duration of Therapy	Results: Median Percent Suppression of PVCs: Flecainide	Quinidine
032-09 G. Lewis	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	12 entered[b] 8 qualified 8 completed	46	11 entered 9 qualified 9 completed	48	Two weeks. 200 mg bid F or 300 mg qid Q 1st week; 200 mg week 2 if effective in first week; otherwise 300 mg bid F or 400 mg qid Q	94.4	84.4
032-10 A. Antlitz	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	7 entered 6 qualified 4 completed	51	5 entered 1 qualified 1 completed	51	Two weeks. 200 mg bid F or 300 mg qid Q 1st week; 200 mg week 2 if effective in first week; otherwise 300 mg bid F or 400 mg qid Q	100	68.0
032-11 F. Marcus	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	5 entered 4 qualified 3 completed	55	5 entered 5 qualified 3 completed	60	Two weeks. 200 mg bid F or 300 mg qid Q 1st week; 200 mg week 2 if effective in first week; otherwise 300 mg bid F or 400 mg qid Q	73.7	62.7
032-12 J. Morganroth	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	14 entered 14 qualified 12 completed	63	13 entered 13 qualified 12 completed	59	Two weeks. 200 mg bid F or 300 mg qid Q 1st week; 200 mg week 2 if effective in first week; otherwise 300 mg bid F or 400 mg qid Q	98.9	85.7

[a] Includes one patient from the quinidine group who received flecainide by accident during second week of active drug therapy.

[b] On this table the word "entered" refers to patients who received at least one dose of active therapy.

TABLE 3: PIVOTAL STUDIES (Concluded)

Protocol	Study Purpose	Study Design	Reference Drug	Patients: Flecainide N	Flecainide Average Age	Patients: Quinidine N	Quinidine Average Age	Duration of Therapy	Results: Median Percent Suppression of PVCs: Flecainide	Results: Median Percent Suppression of PVCs: Quinidine
032-13 C. Oshrain	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	14 entered[a] 11 qualified 10 completed	66	14 entered 14 qualified 13 completed	53	Two weeks. 200 mg bid P or 300 mg qid Q 1st week; 200 mg week 2 if effective in first week; otherwise 300 mg bid P or 400 mg qid Q	99.7	84.4
032-14 P. Reid	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	9 entered 9 qualified 9 completed	59	10 entered 10 qualified 5 completed	48	Two weeks. 200 mg bid P or 300 mg qid Q 1st week; 200 mg week 2 if effective in first week; otherwise 300 mg bid P or 400 mg qid Q	98.3	92.0
032-16 B. Alter	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	5 entered 4 qualified 4 completed	47	7 entered 4 qualified 4 completed	56	Two weeks. 200 mg bid P or 300 mg qid Q 1st week; 200 mg week 2 if effective in first week; otherwise 300 mg bid P or 400 mg qid Q	100	41.5
032-17 M. Platt B. Rosin	Comparative safety & efficacy of flecainide & quinidine in treating chronic PVCs, paired premature beats, and V-tachycardia	Double-blind randomized parallel comparison	Quinidine	14 entered 11 qualified 9 completed	60	14 entered 12 qualified 11 completed	65	Two weeks 200 mg bid For 300 mg qid Q 1st week; 200 mg week 2 if effective in first week; otherwise 300 mg bid For 400 mg qid Q	99.9	80.0
Overall results across 16 centers				141	59	139	58		99.5 P<0.0001	84.7

Conclusions: Flecainide, when compared to quinidine, is a more effective antiarrhythmic drug for suppressing ventricular arrhythmias, has a clinically acceptable side effect profile and incidence and favors patient compliance by a twice-a-day dosing schedule.

[a] On this table the word "entered" refers to patients who received at least one dose of active therapy.

TABLE 4: OTHER CONTROLLED STUDIES

Protocol	Condition Studied	Study Design	Reference Drug	Number of Patients	Average Age	Duration of Therapy & Dose(s)
R-818-019-01 E. Thompson	Chronic PVCs	Open-label multiple dose safety & efficacy	None	20	61	One day 8 Patients 120 mg single dose 4 Patients 180 mg total daily dose 8 Patients 240 mg total daily dose

Conclusions:
The antiarrhythmic effects of flecainide were demonstrated for PVCs in three of seven patients with usable data in this trial. Potential negative inotropic effects may have been demonstrated in two patients.

R-818-019-02 S. Oh	Chronic PVCs	Open-label multiple dose safety & efficacy	None	20	48	One day 2 Patients 120 mg single dose 18 Patients 240 mg total daily dose

Conclusions:
Out of the seven patients with usable data, flecainide appeared to demonstrate antiarrhythmic effect in the two patients who had sufficient numbers of baseline premature ventricular contractions for comparison and one patient with paroxysmal atrial tachycardia.

R-818-019-04 P. Somani A. Miller	Chronic PVCs	Open-label, multiple dose safety & efficacy	None	20	60	One day 5 Patients 120 mg single dose 1 Patient 180 mg total daily dose 14 Patients 240 mg total daily dose

Conclusions:
All 12 patients who met the PVC inclusion criteria demonstrated suppression of their PVCs. One of three patients with atrial fibrillation converted to normal sinus rhythm after receiving flecainide. One patient with episodic ventricular tachycardia did not respond to flecainide.

TABLE 4 : OTHER CONTROLLED STUDIES (Concluded)

Protocol	Condition Studied	Study Design	Reference Drug	N	Patients Average Age	Duration of Therapy & Dose(s)	Results Median Percent Suppression Flecainide	Disopyramide
R-818-060 O. Orning (N-02)	Chronic PVCs	Randomized	Disopyramide double-blind crossover	32 entered 26 completed 25 analyzed	53	14 days Flecainide 200 mg bid Disopyramide 150 mg qid	92%	39% P<0.002

Conclusions:
Flecainide, at a dose of 400 mg/day was superior to disopyramide 600 mg/day in the suppression of simple ventricular ectopic contractions and more complex arrhythmic events. Tolerance was generally good and no differences emerged between the two drugs in the incidence or severity of reported adverse effects.

TABLE 5: CHRONIC-DOSING STUDIES

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Duration of Therapy & Dose(s)
031-01	Chronic PVCs	J. Stewart	Open, long-term safety & efficacy	8	6	Treated one year, Total daily doses 400, 500, 600 mg
031-02	Chronic PVCs	M. Hodges	Open, long-term safety & efficacy	10	9	Treated one year, Total daily doses 200, 300, 400, 600 mg
031-03	Chronic PVCs	R. Woosley	Open, long-term safety & efficacy	11	9	Treated one year, Total daily doses 200, 300, 400, 500, 600 mg
Overall for the 3 Centers	Chronic PVCs		Open, long-term safety & efficacy	29	24	Treated one year, Total daily doses 200, 300, 400, 500, 600 mg

Conclusions: Of 29 patients who enrolled in this study, 24 patients (83%) completed at least one year of long-term therapy, and efficacy evaluation showed a greater than 90% average suppression of both PVCs and multiple PVCs in these patients. Most patients were maintained on a bid dosing schedule and several on a tid schedule, with a median total daily dose by month 12 of 400 mg.

Evidence from this study suggests that blurred vision, accompanied by dizziness in some cases, is probably related to flecainide administration. Lengthening occurred in ECG interval times (most notably PR and QRS), but there were no progressive increases over time, and no patients discontinued for this reason. No trends were evident in blood pressure, pulse, or respiration rate. There were no clinically important changes in laboratory values observed in any patient or across the patient population which would indicate intolerance (or toxicity) to flecainide.

Thus, flecainide continued to be highly effective in suppressing ventricular arrhythmias, without limiting side effects, in 24 patients who completed at least one year of long-term therapy.

TABLE 5 : CHRONIC-DOSING STUDIES (Continued)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
033-01	Chronic PVCs	B. Beller	Open, long-term safety & efficacy	18	14	Flecainide 100, 150, 200, 300, 400, 500, 600
033-02	Chronic PVCs	M. Hodges	Open, long-term safety & efficacy	21	14	Flecainide 200, 300, 350, 400, 450, 500
033-03	Chronic PVCs	W. Cook	Open, long-term safety & efficacy	4	2	Flecainide 100, 150, 200, 300, 400
033-04	Chronic PVCs	J. Farnham	Open, long-term safety & efficacy	10	9	Flecainide 100, 150, 200, 300, 400
033-05	Chronic PVCs	W. Hart	Open, long-term safety & efficacy	20	15	Flecainide 200, 300, 400, 500
033-06	Chronic PVCs	R. Kalmansohn	Open, long-term safety & efficacy	F 9 Q 1	7[b] 0	Flecainide 200, 400 Quinidine 1200

[a]Also known as R-818-EN-03.

[b]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to adverse experiences.

TABLE 5: CHRONIC-DOSING STUDIES (Continued)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
033-07	Chronic PVCs	J. Laidlaw	Open, long-term safety & efficacy	F 16 Q 5	12[b] 5[c]	Flecainide 200, 300, 400, 500, 600 Quinidine 800, 1200
033-08	Chronic PVCs	G. Lee	Open, long-term safety & efficacy	F 11 Q 3	11 1	Flecainide 300, 400, 500, 600 Quinidine 1000, 1200, 1600
033-09	Chronic PVCs	G. Lewis	Open, long-term safety & efficacy	8	6	Flecainide 200, 300, 400
033-10	Chronic PVCs	A. Antlitz	Open, long-term safety & efficacy	F 3 Q 1	3 1	Flecainide 300, 400 Quinidine 1200
033-11	Chronic PVCs	F. Marcus	Open, long-term safety & efficacy	F 7 Q 1	6 1	Flecainide 100, 200, 400 Quinidine 1200

[a]Also known as R-818-EN-03.
[b]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to lack of therapeutic affect.
[c]Number ongoing on quinidine includes one patient who entered study on flecainide and was changed to quinidine due to adverse experiences and lack of therapeutic effect.

TABLE 5: CHRONIC-DOSING STUDIES (Continued)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
033-12	Chronic PVCs	J. Morganroth	Open, long-term safety & efficacy	9	5	Flecainide 200, 300, 400, 500, 600
033-13	Chronic PVCs	C. Oshrain	Open, long-term safety & efficacy	F 16 Q 3	13[b] 2	Flecainide 200, 300, 400 Quinidine 1200, 1600
033-14	Chronic PVCs	P. Reid	Open, long-term safety & efficacy	F 17 Q 2	16 2	Flecainide 200, 250, 300, 350, 400, 500, 600 Quinidine 1200, 1600
033-16	Chronic PVCs	B. Alter	Open, long-term safety & efficacy	4	2	Flecainide 200, 300, 400
033-17	Chronic PVCs	M. Platt B. Rosin	Open, long-term safety & efficacy	F 21 Q 1	17[c] 0	Flecainide 100, 150, 200, 300, 400 Quinidine 1200
Overall Results				F 194 Q 17	F 152 Q 12	

Conclusions: Flecainide remains effective with an acceptable side effect profile and incidence when used chronically in an outpatient population of patients with ventricular arrhythmias requiring antiarrhythmic therapy.

---

[a]Also known as R-818-[illegible]

[b]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to adverse experiences.

[c]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to lack of therapeutic effect.

TABLE 5: CHRONIC-DOSING STUDIES (Continued)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
033-12	Chronic PVCs	J. Morganroth	Open, long-term safety & efficacy	9	5	Flecainide 200, 300, 400, 500, 600
033-13	Chronic PVCs	C. Oshrain	Open, long-term safety & efficacy	F 16 Q 3	13[b] 2	Flecainide 200, 300, 400 Quinidine 1200, 1600
033-14	Chronic PVCs	P. Reid	Open, long-term safety & efficacy	F 17 Q 2	16 2	Flecainide 200, 250, 300, 350, 400, 500, 600 Quinidine 1200, 1600
033-16	Chronic PVCs	B. Alter	Open, long-term safety & efficacy	4	2	Flecainide 200, 300, 400
033-17	Chronic PVCs	M. Platt B. Rosin	Open, long-term safety & efficacy	F 21 Q 1	17[c] 0	Flecainide 100, 150, 200, 300, 400 Quinidine 1200
Overall Results				F 194 Q 17	F 152 Q 12	

Conclusions: Flecainide remains effective with an acceptable side effect profile and incidence when used chronically in an outpatient population of patients with ventricular arrhythmias requiring antiarrhythmic therapy.

---

[a]Also known as R-818-EN-03.

[b]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to adverse experiences.

[c]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to lack of therapeutic effect.

TABLE 5 : CHRONIC-DOSING STUDIES (Concluded)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
R-818-035-01	Chronic PVCs	P. Hugenholtz K. Balakumaran	Open, long-term safety & efficacy	39	28	Flecainide 150, 200, 250, 300, 350, 400
R-818-035-02	Chronic PVCs	P. Hugenholtz F. Hagemeijer	Open, long-term safety & efficacy	7	2	Flecainide 100, 200, 300, 400
R-818-035-03	Chronic PVCs	P. Hugenholtz F. Tencate A. Jovanovic	Open, long-term safety & efficacy	21	13	Flecainide 200, 250, 300, 400

Conclusions: Flecainide was highly effective in suppressing ventricular arrhythmias, without limiting side effects in 43 patients who received long-term treatment and who remain enrolled.

---

[a]Also known as R-818-EN-03.

Table 6

Summary of Plasma Pharmacokinetic Data in Man
Following Single Oral Doses
Lewis #R-818-0C5-01

Subject (and Group) Numbers	R-818 Dose (mg)	(mg/kg)[a]	Plasma Half-life[b] (hours)	Elimination Rate Constant[c] ($hours^{-1}$)	Plasma A.U.C. Values (0-∞)[d] Measured (ng·hours/ml)	per One mg/kg (ng·hours/ml)	per One mg/kg x K_{el} (ng/ml)
1 (A-1)	60	0.65	14.9	0.0464	1327	2057	95.4
2 (A-2)	60	0.85	11.2	0.0621	1182	1385	86.0
3 (A-3)	60	0.84	18.4	0.0377	3443	4114	155.1
4 (A-4)	60	0.78	17.3	0.0400	1734	2228	89.1
5 (B-1)	120	1.64	14.5	0.0479	3356	2042	97.8
6 (B-2)	120	1.70	10.9	0.0638	2985	1754	111.9
7 (B-3)	120	1.70	14.1	0.0493	4350	2552	125.8
8 (B-4)	120	1.32	7.2	0.0957	2474	1876	179.5
9 (C-1)	180	2.26	15.2	0.0457	7557	3338	152.5
10 (C-2)	180	2.57	9.5	0.0731	6097	2371	173.3
11 (C-3)	180	2.22	22.0	0.0315	7354	3309	104.2
12 (C-4)	180	2.95	14.7	0.0471	8697	2947	138.8
13 (D-1)	240	3.53	12.5	0.0555	4309	1221	67.8
14 (D-2)	240	2.25	12.0	0.0579	4460	1981	114.7
15 (D-3)	240	3.41	19.4	0.0357	8783	2573	91.9
16 (D-4)	240	3.41	12.8	0.0543	5102	1495	81.2
Mean			14.2	0.0527		2328	116.6
S_x[e]			± 1.0	± 0.0040		± 197	± 8.5

[a] Dose level (mg/kg) is based on weight at the time of drug administration.

[b] The terminal or beta phase plasma half-life was estimated from the log plasma concentration versus time graph by calculation of the least squares line.

[c] The terminal elimination rate constant (K_{el}) is 0.693 divided by the terminal plasma half-life.

[d] Area under the plasma R-818 concentration-time curve from zero to infinity.

[e] Standard deviation of the mean.

Comparison of Plasma R-818 Concentration Data in Man
Following Single Oral and Intravenous Doses
Lewis #R-818-005-01

Subject (and Group) Numbers	R-818 Dose (mg)	R-818 Dose (mg/kg)[a]	Plasma Half-life[b] (hours) Oral	Plasma Half-life[b] (hours) IV	Plasma A.U.C. Values (0 to ∞)[c] (ng·hours/ml) Oral	Plasma A.U.C. Values (0 to ∞)[c] (ng·hours/ml) IV	Ratio Oral/IV
1 (A-1)	60	0.65	14.9	9.2	1327	1073	1.237
2 (A-2)	60	0.85	11.2	12.7	1182	1172	1.009
3 (A-3)	60	0.84	18.4	19.1	3443	2807	1.227
4 (A-4)	60	0.78	17.3	18.7	1734	1856	0.934
5 (B-1)	120	1.64	14.5	15.6	3356	4375	0.767
6 (B-2)	120	1.70	10.9	15.1	2985	3959	0.754
7 (B-3)	120	1.70	14.1	15.3	4350	6170	0.705
8 (B-4)	120	1.32	7.2	6.9	2474	2635	0.939
Mean			13.6	14.1			0.947
S_x[d]			± 1.3	± 1.5			± 0.073

[a] Dose level (mg/kg) is based on weight at the time of drug administration.

[b] The terminal or beta phase plasma half-life was estimated from the log plasma concentration versus time graph by calculation of the least squares line.

[c] Area under the plasma R-818 concentration-time curve from zero to infinity.

[d] Standard deviation of the mean.

Comparison of Plasma R-818 Concentration Data in Man
Following Single Oral and Intravenous Doses
Lewis #R-818-005-01

Subject (and Group) Numbers	R-818 Dose (mg)	R-818 Dose (mg/kg)[a]	Plasma Half-life[b] (hours) Oral	Plasma Half-life[b] (hours) IV	Plasma A.U.C. Values (0 to ∞)[c] (ng·hours/ml) Oral	Plasma A.U.C. Values (0 to ∞)[c] (ng·hours/ml) IV	Ratio Oral/IV
1 (A-1)	60	0.65	14.9	9.2	1327	1073	1.237
2 (A-2)	60	0.85	11.2	12.7	1182	1172	1.009
3 (A-3)	60	0.84	18.4	19.1	3443	2807	1.227
4 (A-4)	60	0.78	17.3	18.7	1734	1856	0.934
5 (B-1)	120	1.64	14.5	15.6	3356	4375	0.767
6 (B-2)	120	1.70	10.9	15.1	2985	3959	0.754
7 (B-3)	120	1.70	14.1	15.3	4350	6170	0.705
8 (B-4)	120	1.32	7.2	6.9	2474	2635	0.939
Mean			13.6	14.1			0.947
S_x[d]			± 1.3	± 1.5			± 0.073

[a] Dose level (mg/kg) is based on weight at the time of drug administration.

[b] The terminal or beta phase plasma half-life was estimated from the log plasma concentration versus time graph by calculation of the least squares line.

[c] Area under the plasma R-818 concentration-time curve from zero to infinity.

[d] Standard deviation of the mean.

TABLE 8

Comparison of Percent of Dose Excreted in Urine as Unchanged Flecainide Acetate Within 24 Hours Following Oral and Intravenous Administration of a Single Dose to Human Subjects
Lewis #R-818-005-01

Subject No. (Group)	Dose[a] mg	Dose[a] mg/kg[c]	Percent of Dose Excreted as Flecainide Acetate[b] Oral	Intravenous	Ratio (Oral/IV)
1 (A-1)	60	0.65	19.00	21.33	0.891
5 (B-1)	120	1.64	11.81	30.44	0.388
6 (B-2)	120	1.70	9.09	32.89	0.276
7 (B-3)	120	1.70	43.98	38.76	1.135
Mean[d]			20.97	30.86	0.673
Std. Dev.			15.90	7.25	0.408

[a] Oral dose (Formulation U-1c 60 mg capsule) was given seven days prior to intravenous dose (Formulation U-1b 10 mg/ml sterile parenteral solution).
[b] Percent of dose excreted in urine within 24 hours following dosage.
[c] Dose level based on weight on dosage day.
[d] Mean values and standard deviations for four subjects.

Notebook Reference: NB-58838-41

Table 9: Kinetic parameters of Flecainide from five healthy male volunteers following intravenous (2 mg/kg in 5 min) or oral (200 mg) single dose administrations (mean ± SD and range values)
Tjandramaga #82-105-FRV-BE-002 & #81-152-FRO-BE-002

	INTRAVENOUS	O R A L
CONDITION	*Fasting*	*Fasting*
C_{max} (ng/ml)	1710 ± 788 (429-2510)	355 ± 48 (281-397)
T_{max} (h)	-	2.3 ± 0.7 (1.5-3.0)
α (min^{-1})	0.066 ± 0.022 (0.032-0.093)	-
$t\ 1/2_{\alpha}$ (min)	12.04 ± 5.70 (7.44-21.84)	-
β (h^{-1})	0.040 ± 0.006 (0.030-0.044)	0.061 ± 0.009 (0.053-0.074)
$t\ 1/2_{\beta}$ (h)	17.5 ± 3.1 (15.8-23.1)	11.5 ± 1.6 (9.3-13.0)
Vd_{area}/F (L)	522.2 ± 69.2 (440.2-601.4)	566.0 ± 91.2 (466.8-696.0)
(L/kg)	7.27 ± 1.14 (6.01-8.94)	7.83 ± 1.04 (6.43-8.87)
Vd_{ss}/F (L)	512.3 ± 66.2 (432.6-584.8)	-
(L/kg)	7.13 ± 1.11 (5.92-8.79)	-
Cl_{TB}/F (ml/min)	355.2 ± 84.6 (231.5-439.3)	563.5 ± 180.4 (340.7-777.2)
(ml/min/kg)	4.96 ± 1.28 (3.01-6.44)	7.8 ± 2.6 (4.4-10.9)
Cl_R (ml/min)	169.5 ± 49.3 (120.9-223.8)	181.7 ± 63.1 (95.3-265.0)
(ml/min/kg)	2.36 ± 0.76 (1.59-3.50)	2.5 ± 0.6 (1.6-3.2)

Table 9 continued

Cl_{NR} (ml/min)	185.7 ± 46.2 (108.8-222.9)	381.8 ± 183.7 (139.3-581.5)
(ml/min/kg)	2.59 ± 0.68 (1.41-3.13)	5.4 ± 2.7 (1.8-8.5)
AUC_{0-48} (ng/ml.h)	5797 ± 1601 (3761-8149)	-
$AUC_{0-\infty}$ (ng/ml.h)	7201 ± 2305 (5188-11108)	6047 ± 1566 (4289-7651)
Normalized $[AUC]_0^{\infty} \times \beta$ (ng/ml)	287 ± 49 (220-348)	361 ± 57 (287-428)
F (%)[a]	91.0 ± 6.7 (86.2-102.7)	
Cumulative Urinary Excretion (0 - 48 h)		
(mg)	55.85 ± 9.27 (42.66-66.23)	57.46 ± 20.85 (40.72-82.93)
(% of dose)	38.39 ± 2.62 (35.55-41.92)	28.73 ± 10.42 (20.36-41.46)

[a] F = extent of bioavailability derived from :

$$\frac{[AUC]_0^{\infty} \times \beta \text{ PO}}{[AUC]_0^{\infty} \times \beta \text{ IV}} \times \frac{\text{Dose IV}}{\text{Dose PO}}$$

STUDY: R-818V-003-01
INVESTIGATOR: PAUL H. MILLER, MD

TABLE 10

SYSTEMIC CARDIAC OUTPUT (1/min)

PATIENT NUMBER	BASELINE VALUE	10 MIN AFTER DOSE	30 MIN AFTER DOSE	60 MIN AFTER DOSE
1	6.56	5.55	4.75	5.50
2	4.74	4.34	3.86	3.40
3	5.12	4.63	4.61	4.60
4	4.95	4.68	4.44	4.71
GROUP A MEAN 0.5 MG/KG	5.34	4.80	4.41	4.55
5	5.74	5.39	4.94	4.97
6	5.11	4.98	4.40	4.56
GROUP B MEAN 0.75MG/KG	5.42	5.18	4.67	4.76
7	6.24	6.14	6.01	5.78
8	5.65	4.46	5.12	4.82
10	6.26	5.79	5.78	5.66
GROUP C MEAN 1.0 MG/KG	6.26	5.46	5.64	5.42
9	3.48	2.79	2.67	2.63
11	3.18	2.72	3.25	2.27
12	8.32	6.48	6.73	5.42
GROUP D MEAN 1.5 MG/KG	4.99	4.00	4.22	3.44

STUDY: R-818V-003-01
INVESTIGATOR: PAUL H. MILLER, MD

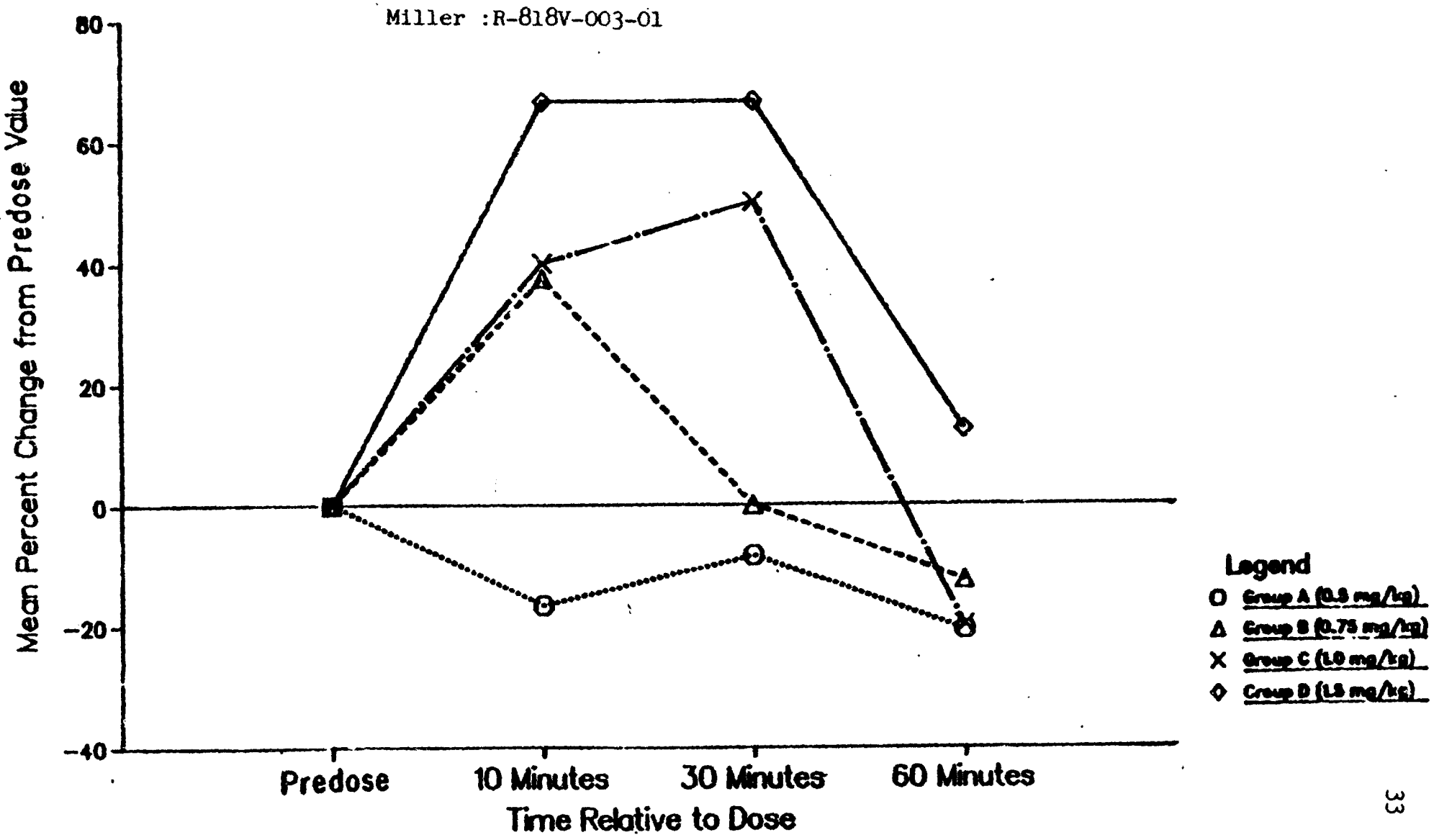
TABLE 11

LEFT VENTRICULAR END DIASTOLIC PRESSURE (mmHg)

PATIENT NUMBER	BASELINE VALUE	10 MIN AFTER DOSE	30 MIN AFTER DOSE	60 MIN AFTER DOSE
1	2.0	2.0	2.0	1.0
2	12.0	8.0	12.0	12.0
3	12.0	8.0	8.0	6.0
4	12.0	12.0	12.0	14.0
GROUP A MEAN 0.5 MG/KG	9.5	7.5	8.5	8.3
5	4.0	8.0	4.0	4.0
6	16.0	12.0	16.0	12.0
GROUP B MEAN 0.75MG/KG	10.0	10.0	10.0	8.0
7	10.0	14.0	15.0	8.0
8	[a]	[a]	[a]	[a]
10	[b]	[b]	[b]	[b]
GROUP C MEAN 1.0 MG/KG	10.0	14.0	15.0	8.0
9	12.0	16.0	16.0	12.0
11	[b]	[b]	[b]	[b]
12	4.0	8.0	8.0	5.0
GROUP D MEAN 1.5 MG/KG	8.0	12.0	12.0	8.5

[a] DATA RECORDED INCORRECTLY ON CASE REPORT FORM AND WAS NOT USED IN THE ANALYSIS.
[b] DATA NOT RECORDED.

Figure 1: MEAN PERCENT CHANGE OF LEFT VENTRICULAR END DIASTOLIC PRESSURE FOR EACH DOSE GROUP



STUDY: R-818V-003-01
INVESTIGATOR: PAUL H. MILLER, MD

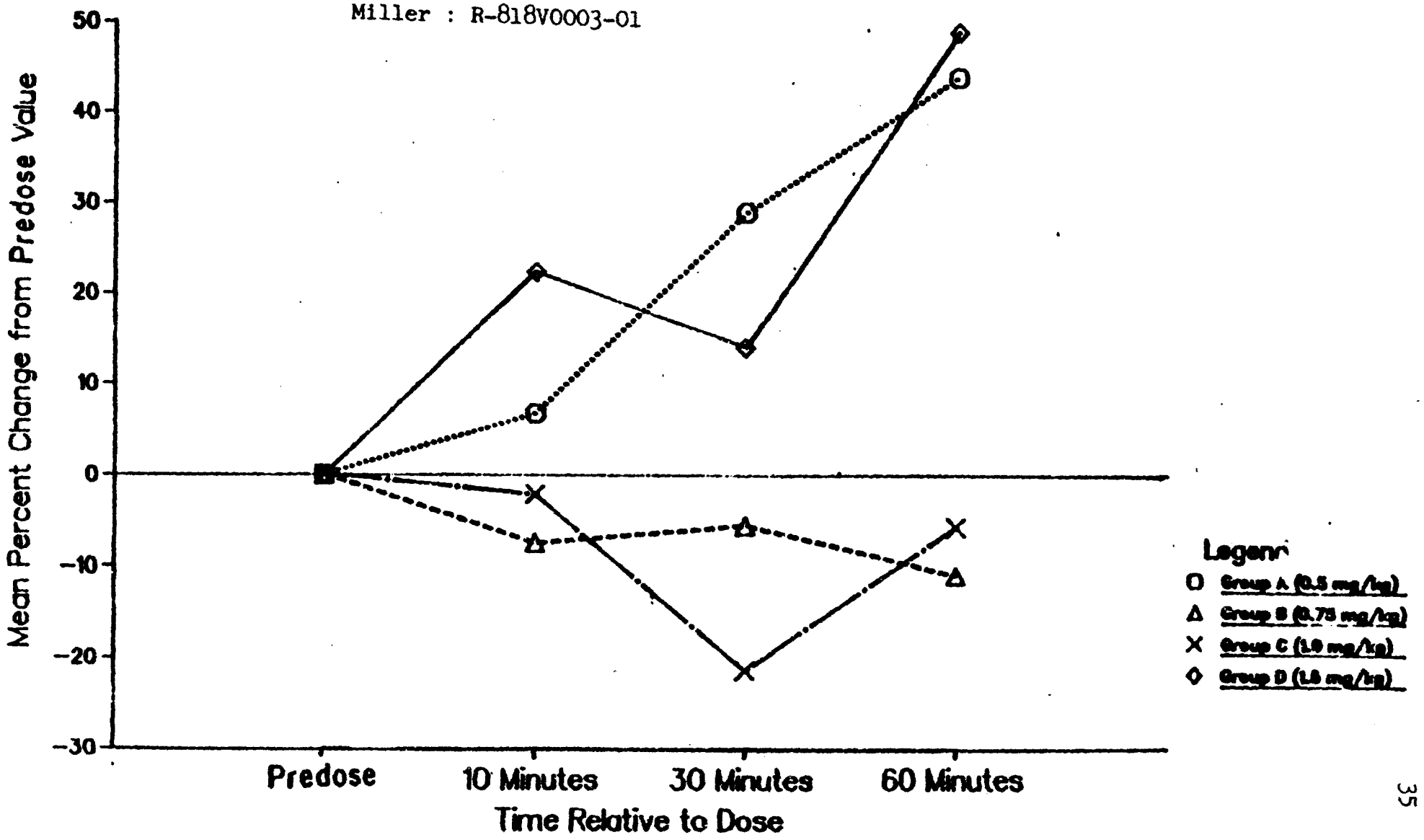
TABLE 25 12

LEFT VENTRICULAR DP/DT RATIO

PATIENT NUMBER	BASELINE VALUE	10 MIN AFTER DOSE	30 MIN AFTER DOSE	60 MIN AFTER DOSE
1	2714.0	2714.0	2950.0	3068.0
2	1250.0	1500.0	2500.0	2500.0
3	3200.0	3120.0	3040.0	3120.0
4	920.0	1006.0	1030.0	1520.0
GROUP A MEAN 0.5 MG/KG	2021.0	2085.0	2380.0	2552.0
5	1650.0	1650.0	1550.0	1450.0
6	1000.0	850.0	950.0	900.0
GROUP B MEAN 0.75MG/KG	1325.0	1250.0	1250.0	1175.0
7	2300.0	2200.0	2000.0	2100.0
8	[a]	[b]	[a]	[a]
10	[a]	[a]	[a]	[a]
GROUP C MEAN 1.0 MG/KG	2300.0	2200.0	2000.0	2100.0
9	2000.0	1537.0	1850.0	1783.0
11	[a]	[a]	[a]	[b]
12	1062.5	2000.0	1650.0	2216.0
GROUP D MEAN 1.5 MG/KG	1531.3	1768.5	1750.0	1999.5

[a] AORTIC DP/DT RATIO WAS OBTAINED IN PLACE OF THE LEFT VENTRICULAR DP/DT RATIO AND IS DISPLAYED IN TABLE 27.
[b] DATA WAS NOT RECORDED.

Figure 2: MEAN PERCENT CHANGE OF dP/dt RATIO FOR EACH DOSE GROUP



STUDY: R-818V-003-01
INVESTIGATOR: PAUL H. MILLER, MD

TABLE 13

P-A + A-H INTERVAL (MSEC)[a]

	PATIENT NUMBER	BASELINE VALUE	10 MIN AFTER DOSE	30 MIN AFTER DOSE	60 MIN AFTER DOSE
	1	110.0	110.0	100.0	105.0
	2	125.0	125.0	124.0	130.0
	4	145.0	150.0	150.0	150.0
GROUP A MEAN 0.5 MG/KG		126.7	128.3	124.7	128.3
	5	[b]	119.0	98.0	97.0
	6	106.0	105.0	102.0	107.0
GROUP B MEAN 0.75MG/KG		106.0	112.0	100.0	102.0
	7	150.0	150.0	150.0	138.0
	8	138.0	140.0	137.0	116.0
	10	140.0	145.0	120.0	130.0
GROUP C MEAN 1.0 MG/KG		142.7	145.0	135.7	128.0
	9	120.0	123.0	115.0	111.0
	12	98.0	110.0	120.0	120.0
GROUP D MEAN 1.5 MG/KG		109.0	116.5	117.5	115.5

[a] HIS BUNDLE ELECTROGRAMS WERE NOT OBTAINED FOR PATIENTS 3 AND 11.
[b] DATA NOT RECORDED.

STUDY: R-818V-022-01
INVESTIGATOR: MONTY BODENHEIMER, MD

TABLE 14

SUMMARY OF EFFECTS OF FLECAINIDE ACETATE ON RIGHT AND LEFT VENTRICULAR EJECTION FRACTIONS AND WALL MOTIONS BY DOSING GROUP

	PREDRUG	POSTDRUG					
		EJECTION FRACTION NO. OF PATIENTS			WALL MOTION NO. OF PATIENTS		
WALL MOTION	NO. OF PATIENTS	INCREASE[a]	DECREASE[a]	NO CHANGE[b]	IMPROVED	WORSENED	NO CHANGE
0.7 MG/KG (n=1)							
RIGHT VENTRICLE							
NORMAL	0	0	0	0	0	0	0
ABNORMAL	1	1	0	0	0	0	1
LEFT VENTRICLE							
NORMAL	0	0	0	0	0	0	0
ABNORMAL	1	1	0	0	0	0	1
1.0 MG/KG (n=4)							
RIGHT VENTRICLE							
NORMAL	3	1	1	1	0	1	2
ABNORMAL	1	0	0	1	0	0	1
LEFT VENTRICLE							
NORMAL	3	0	2	1	0	1	2
ABNORMAL	1	0	0	1	0	1	0
1.5 MG/KG (n=5)							
RIGHT VENTRICLE							
NORMAL	5	0	4	1	0	3	2
ABNORMAL	0	0	0	0	0	0	0
LEFT VENTRICLE							
NORMAL	2	0	0	2	0	0	2
ABNORMAL	3	0	3	0	0	3	0
2.0 MG/KG (n=10)							
RIGHT VENTRICLE							
NORMAL	9	1	7	1	0	5	4
ABNORMAL	1	0	1	0	0	0	1
LEFT VENTRICLE							
NORMAL	6	2	3	1	0	4	2
ABNORMAL	4	0	3	1	1	3	0

[a] Includes changes of 4% or more from predrug to postdrug ejection fraction.
[b] Includes changes of 3% or less in ejection fractions.

STUDY: R-818V-022-01
INVESTIGATOR: MONTY BODENHEIMER, MD

TABLE 15

SUMMARY OF EFFECT OF FLECAINIDE ACETATE ON SYSTEMIC PRESSURE, HEART RATE, AND RIGHT AND LEFT VENTRICULAR EJECTION FRACTION BY DOSING GROUP

AGE	BLOOD PRESSURE (MMHG) SYSTOLIC PRE	SYSTOLIC POST	DIASTOLIC PRE	DIASTOLIC POST	HEART RATE PRE	HEART RATE POST	RVEF (%)[a] PRE	RVEF (%)[a] POST	LVEF (%)[b] PRE	LVEF (%)[b] POST
0.7 MG/KG DOSE (n=1)										
54	140	125	90	70	76	75	12	27	17	21
1.0 MG/KG DOSE (n=4)										
56.5 ± 4.0	140.0 ± 22.7	135.0 ± 19.6	82.5 ± 6.5	85.5 ± 6.4	78.8 ± 6.7	78.8 ± 12.5	30.0 ± 6.3	27.5 ± 8.2	58.8 ± 21.3	51.5 ± 18.8
	p=0.092		p=0.092		p=1.00		p=0.63		p=0.15	
1.5 MG/KG DOSE (n=5)										
54.0 ± 3.7	140.0 ± 16.2	139.2 ± 21.5	89.0 ± 9.6	90.0 ± 8.6	70.6 ± 10.8	72.8 ± 9.8	31.2 ± 3.4	26.2 ± 3.8	64.4 ± 12.4	56.4 ± 18.6
	p=0.88		p=0.71		p=0.18		p=0.019		p=0.098	
2.0 MG/KG DOSE (n=10)										
52.4 ± 8.3	138.4 ± 21.1	144.9 ± 24.1	89.3 ± 10.2	98.0 ± 12.3	69.9 ± 11.9	71.9 ± 7.9	33.0 ± 6.5	24.9 ± 5.4	65.0 ± 7.3	59.8 ± 11.8
	p=0.25		p=0.0083		p=0.52		p=0.0034		p=0.14	

[a] RVEF = Right ventricular ejection fraction.
[b] LVEF = Left ventricular ejection fraction.

STUDY: R-818V-022-01
INVESTIGATOR: MONTY BODENHEIMER, MD

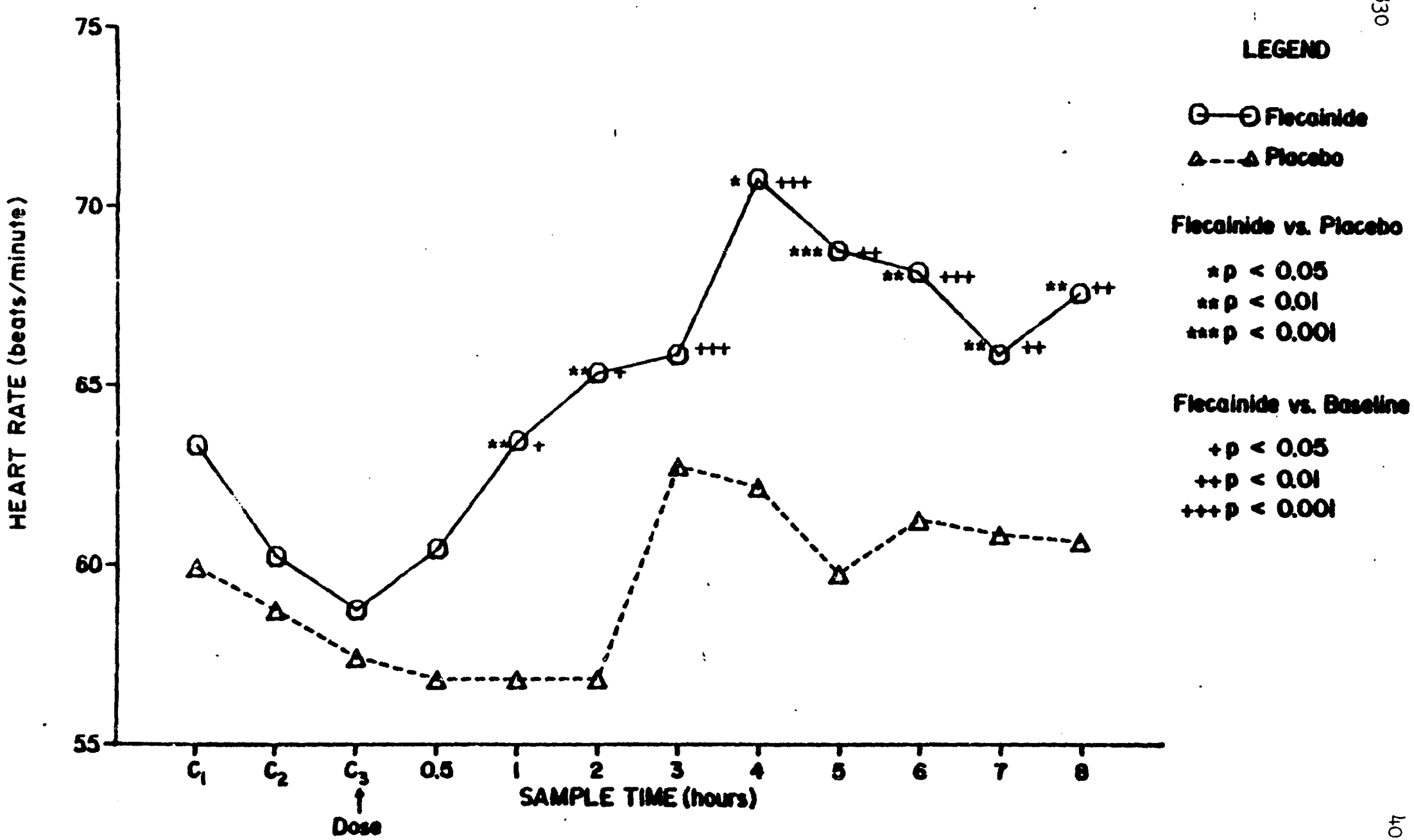
TABLE 16

MEAN VALUES OF HEART RATE AND BLOOD PRESSURE BY FLECAINIDE DOSING GROUP

PROCEDURE SCHEDULE		HEART RATE (±SD)	BLOOD PRESSURE SYSTOLIC (±SD)	BLOOD PRESSURE DIASTOLIC (±SD)
0.7 MG/KG DOSE (n=1)				
BASELINE (PREISOTOPE)	0-30 MIN	75	142	92
FIRST ISOTOPE PASS POSTISOTOPE	5-10 MIN	76	140	90
FLECAINIDE ADMINISTRATION POSTDRUG	5 MIN	78	125	75
	10 MIN	77	135	75
	14 MIN	75	125	70
SECOND ISOTOPE PASS POSTISOTOPE	15-16 MIN			
	10 MIN	75	136	75
	20 MIN	75	130	75
	30 MIN	73	135	78
1.0 MG/KG DOSE (n=4)				
BASELINE (PREISOTOPE)	0-30 MIN	76.8 (±10.5)	142.5 (±18.3)	85.2 (± 6.6)
FIRST ISOTOPE PASS POSTISOTOPE	5-10 MIN	78.8 (± 6.7)	140.0 (±22.7)	82.5 (± 6.5)
FLECAINIDE ADMINISTRATION POSTDRUG	5 MIN	80.0 (± 9.9)	133.5 (±15.5)	83.8 (± 8.5)
	10 MIN	82.0 (±10.9)	135.8 (±17.9)	84.0 (± 5.9)
	14 MIN	78.8 (±12.5)	135.0 (±19.6)	85.5 (± 6.4)
SECOND ISOTOPE PASS POSTISOTOPE	15-16 MIN			
	10 MIN	79.0 (±11.0)	140.5 (±23.8)	90.2 (± 4.6)
	20 MIN	76.0 (±11.0)	132.8 (±23.3)	89.8 (±11.8)
	30 MIN	76.2 (±11.5)	134.0 (±20.3)	88.2 (± 9.6)
1.5 MG/KG DOSE (n=5)				
BASELINE (PREISOTOPE)	0-30 MIN	71.2 (±10.6)	144.0 (±22.2)	89.4 (± 8.2)
FIRST ISOTOPE PASS POSTISOTOPE	5-10 MIN	70.6 (±10.8)	140.0 (±16.2)	89.0 (± 9.6)
FLECAINIDE ADMINISTRATION POSTDRUG	5 MIN	75.4 (± 6.1)	139.8 (±24.7)	91.4 (± 8.8)
	10 MIN	71.8 (± 5.9)	140.4 (±26.2)	89.8 (± 9.0)
	14 MIN	72.8 (± 9.8)	139.2 (±21.5)	90.0 (± 8.6)
SECOND ISOTOPE PASS POSTISOTOPE	15-16 MIN			
	10 MIN	73.8 (±10.1)	140.0 (±17.9)	89.2 (±11.8)
	20 MIN	68.4 (±11.8)	139.2 (±16.2)	90.4 (±11.8)
	30 MIN	72.4 (± 9.1)	145.6 (±18.1)	92.0 (± 2.4)
2.0 MG/KG DOSE (n=10)				
BASELINE (PREISOTOPE)	0-30 MIN	69.4 (±12.6)	135.0 (±23.8)	88.0 (± 8.9)
FIRST ISOTOPE PASS POSTISOTOPE	5-10 MIN	69.9 (±11.9)	138.4 (±21.1)	89.3 (±10.2)
FLECAINIDE ADMINISTRATION POSTDRUG	5 MIN	73.3 (± 5.9)	140.5 (±20.9)	96.4 (±10.9)
	10 MIN	73.2 (± 8.1)	141.9 (±21.0)	97.2 (±11.4)
	14 MIN	71.9 (± 7.9)	144.9 (±24.1)	98.0 (±12.3)
SECOND ISOTOPE PASS POSTISOTOPE	15-16 MIN			
	10 MIN	71.3 (± 7.1)	141.4 (±21.1)	92.5 (±13.8)
	20 MIN	73.1 (± 6.8)	135 0 (±14.4)	92.9 (± 9.8)
	30 MIN	71.7 (± 8.1)	133.5 (±14.7)	95.1 (± 8.9)

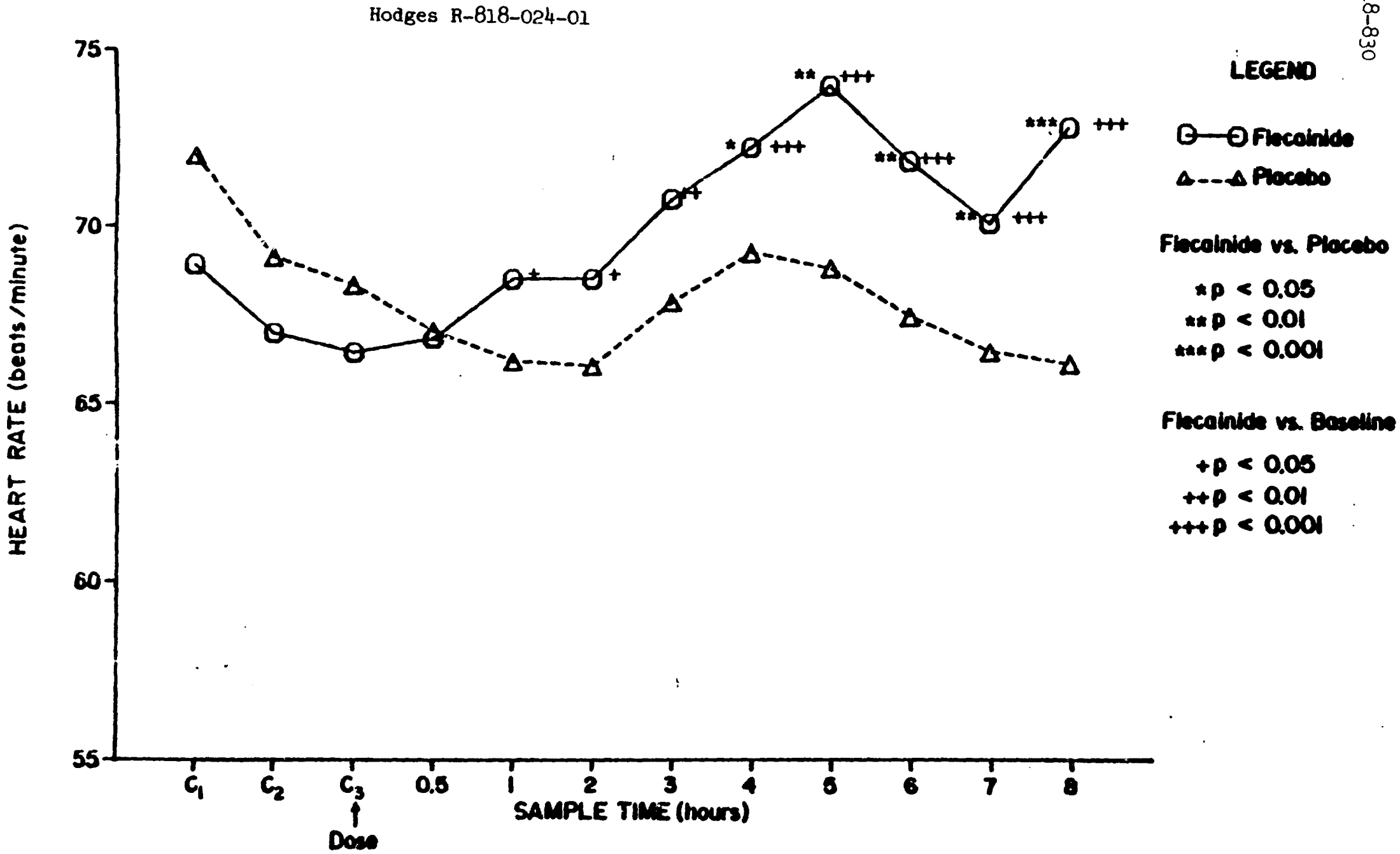
Figure 3: MEANS OF HEART RATE IN SUBJECTS DURING M-MODE ECHOCARDIOGRAPHY

Hodges R-818-024-01



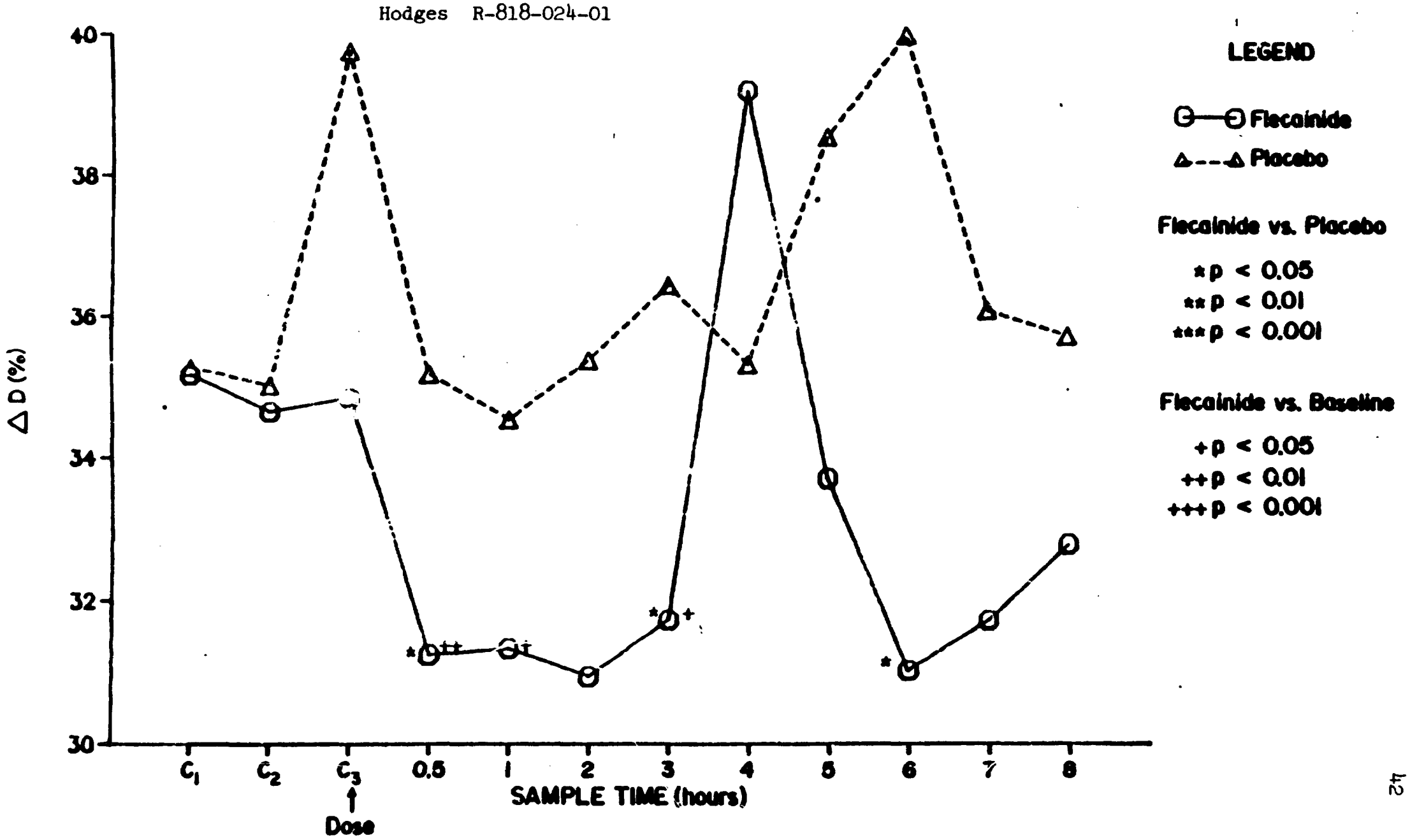
All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with the last measurement (C_3) made just prior to dose.

Figure 4: MEANS OF HEART RATE IN PATIENTS DURING M-MODE ECHOCARDIOGRAPHY



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with the last measurement (C_3) made just prior to dose.

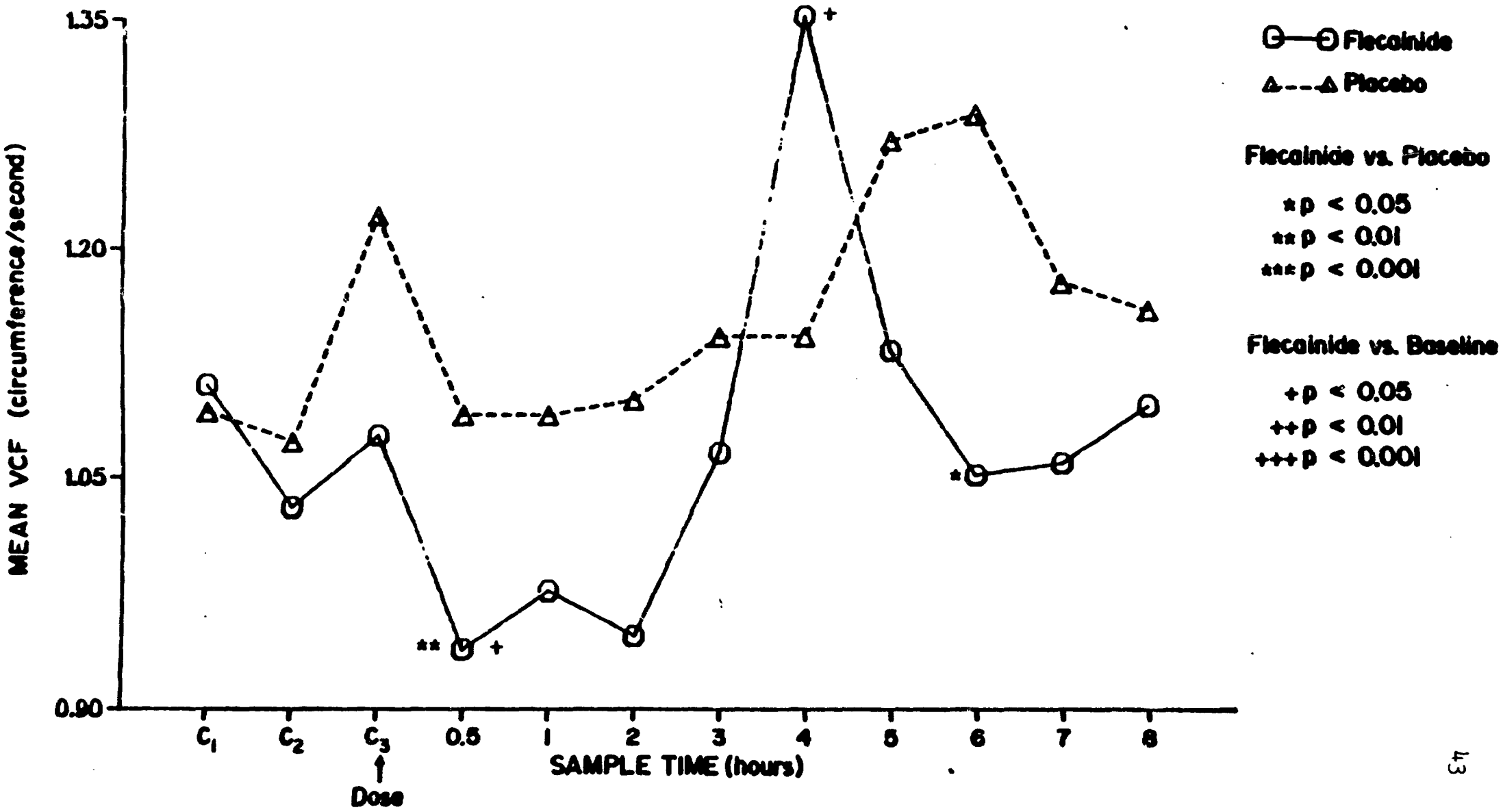
Figure 5: MEANS OF PERCENT SHORTENING OF LEFT VENTRICULAR DIAMETER (%ΔD) IN SUBJECTS: M-MODE ECHOCARDIOGRAPHY DATA



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with

Figure 6: MEANS OF MEAN RATE OF CIRCUMFERENTIAL FIBER SHORTENING (MEAN VCF) IN SUBJECTS – M-MODE ECHOCARDIOGRAPHY DATA

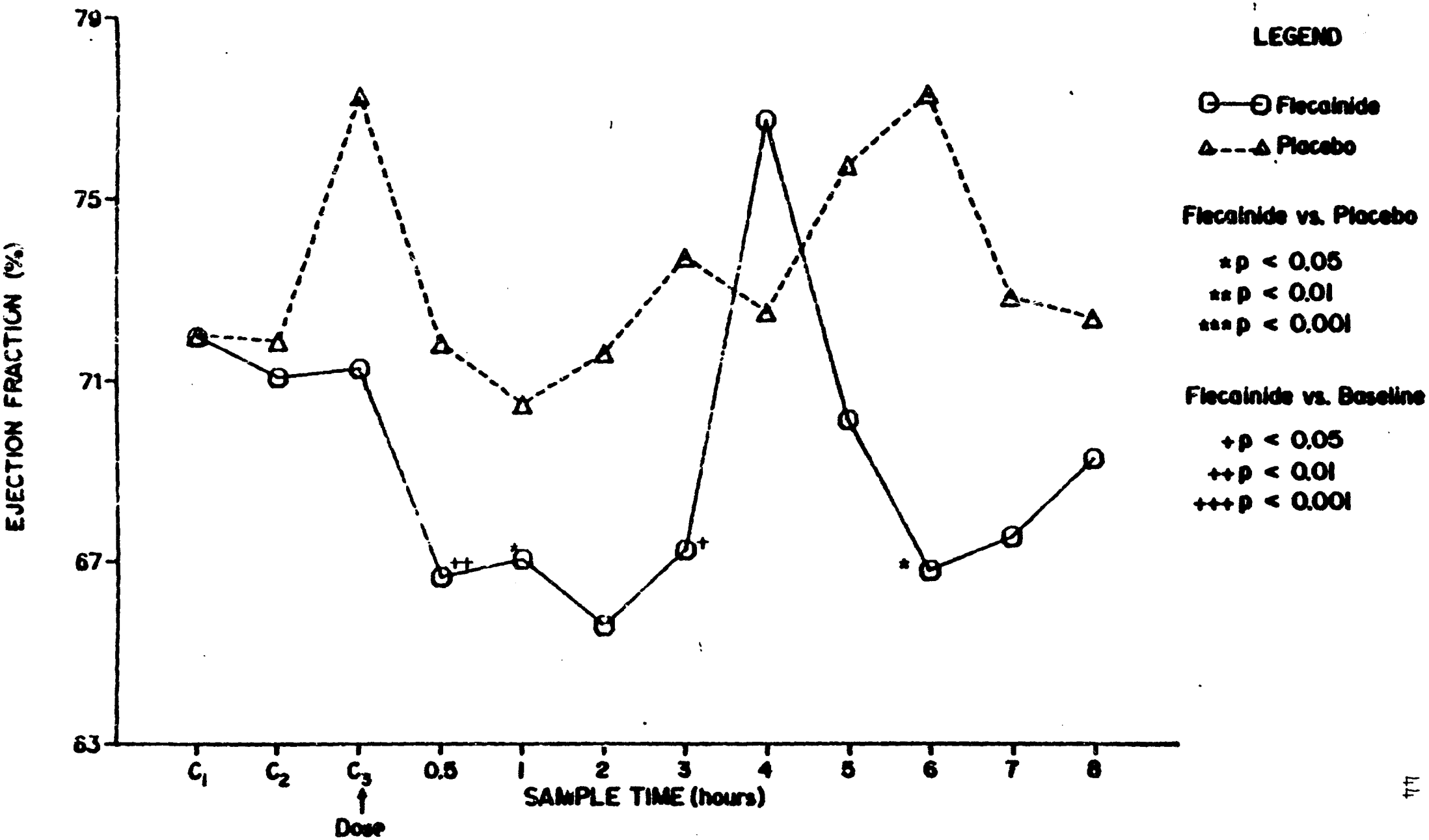
Hodges R-818-024-01



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with the last measurement (C_3) made just prior to dose.

Figure 7: MEANS OF EJECTION FRACTION IN SUBJECTS — M-MODE ECHOCARDIOGRAPHY DATA

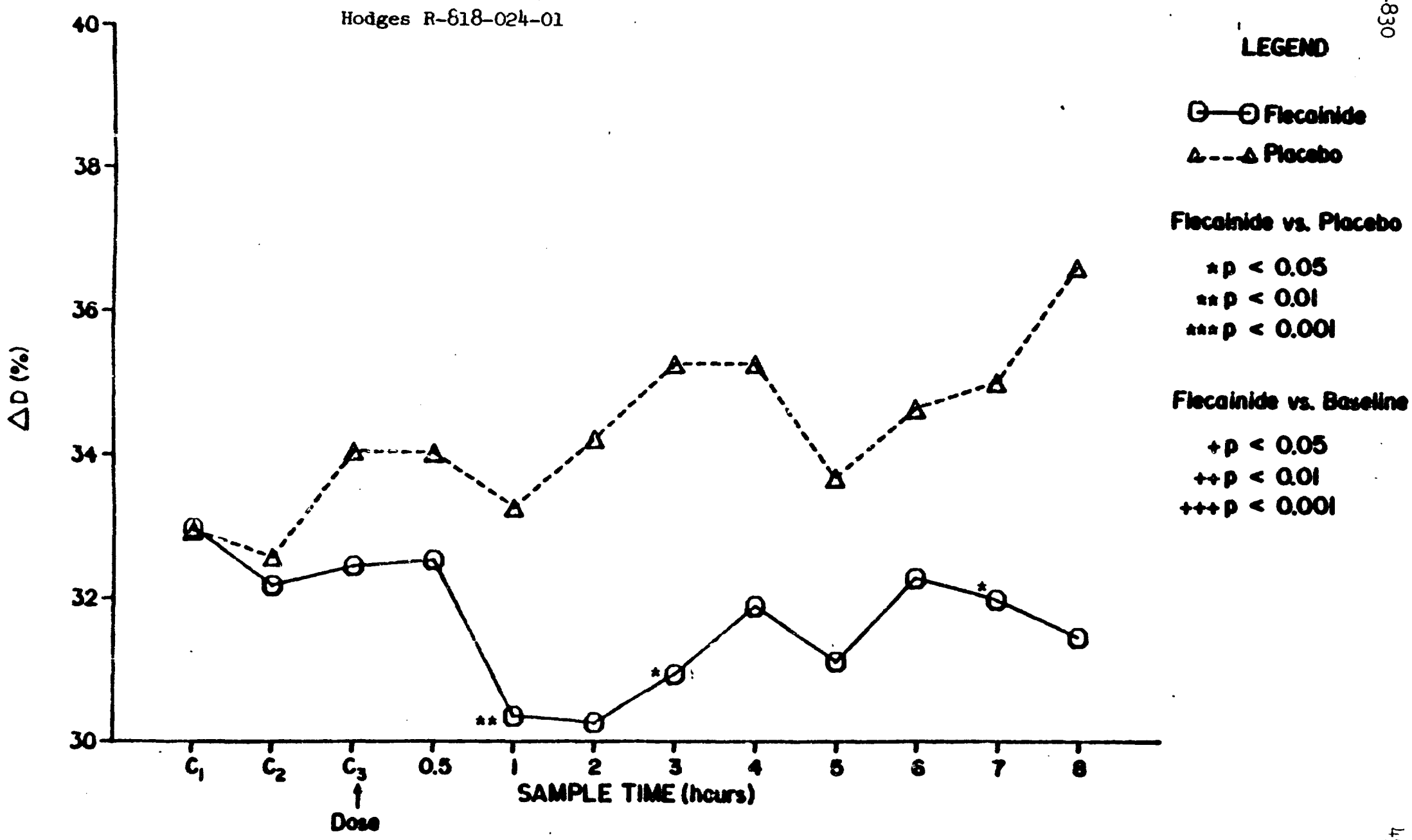
Hodges R-818-024-01



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with the last measurement (C_3) made just prior to dose.

Figure 8: MEANS OF PERCENT SHORTENING OF LEFT VENTRICULAR DIAMETER (%ΔD) IN PATIENTS M-MODE ECHOCARDIOGRAPHY DATA

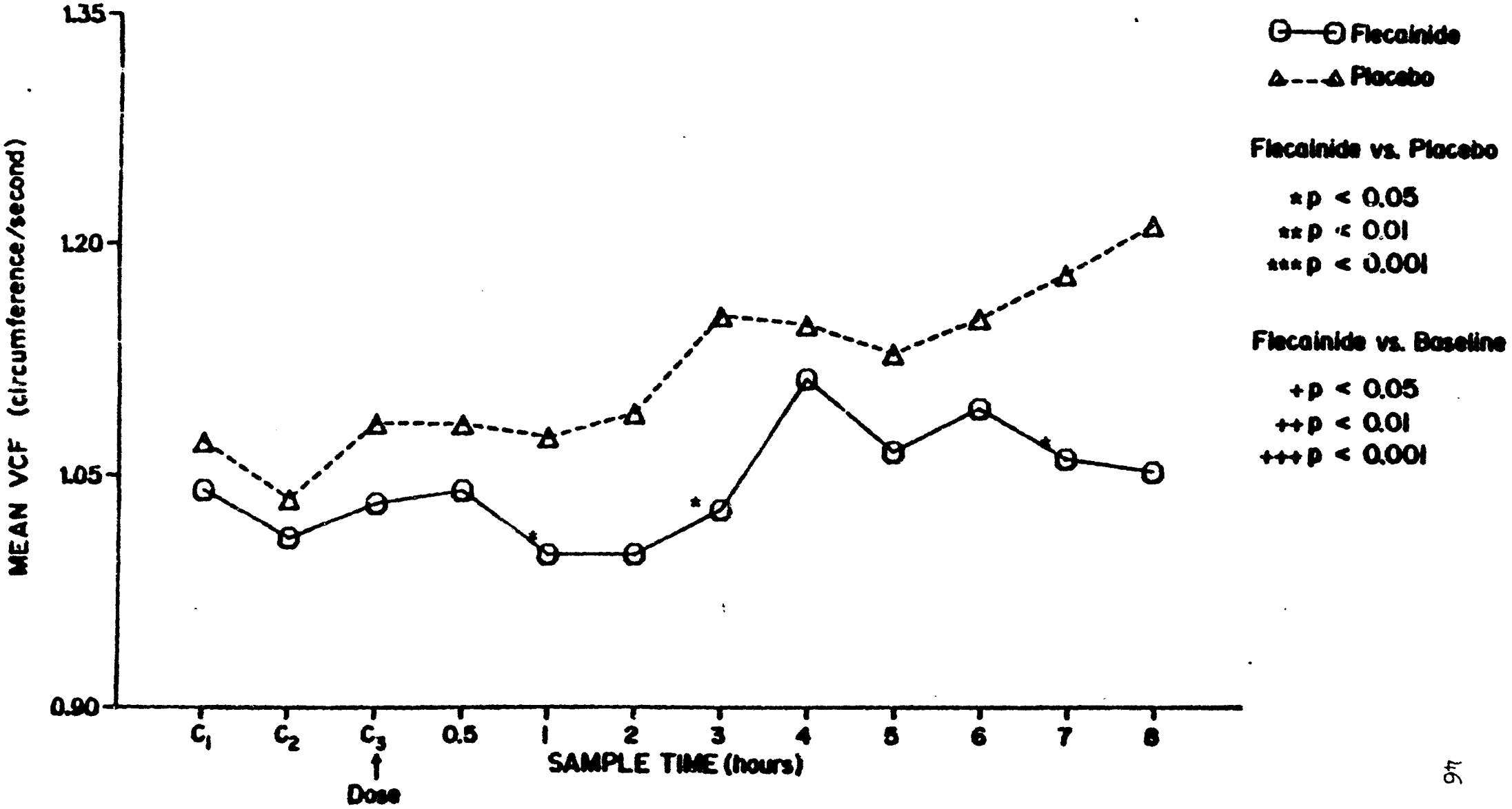
Hodges R-818-024-01



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with the last measurement (C_3) made just prior to dose.

Figure 9: MEANS OF MEAN RATE OF CIRCUMFERENTIAL FIBER SHORTENING (MEAN VCF) IN PATIENTS – M-MODE ECHOCARDIOGRAPHY DATA

Hodges R-818-024-01



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with the last measurement (C_3) made just prior to dose.

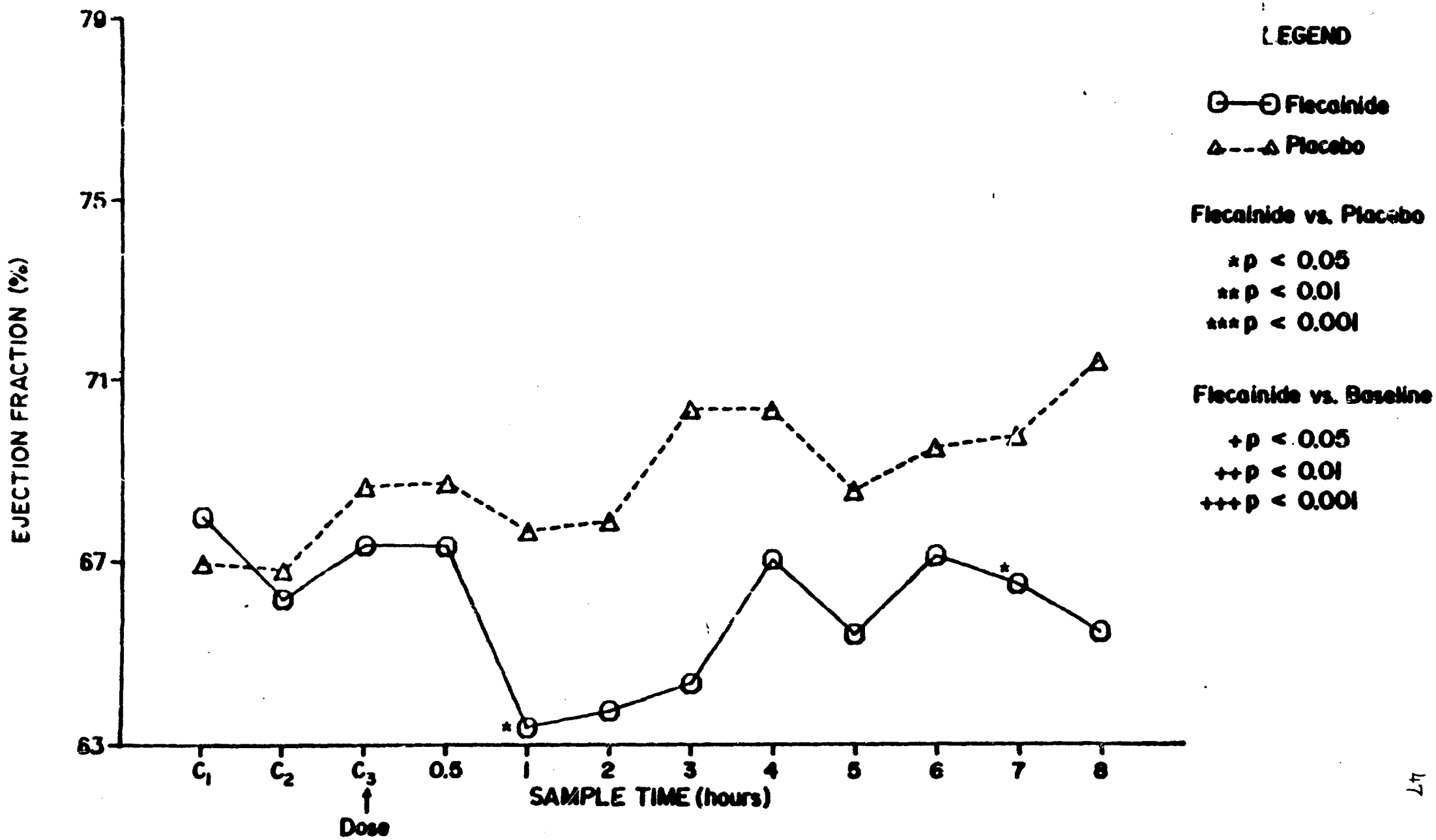
TABLE 1: Listing of NDA Locations and Pages for Highlighted Study Reports

Study	Volume Number	pages
R-818-001	1.3	
R-818-003	1.5	
R-818-005	1.8	
R-818-015	1.7	
R-818-018	1.9	
R-818-019	1.24	
R-818-022	1.5	
R-818-023	1.5	
R-818-024	1.6	
R-818-026	1.9	
R-818-030-01	1.21	
R-818-030-02	1.22	
R-818-030-03	1.22	
R-818-031	1.25	
R-818-032	1.23	
R-818-033	1.26	
R-818-035[a]	1.27	
R-818-038	1.12	
R-818-039	1.6	
R-818-041	1.4	
R-818-045	1.4	
R-818-049	1.10	
R-818-050	1.14	
R-818-054	1.7	
R-818-060	1.23	

[a]Otherwise known as R-818-EN-03

Figure 10: MEANS OF EJECTION FRACTION IN PATIENTS – M-MODE ECHOCARDIOGRAPHY DATA

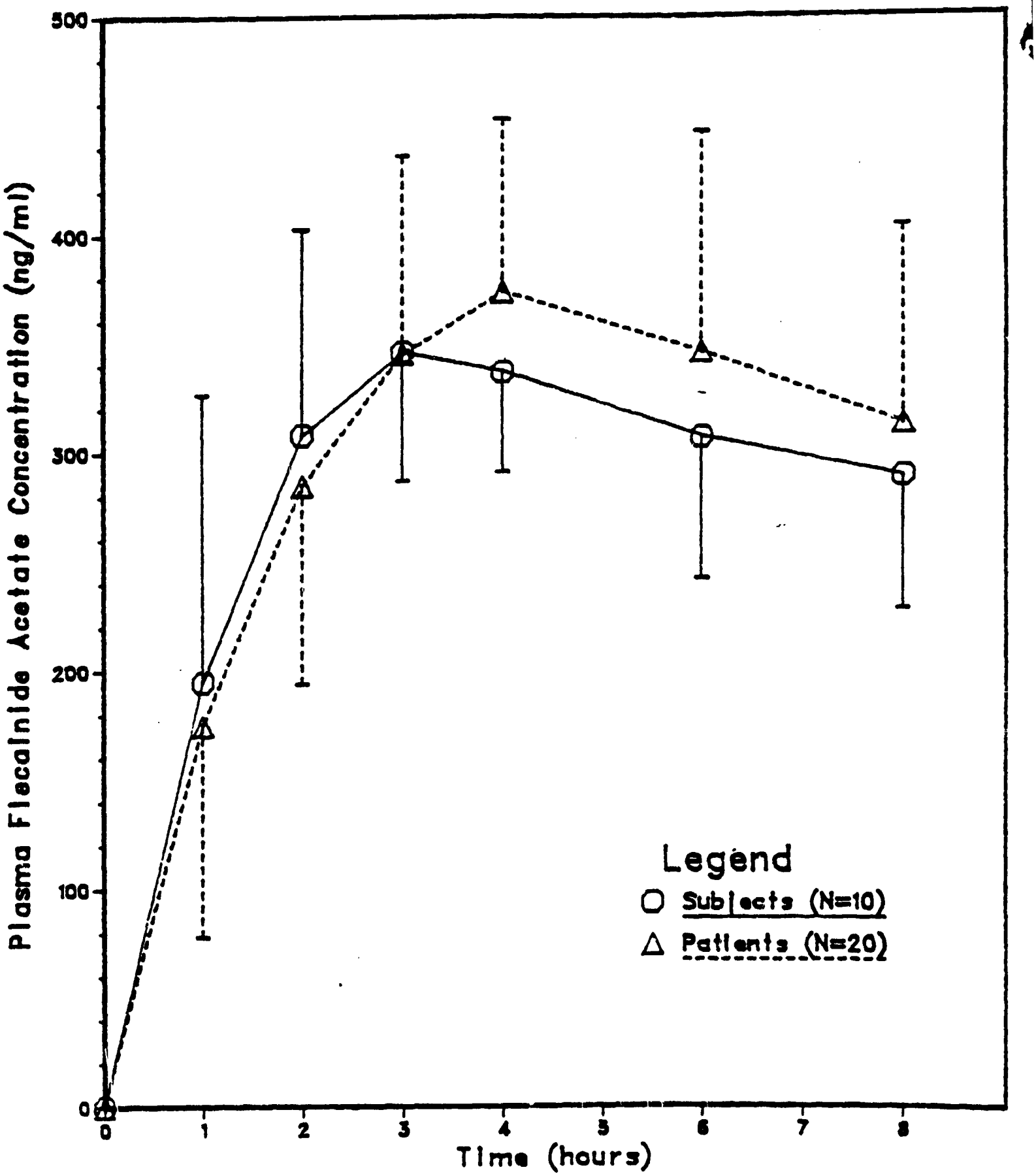
Hodges R-818-024-01



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with

Figure 11: Mean Plasma Concentrations of Flecainide Acetate Following a Single 250 mg Oral Dose

Hodges R-818-024-01



Study: R-818-024-01
Investigator: Morrison Hodges, MD

Table 17

Correlation Between Plasma Flecainide Levels and Pharmacologic Measurements
(Differences Between Drug and Placebo Values)

Pharmacologic Measurement	P-Value from Correlation Analysis[a] Subjects		Patients	
	[b]	[c]		
Heart Rate (M-Mode)	0.0014 *	(120)	<0.0001 *	(237)
LVES	0.52	(88)	0.83	(151)
LVED	0.48	(88)	0.72	(151)
LVdD/dt	0.45	(88)	0.39	(151)
LVd^{2}D/dt^2	0.10	(88)	0.97	(151)
% D	0.91	(88)	0.37	(151)
Mean V_{cf}	0.62	(84)	0.72	(151)
Ejection Fraction	0.98	(88)	0.46	(151)
QS_2 Index	0.0043 *	(119)	0.0012 *	(237)
LVET Index	0.79	(115)	0.53	(235)
PEP Index	0.0003 *	(114)	0.0046 *	(235)
PEP:LVET	0.0003 *	(114)	0.0093 *	(235)
Systolic BP	0.27	(120)	0.015 *	(240)
Diastolic BP	0.87	(120)	0.57	(240)
Heart Rate (2-D)	0.37	(20)	0.59	(55)
End Systolic Volume	0.83	(20)	0.93	(55)
End Diastolic Volume	0.78	(20)	0.64	(55)
Ejection Fraction	0.093	(20)	0.43	(55)
Stroke Volume	0.46	(20)	0.29	(55)
Cardiac Output	0.72	(19)	0.45	(55)
Forearm Blood Flow	0.027 *	(62)	0.43	(119)
Forearm Venous Capacitance	0.18	(60)	0.94	(117)
Forearm Venous Resistance	0.14	(62)	0.90	(119)
Atrial Rate	0.022 *	(100)	0.0003 *	(190)
Ventricular Rate	0.022 *	(100)	0.0001 *	(200)
PR Interval	0.0003 *	(100)	<0.0001 *	(190)
QRS Duration	0.0061 *	(100)	0.0001 *	(199)
QT Interval (Corrected)	0.0044 *	(100)	0.0006 *	(179)

[a] For each pharmacologic measurement (drug treatment value minus placebo treatment value), the overall P-value for the correlation between plasma flecainide level and each difference over all time points and over all subjects or patients was determined.

[b] An * indicates a statistically significant correlation.

[c] The number of paired data values used for each correlation analysis is shown in parentheses.

STUDY: R-818-039-01
INVESTIGATOR: JOSEPH A. FRANCIOSA, MD

CARDIAC INDEX (L/MIN/M2) AT VARIOUS WORK LOAD LEVELS

TABLE 18

PATIENTS	ID NO	PREDRUG SUPINE	PREDRUG SITTING	PREDRUG MAXIMAL EXERCISE	2 HOURS POSTDOSE SUPINE	4 HOURS POSTDOSE SUPINE	4 HOURS POSTDOSE SITTING	4 HOURS POSTDOSE MAXIMAL EXERCISE	8 HOURS POSTDOSE SUPINE	24 HOURS POSTDOSE SUPINE	24 HOURS POSTDOSE SITTING	24 HOURS POSTDOSE MAXIMAL EXERCISE
	1	1.26	1.14	3.50	1.66	1.46	1.50	5.85	1.68	1.39	1.89	5.66
	2	2.43	2.18	7.04	2.19	2.02	1.71	7.42		2.60	2.43	
	3	1.75	1.91		1.30	1.66	1.52		2.36	2.14	1.16	5.88
	4	2.44	2.14	8.40	2.39	2.03	2.59	8.73	2.78	2.54	2.41	
	5	2.51	2.39	5.69	4.02	2.27	2.08	5.69		2.40	2.51	7.23
	6	2.11	2.41	5.81	2.08	1.84	2.27	6.58	1.94	1.93	3.58	8.49
	7	1.68	1.41	4.12	2.14	2.01	1.87	3.24	1.60	1.87	1.62	3.08
	8	2.37	2.73	4.82	2.42	2.39	1.19	7.07	3.48	3.01	2.63	6.01
	9	1.24	1.28	3.41	1.45	1.55	1.30	2.55	1.91	1.98	1.89	4.02
	10	1.64	1.43	3.46	2.03	2.03	1.39	4.35	2.50	1.68	1.41	4.08
	MEAN	1.94	1.90	5.14	2.17	1.93	1.74	5.71	2.28	2.15	2.15	5.56
	STD DEV	0.49	0.55	1.75	0.75	0.30	0.45	2.02	0.63	0.48	0.71	1.79

SUBJECTS	ID NO	PREDRUG SUPINE	PREDRUG SITTING	PREDRUG MAXIMAL EXERCISE	2 HOURS POSTDOSE SUPINE	4 HOURS POSTDOSE SUPINE	4 HOURS POSTDOSE SITTING	4 HOURS POSTDOSE MAXIMAL EXERCISE	8 HOURS POSTDOSE SUPINE	24 HOURS POSTDOSE SUPINE	24 HOURS POSTDOSE SITTING	24 HOURS POSTDOSE MAXIMAL EXERCISE
	101	3.26	2.11	8.73	3.48	2.69	2.79	9.28	4.02	3.66	3.49	7.33
	102	2.75	2.14	8.33	2.06	2.22	2.73	6.81	2.60	2.74	2.83	
	103	5.59	3.66	9.76	5.23	3.84	4.06		4.44	5.83	2.76	8.37
	104	2.90	3.73	8.94	2.29	2.46	3.04		3.39	3.75	3.98	8.10
	105	3.05	2.76	6.79	2.47	2.16	2.12	5.87	3.66	2.34	2.29	
	106	4.08	2.42	10.20	4.26	3.50	2.10	10.96	5.10	5.38	3.55	9.95
	107	2.75	2.87	9.60	3.25	2.85	2.30	6.10	2.83	3.47	1.99	6.55
	108	2.87	2.79	10.08	3.16	2.48	1.84	10.32	4.00	2.63	2.19	8.37
	109	2.71	2.38	8.71	2.47	2.53	2.28		2.55	2.65	2.30	5.58
	MEAN	3.33	2.76	9.02	3.19	2.75	2.58	8.22	3.62	3.61	2.82	7.75
	STD DEV	0.95	0.59	1.06	1.03	0.57	0.67	2.24	0.87	1.24	0.70	1.42

STUDY: H-818-039-01
INVESTIGATOR: JOSEPH A. FRANCIOSA, MD

HEART RATE (BEATS/MIN) AT VARIOUS WORK LOAD LEVELS

TABLE 19

PATIENTS	ID NO	PREDRUG SUPINE	PREDRUG SITTING	PREDRUG MAXIMAL EXERCISE	2 HOURS POSTDOSE SUPINE	4 HOURS POSTDOSE SUPINE	4 HOURS POSTDOSE SITTING	4 HOURS POSTDOSE MAXIMAL EXERCISE	8 HOURS POSTDOSE SUPINE	24 HOURS POSTDOSE SUPINE	24 HOURS POSTDOSE SITTING	24 HOURS POSTDOSE MAXIMAL EXERCISE
	1	80.0	90.0	144.0	92.0	89.0	94.0	136.0	90.0	79.0	84.0	136.0
	2	68.0	68.0	122.0	74.0	72.0	74.0	138.0		80.0	87.0	125.0
	3	75.0	66.0	146.0	68.0	74.0	75.0	144.0	88.0	60.0	62.0	128.0
	4	70.0	70.0	117.0	72.0	74.0	74.0	108.0	77.0	80.0	77.0	108.0
	5	58.0	57.0	136.0	52.0	65.0	73.0	153.0		64.0	86.0	148.0
	6	56.0	60.0	100.0	56.0	68.0	68.0	136.0	65.0	68.0	88.0	152.0
	7	68.0	71.0	107.0	88.0	83.0	88.0	125.0	83.0	76.0	75.0	115.0
	8	107.0	115.0	155.0	118.0	121.0	129.0	150.0	117.0	115.0	115.0	158.0
	9	70.0	91.0	129.0	80.0	80.0	94.0	136.0	88.0	78.0	81.0	129.0
	10	87.0	88.0	120.0	71.0	82.0	82.0	136.0	92.0	75.0	85.0	125.0
	MEAN	73.9	77.6	127.6	77.1	80.8	85.1	136.2	86.5	77.5	83.2	132.4
	STD DEV	14.8	18.0	17.7	19.0	15.9	17.9	12.7	15.0	14.9	13.4	16.1

SUBJECTS	ID NO	PREDRUG SUPINE	PREDRUG SITTING	PREDRUG MAXIMAL EXERCISE	2 HOURS POSTDOSE SUPINE	4 HOURS POSTDOSE SUPINE	4 HOURS POSTDOSE SITTING	4 HOURS POSTDOSE MAXIMAL EXERCISE	8 HOURS POSTDOSE SUPINE	24 HOURS POSTDOSE SUPINE	24 HOURS POSTDOSE SITTING	24 HOURS POSTDOSE MAXIMAL EXERCISE
	101	70.0	86.0	188.0	64.0	64.0	75.0	188.0	103.0	75.0	86.0	176.0
	102	65.0	77.0	128.0	70.0	77.0	102.0	107.0	79.0	70.0	71.0	133.0
	103	96.0	96.0	167.0	97.0	86.0	94.0	172.0	98.0	90.0	94.0	174.0
	104	62.0	86.0	192.0	76.0	86.0	97.0	167.0	94.0	94.0	106.0	188.0
	105	78.0	75.0	188.0	75.0	70.0	74.0	167.0	83.0	70.0	75.0	163.0
	106	69.0	71.0	184.0	60.0	66.0	68.0	188.0	78.0	72.0	75.0	183.0
	107	68.0	79.0	197.0	72.0	79.0	93.0	197.0	79.0	80.0	105.0	197.0
	108	74.0	81.0	136.0	61.0	67.0	71.0	119.0	80.0	68.0	75.0	121.0
	109	94.0	100.0	168.0	88.0	79.0	91.0		94.0	87.0	91.0	149.0
	MEAN	75.1	83.4	172.0	73.7	74.9	85.0	163.1	87.6	78.4	86.4	164.9
	STD DEV	12.2	9.6	24.9	12.3	8.4	12.8	32.9	9.7	9.7	13.4	25.7

STUDY: R-818-039-01
INVESTIGATOR: JOSEPH A. FRANCIOSA, MD

TABLE 20

DATA AT MAXIMUM WORK LOADS

PATIENTS	PREDRUG					4 HOURS POSTDOSE					24 HOURS POSTDOSE				
ID NO	DUR	WORK	VCO2	VO2	RQ	DUR	WORK	VCO2	VO2	RQ	DUR	WORK	VCO2	VO2	RQ
1	7:34	300	16.3	10.5	1.55	6:36	300	14.9	12.0	1.24	7:30	300	17.3	12.8	1.36
2	8:50	300	14.5	11.7	1.24	7:20	300	15.1	13.5	1.12	9:10	450	15.5	12.3	1.26
3	5:41	300	8.9	8.6	1.04	5:30	300	8.9	8.7	1.02	4:05	150	8.1	7.5	1.08
4	14:23	600	19.2	15.6	1.23	13:16	600	16.8	14.7	1.28	13:00	600	19.2	17.5	1.10
5	6:36	300	16.4	12.3	1.33	6:50	300	14.9	12.2	1.22	7:31	300	16.7	13.6	1.23
6	10:54	450	16.7	12.6	1.32	10:32	450	16.3	12.2	1.34	10:05	450	20.6	14.2	1.43
7	5:31	300	13.6	11.4	1.20	5:30	300	12.6	11.0	1.16	6:10	300	10.9	11.8	0.93
8	8:05	300	21.5	16.2	1.33	7:17	300	21.8	17.1	1.29	10:23	450	23.2	19.7	1.18
9	10:00	450	10.4	16.5	0.63	10:04	450	7.5	12.0	0.62	10:13	450	10.8	13.0	0.82
10	3:06	150	12.2	13.0	0.94	2:36	150	15.8	16.3	0.98	1:58	150	14.3	13.2	1.08
MEAN	8:04	345	15.0	12.8	1.18	7:33	345	14.7	13.0	1.13	8:00	360	15.6	13.6	1.15
STD DEV	3:11	123	3.9	2.6	0.26	3:01	123	4.2	2.5	0.21	3:16	145	4.7	3.3	0.19

SUBJECTS	PREDRUG					4 HOURS POSTDOSE					24 HOURS POSTDOSE				
ID NO	DUR	WORK	VCO2	VO2	RQ	DUR	WORK	VCO2	VO2	RQ	DUR	WORK	VCO2	VO2	RQ
101	13:32	600	33.0	32.8	1.00	13:24	600	32.3	25.5	1.27	13:52	600	29.9	29.3	1.01
102	17:42	750	24.8	23.9	1.04	10:15	450	15.0	15.4	0.97	17:40	750	20.6	19.0	1.08
103	16:40	600	27.9	26.2	1.06	10:10	450	22.9	23.4	0.99	11:25	450	32.1	27.1	1.19
104	18:04	750	26.9	21.3	1.26	13:24	600	18.5	17.3	1.07	14:10	600	22.6	23.4	0.96
105	17:43	750	24.3	30.0	0.81	15:41	600	23.6	24.4	0.97	17:06	750	29.3	26.7	1.10
106	22:07	900	33.2	32.3	1.03	21:51	900	34.4	35.0	0.99	18:12	750	27.0	32.0	0.84
107	14:14	600	30.0	24.8	1.21	14:35	600	29.6	27.7	1.07	15:19	600	27.8	23.8	1.17
108	15:38	600	23.5	20.8	1.13	15:28	600	23.9	22.4	1.07	17:26	750	24.0	19.8	1.21
109	13:50	600	23.8	25.7	0.93	12:50	600	21.2	23.3	0.91	13:32	600	21.7	22.0	0.97
MEAN	16:36	683	27.5	26.4	1.05	14:10	600	24.6	23.8	1.03	15:24	650	26.1	24.8	1.06
STD DEV	2:42	109	3.8	4.4	0.14	3:29	130	6.4	5.7	0.10	2:19	106	4.0	4.3	0.12

NOTE: DUR = DURATION OF EXERCISE (MIN:SEC)
WORK = MAXIMAL WORK LOAD (KPM/MIN)
VCO2 = TOTAL BODY CO2 PRODUCTION (ML/KG/MIN)
VO2 = TOTAL BODY O2 CONSUMPTION (ML/KG/MIN)
RQ = RESPIRATORY QUOTIENT (VCO2 / VO2)

TABLE 21

Time to Peak Plasma Concentration, Peak Plasma Concentration, and Area Under the Plasma Concentration Versus Time Curve (AUC) for Flecainide Acetate Following Oral Administration of a Single, 200 mg Dose to Patients and Subjects

Patient/Subject Number	Dose (mg/kg)	Time to Peak Level (hours)	Peak Plasma Concentration (ng/ml)	Plasma AUC Value Zero to Infinity (ng.hours/ml)	AUC.k_{el} per one mg/kg (ng/ml)
Congestive Heart Failure Patients					
1	3.39	3.8	186	4592	59.2
2	2.86	7.8	136	3567	63.1
3	2.30	3.0	193	5845	71.9
4	2.67	5.0[a]	209	9216	91.8
5	2.25	6.0	176	5204	96.0
6	2.45	4.0	204	4769	92.7
7	2.28	3.0	327	12240	146.0
8	3.51	2.9	194	5020	64.9
9	2.30	8.0	213	8695	103.6
10	3.93	6.1	265	7378	76.4
Mean	2.79	5.0	210	6653	86.6
Std. Dev.	0.61	1.9	52	2692	26.0
Healthy Subjects					
101	3.57	5.3	203	4059	75.4
102	2.22	2.0	212	4599	100.9
103	2.81	8.0	255	8119	111.0
104	2.09	4.0	282	6481	152.9
105	2.73	4.0	250	4781	113.0
106	2.80	4.0[a]	241	5172	100.5
107	3.53	3.2	194	3462	63.1
108	2.84	6.0	150	4018	65.2
109	3.18	8.0	156	4998	60.5
Mean	2.86	4.3	216	5077	93.6
Std. Dev.	0.51	2.1	45	1428	30.5

[a] Value obtained by interpolation between adjacent time points.

TABLE 22

Plasma Pharmacokinetic Parameters of Flecainide Acetate Following Oral Administration of a Single, 200 mg Dose to Patients and Subjects

Patient/Subject Number	Plasma Half-Life (hours)	Elimination Rate Constant ($hours^{-1}$)	Plasma Clearance[a] (ml/min/kg)	Volume of Distribution[b] (l/kg)
Congestive Heart Failure Patients				
1	15.8	0.0437	12.3	16.9
2	13.7	0.0506	13.4	15.8
3	24.5	0.0283	6.6	13.9
4	26.0	0.0266	4.8	10.9
5	16.7	0.0415	7.2	10.4
6	14.5	0.0476	8.6	10.8
7	25.5	0.0272	3.1	6.8
8	15.3	0.0454	11.7	15.4
9	25.3	0.0274	4.4	9.7
10	17.0	0.0407	8.9	13.1
Mean	19.4	0.0379	8.1	12.4
Std. Dev.	5.2	0.0095	3.5	3.2
Healthy Subjects				
101	10.4	0.0663	14.7	13.2
102	14.2	0.0487	8.0	9.9
103	18.1	0.0384	5.8	9.0
104	14.1	0.0493	5.4	6.6
105	10.7	0.0645	9.5	8.9
106	12.7	0.0544	9.0	10.0
107	10.8	0.0643	17.0	15.9
108	15.0	0.0461	11.8	15.3
109	18.0	0.0385	10.6	16.5
Mean	13.8	0.0523	10.2	11.7
Std. Dev.	2.9	0.0108	3.8	3.6

[a] Plasma clearance or total body clearance is the dose divided by the plasma AUC from zero to infinity.

[b] Apparent volume of distribution is the dose divided by the product of the plasma AUC from zero to infinity and the elimination rate constant.

FIGURE 12

R-818-054-01 SINGH
Means of Heart Rate (beats per minute)

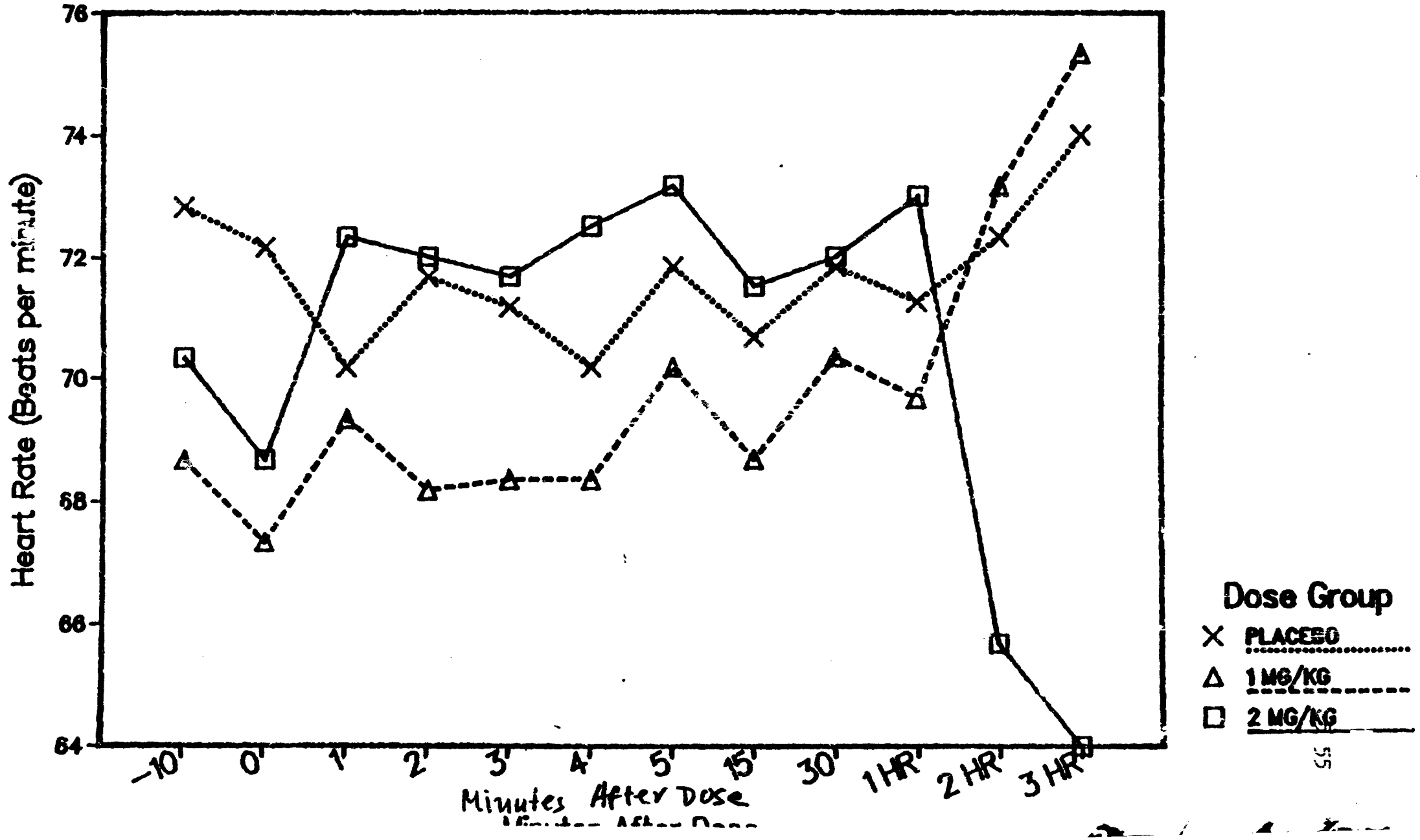


FIGURE 23

R-818-054-01 SINGH
Means of Corrected QT Interval (secs)

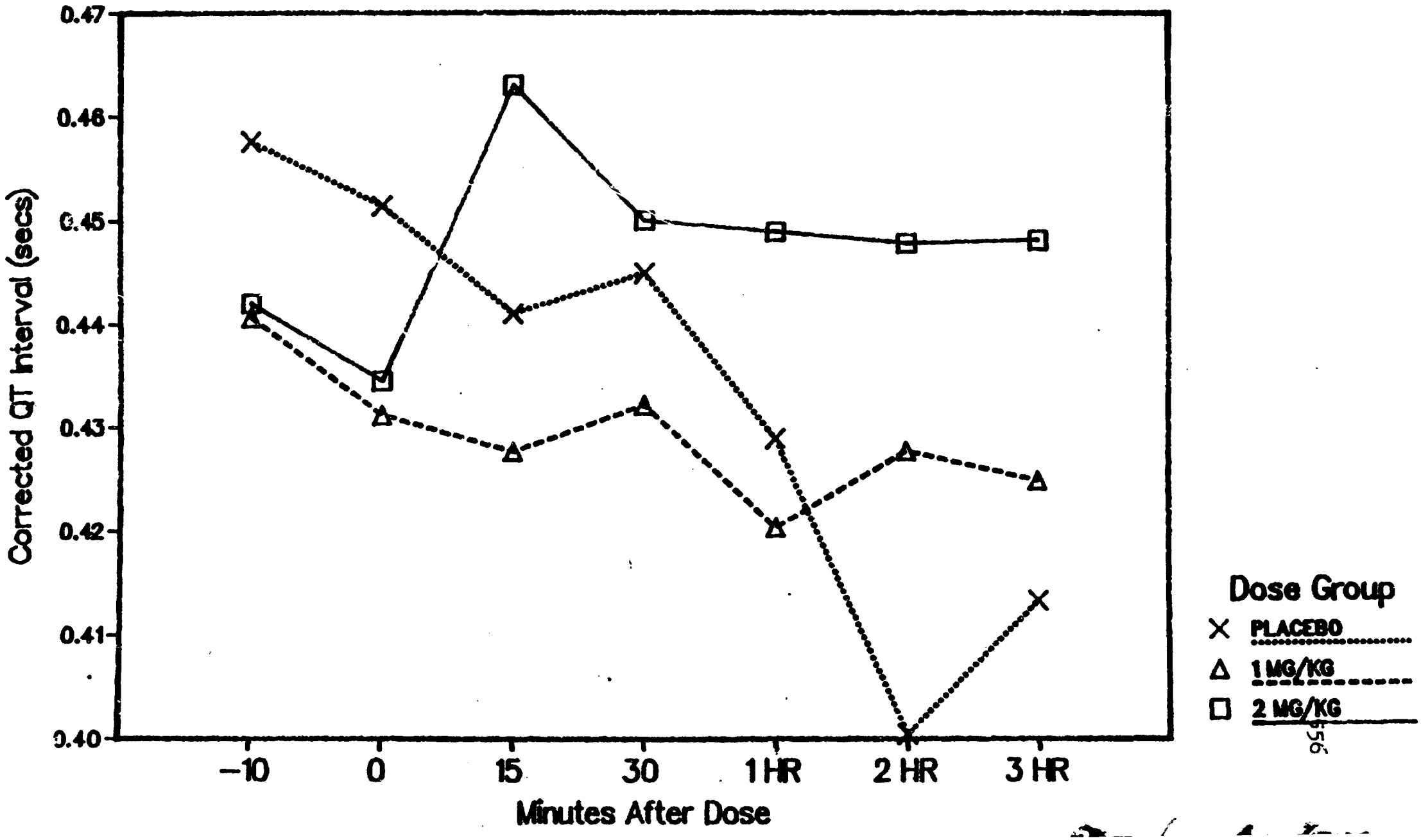


FIGURE 14

R-818-054-01 SINGH
Means of Systolic Blood Pressure (mmHg)

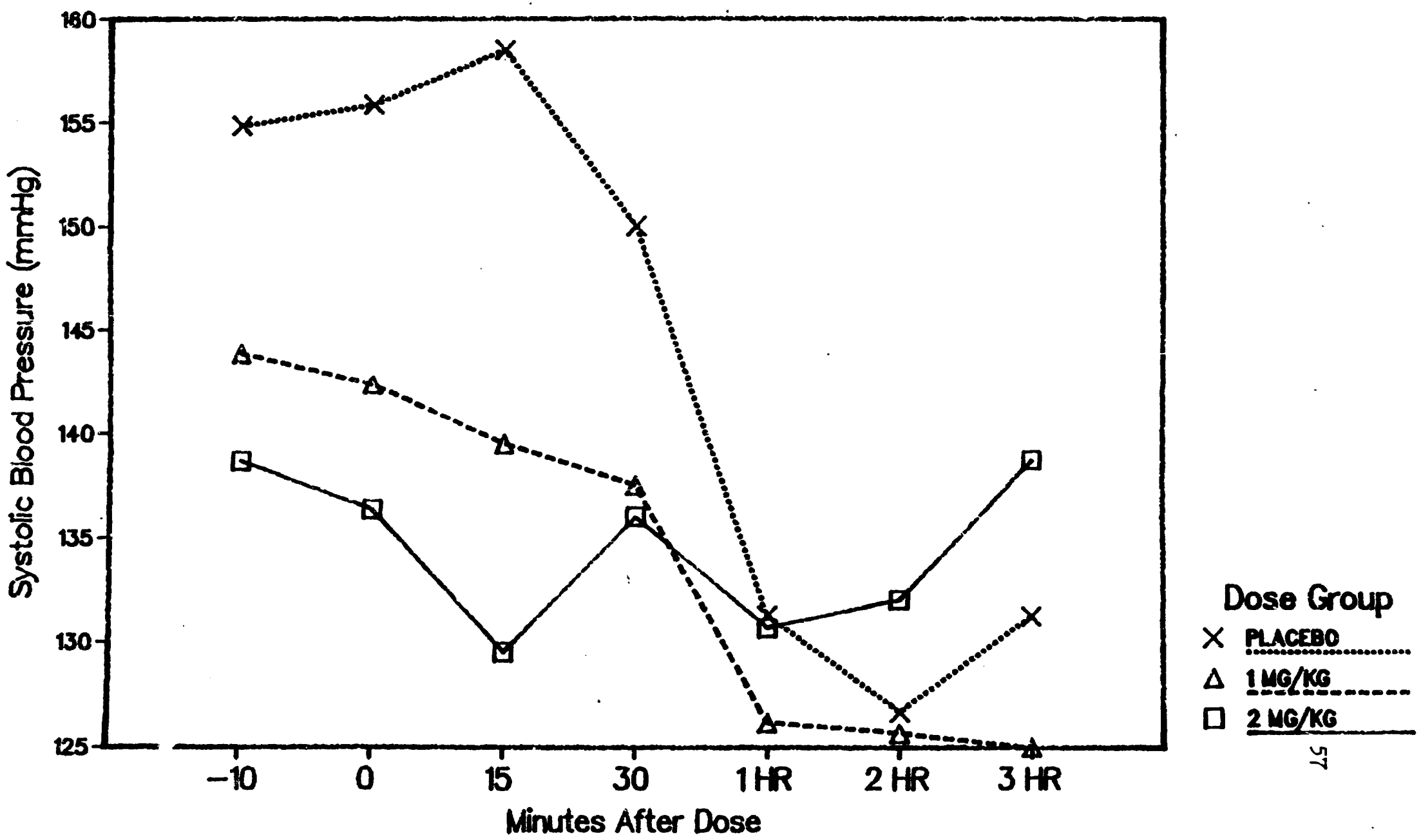


FIGURE 15

R-818-054-01 SINGH
Means of Diastolic Blood Pressure (mmHg)

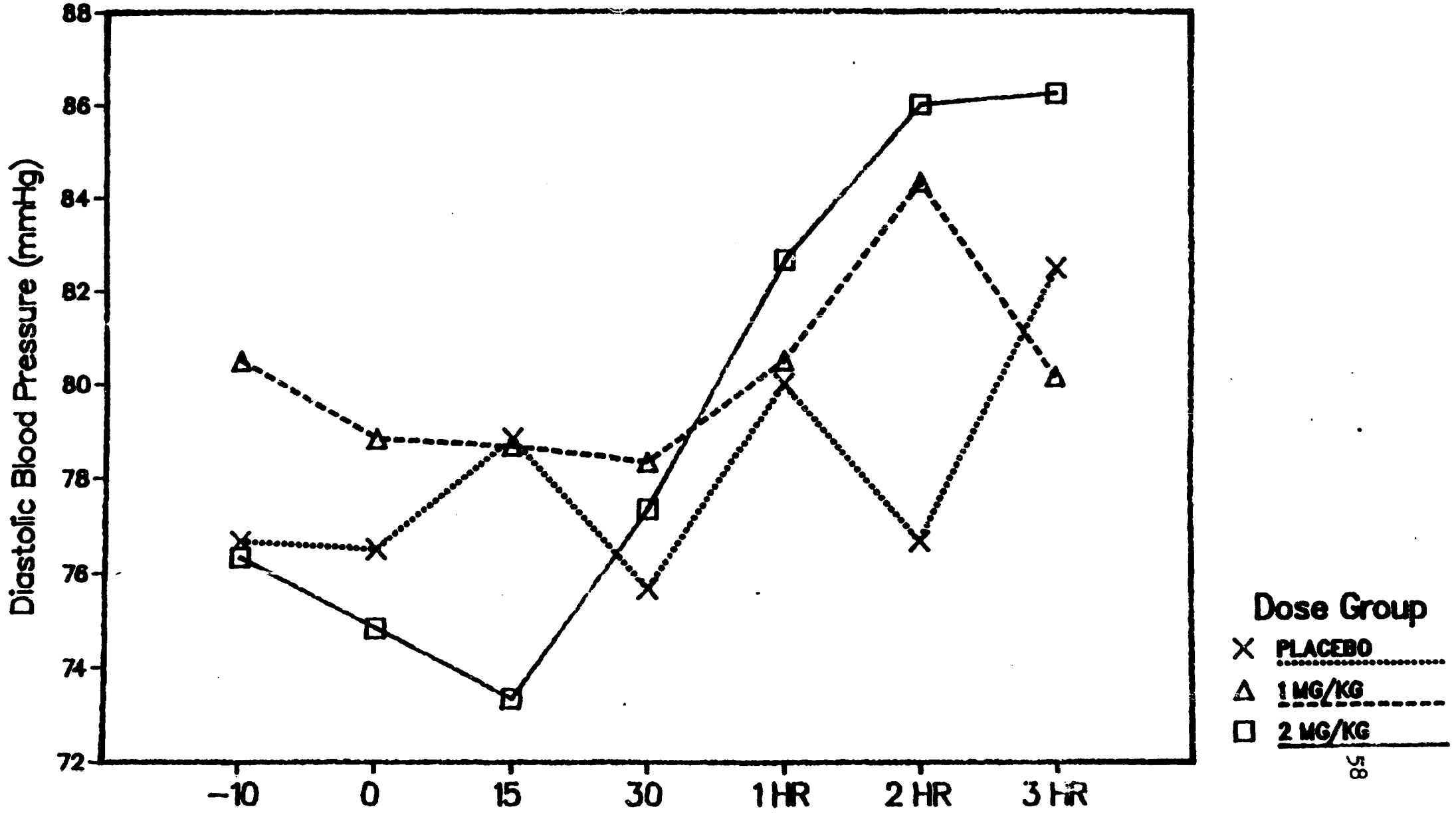


FIGURE 16

R-818-054-01 SINGH
Means of Thermodilution Stroke Volume (ml)

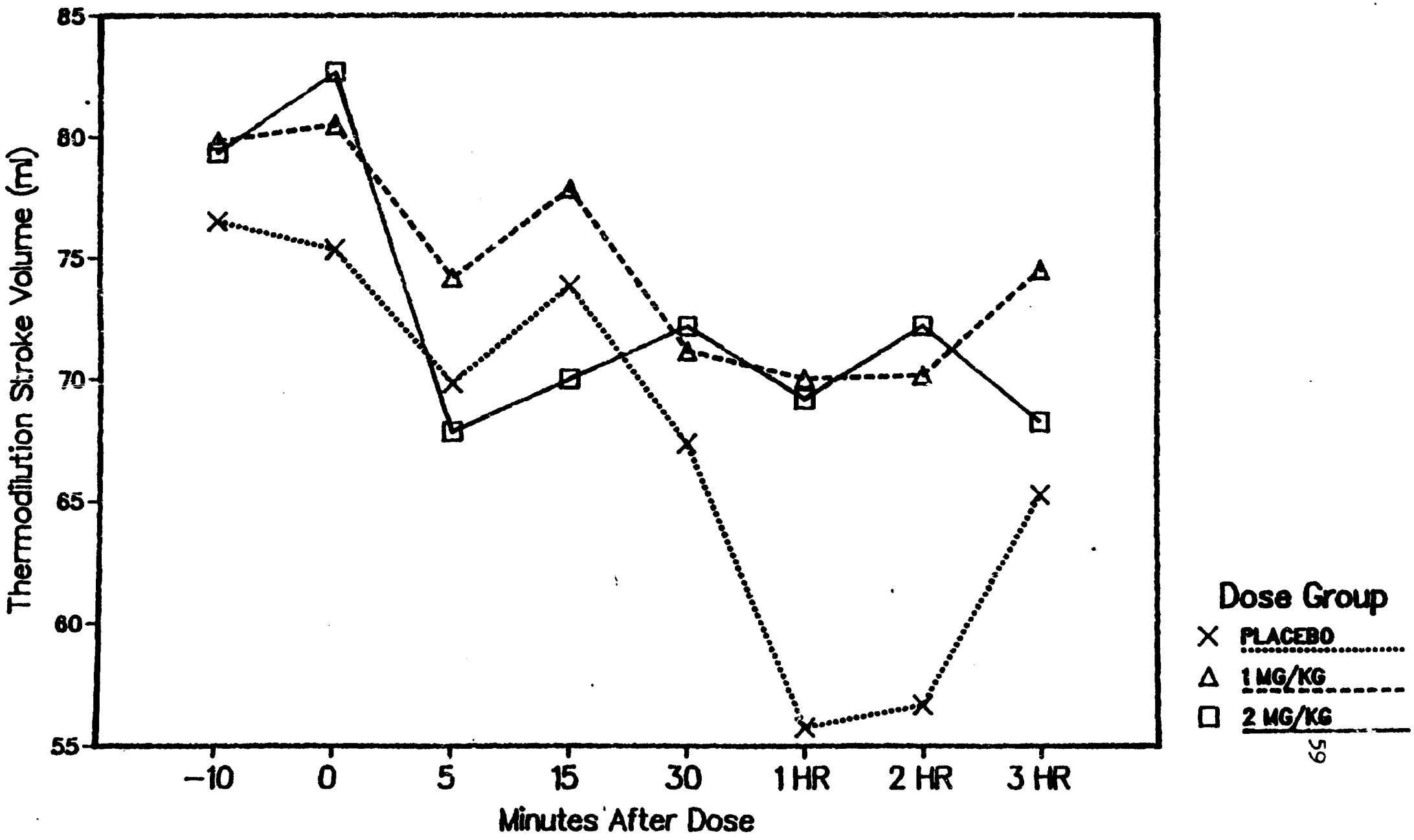


FIGURE 17

R-818-054-01 SINGH
Means of Stroke Work (gram meters)

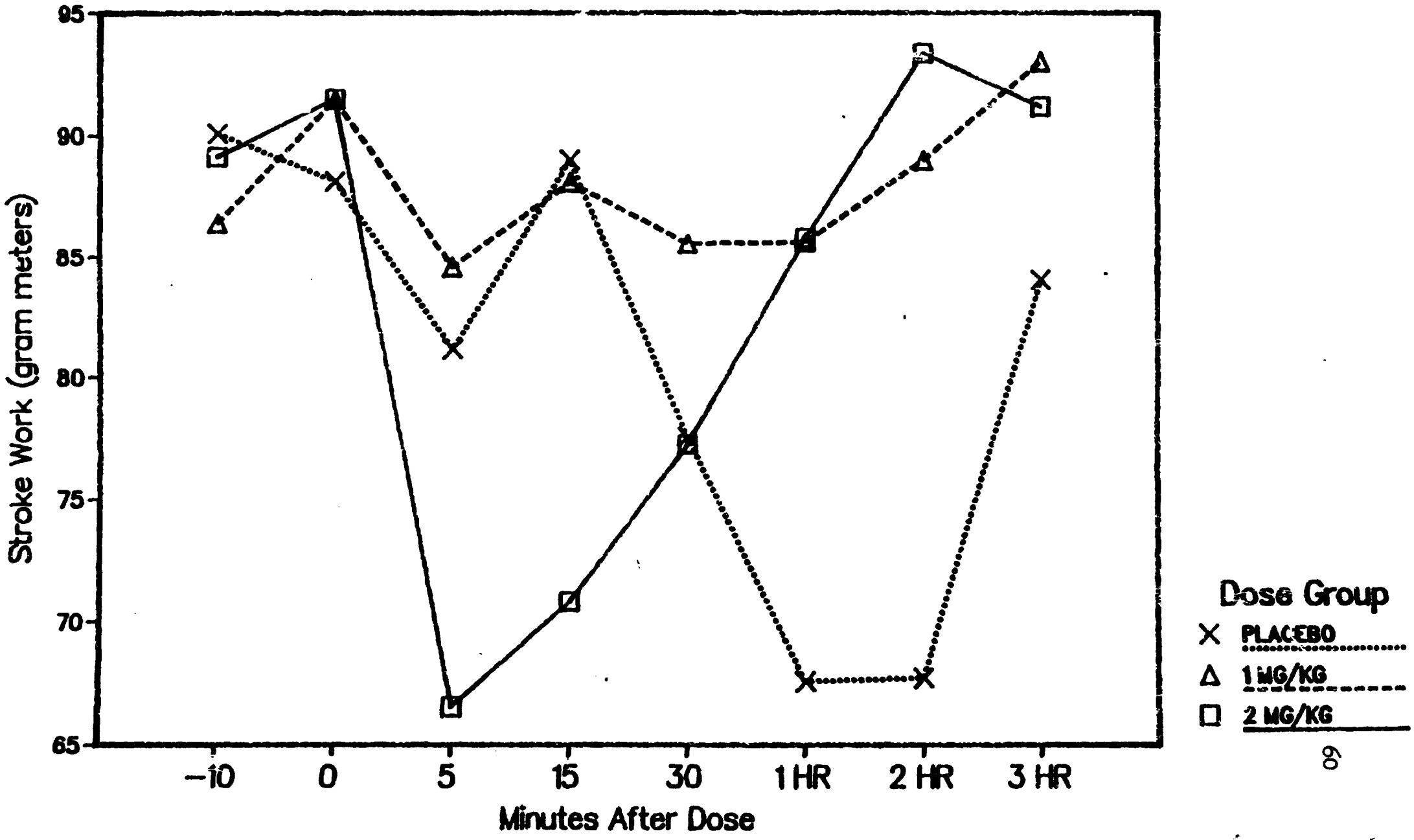


FIGURE 18

R-818-054-01 SINGH
Means of Left Ventricular Systolic Pressure (mmHg)

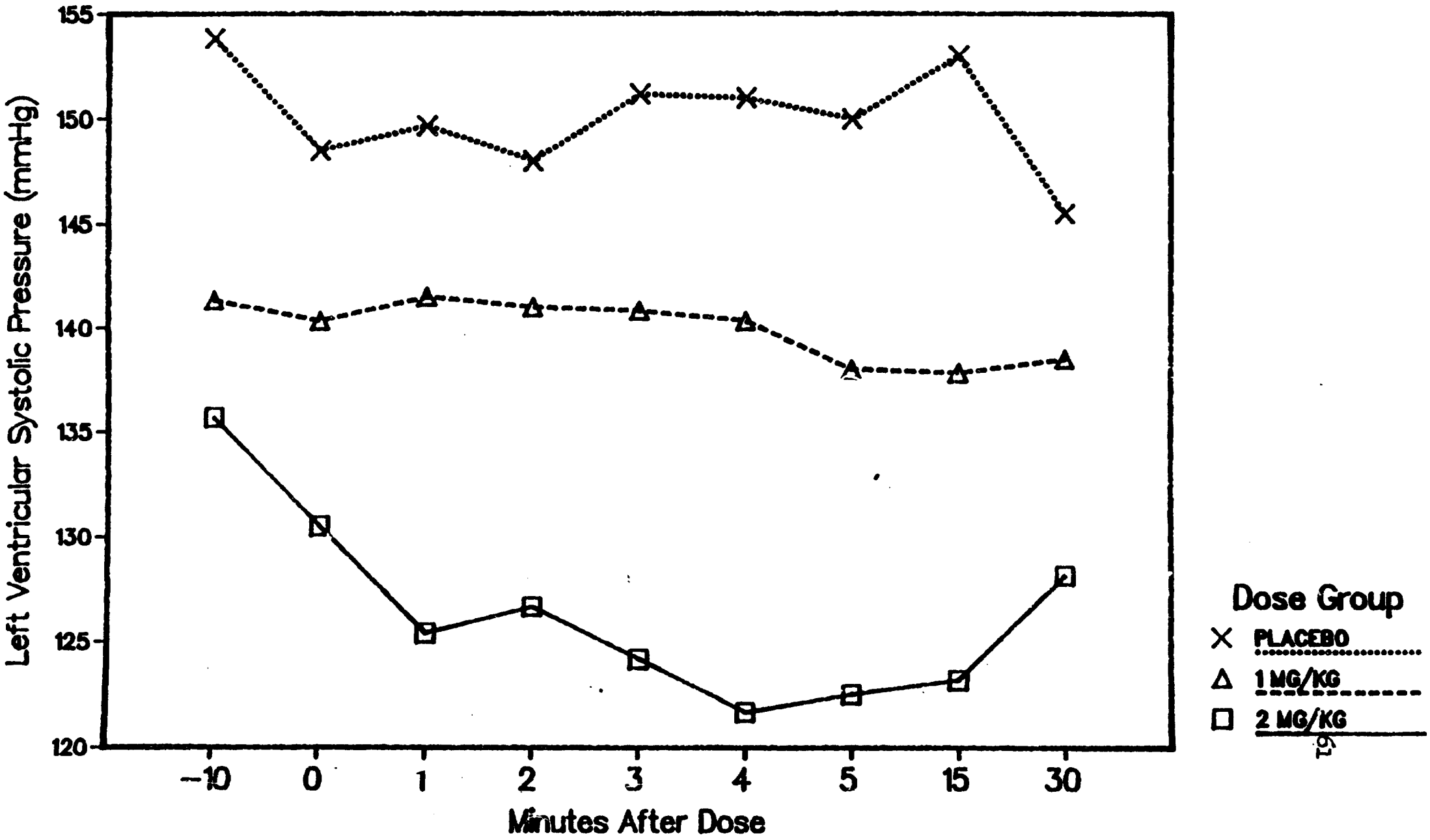


FIGURE 19

R-818-054-01 SINGH
Means of Left Ventricular End Diastolic Pressure (mmHg)

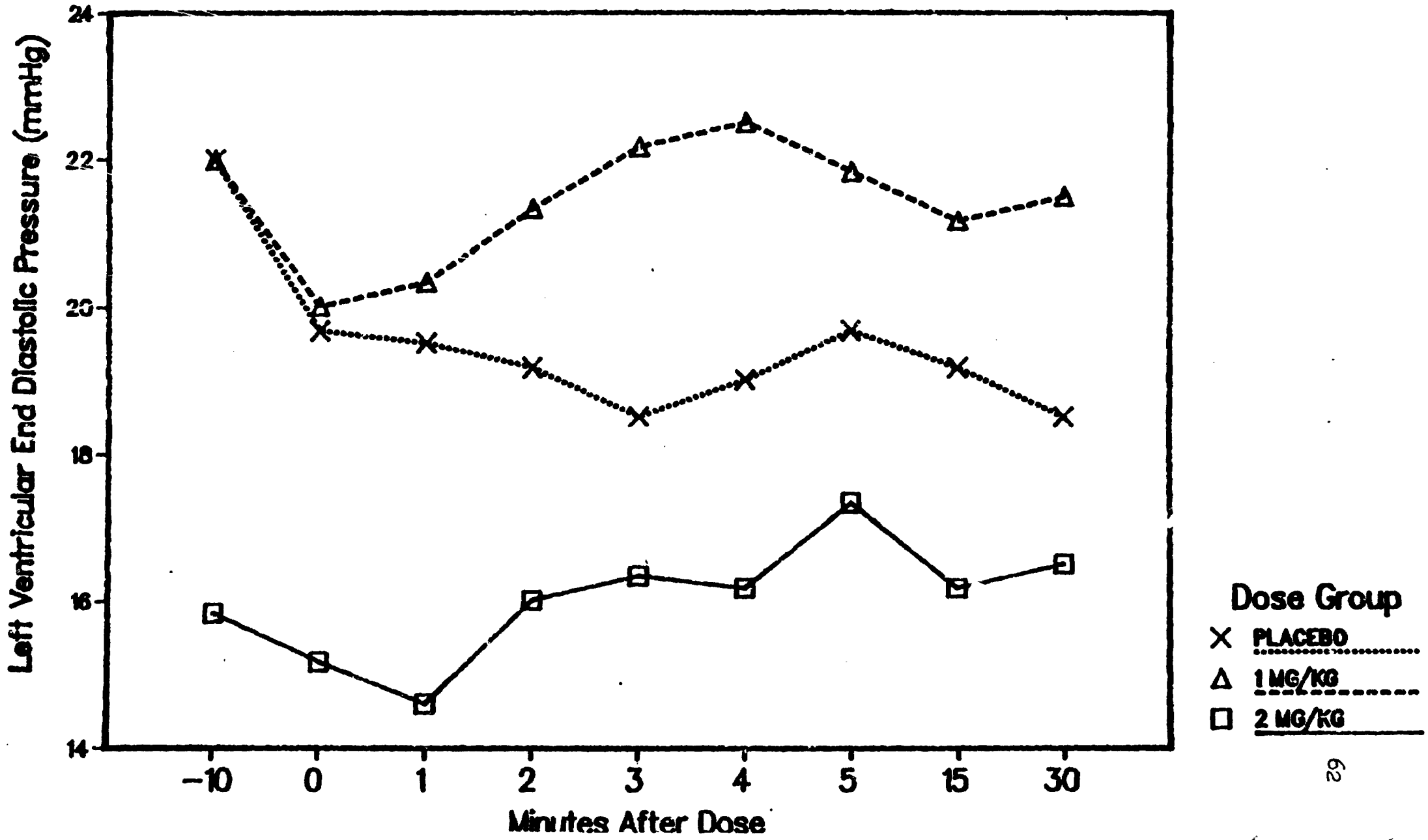


FIGURE 20

R-818-054-01 SINGH
Means of Pulmonary Artery Systolic Pressure (mmHg)

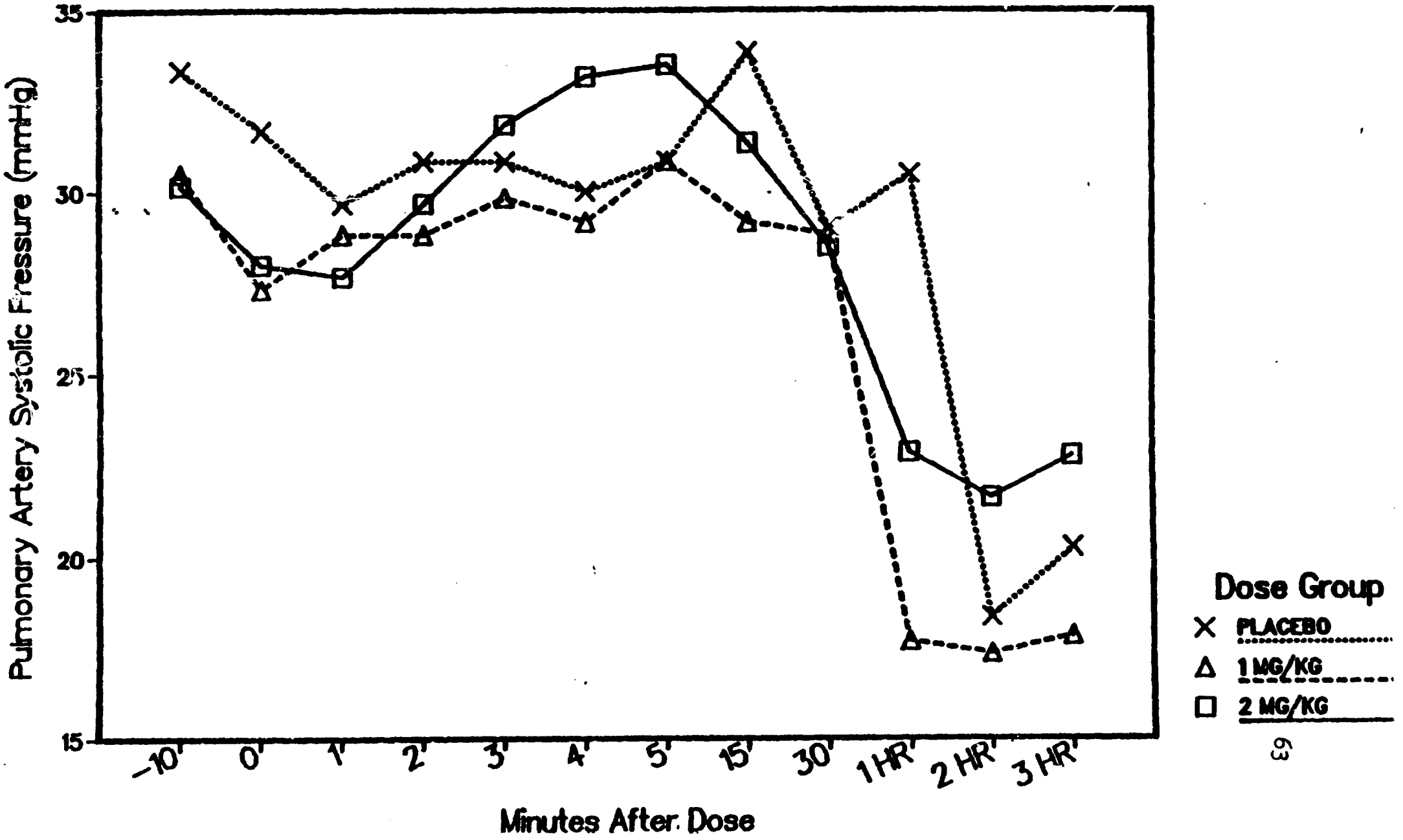


FIGURE 24

R-818-054-01 SINGH
Means of Pulmonary Wedge Pressure (mmHg)

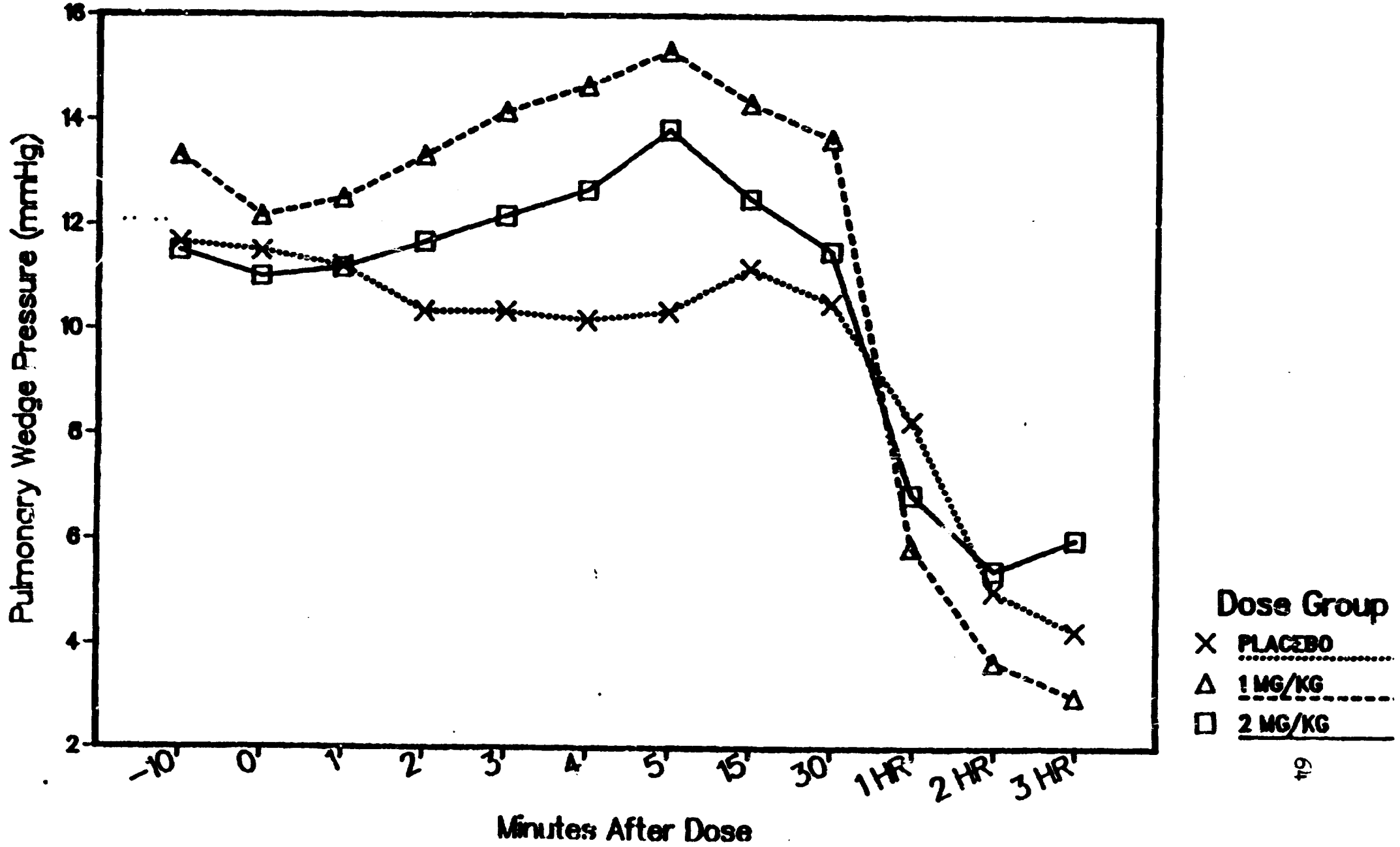


Figure 22: Hemodynamic effects of flecainide

V. Legrand et al.

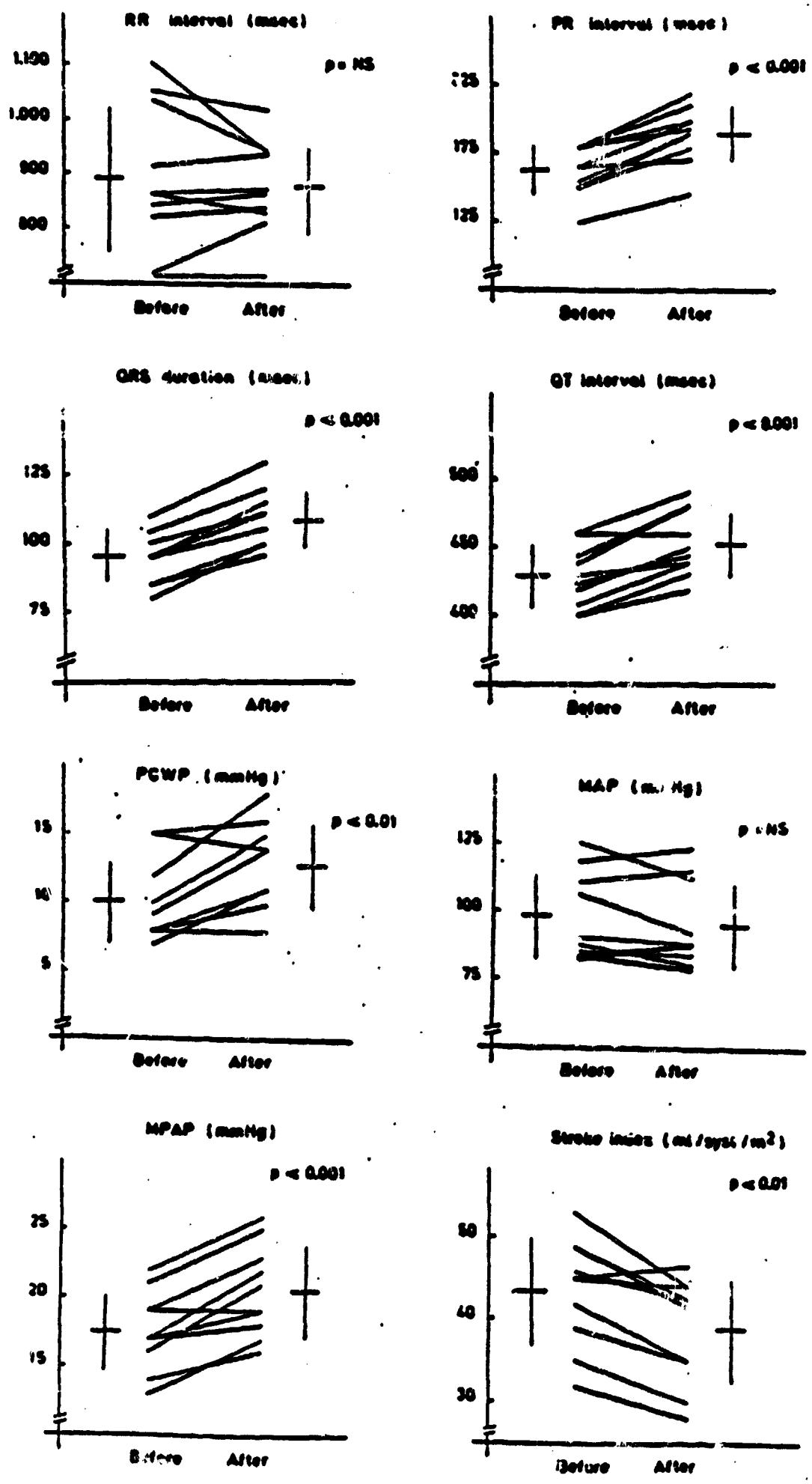


Figure 22 : Hemodynamic effects of flecainide
V. Legrand (continued)

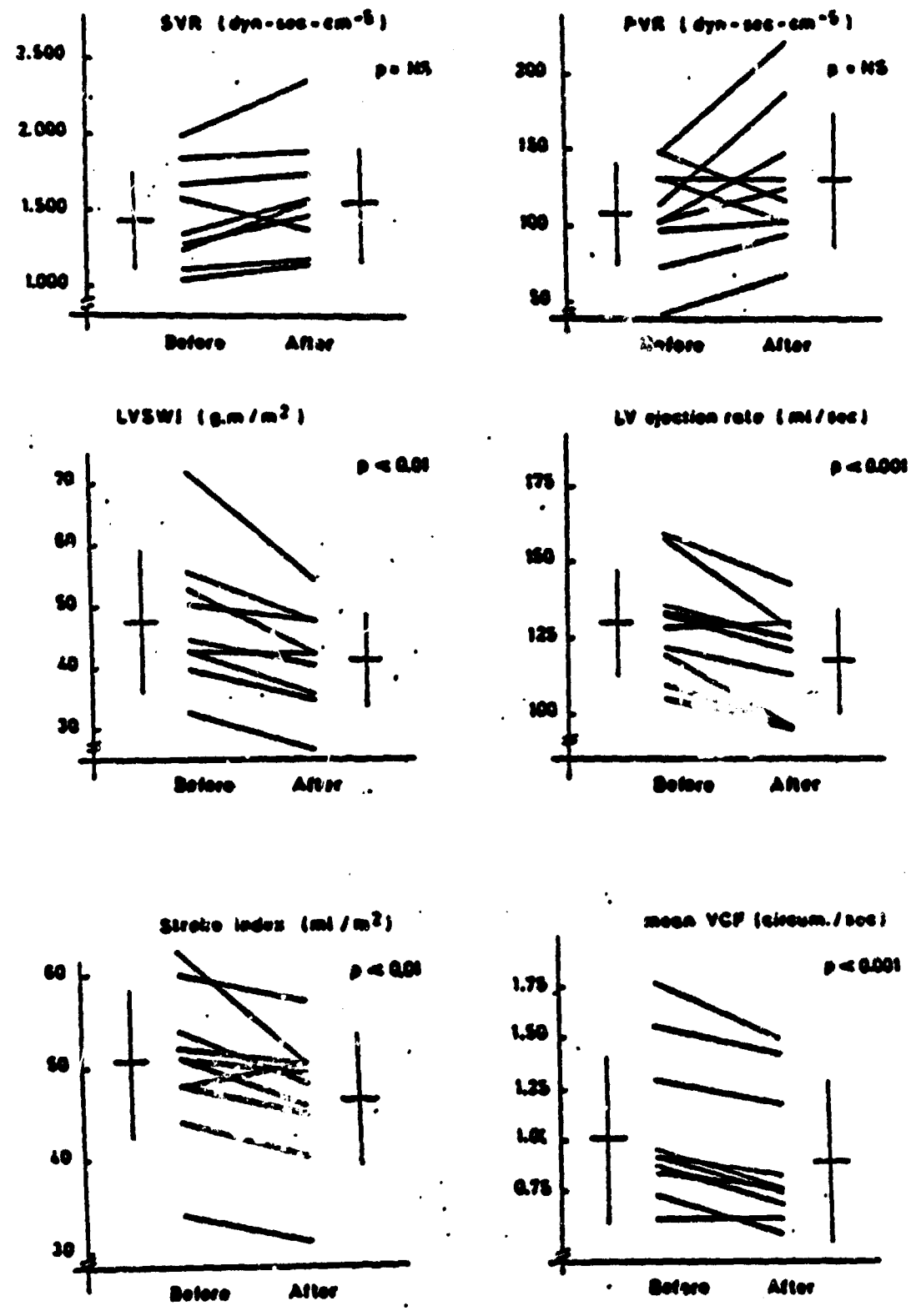
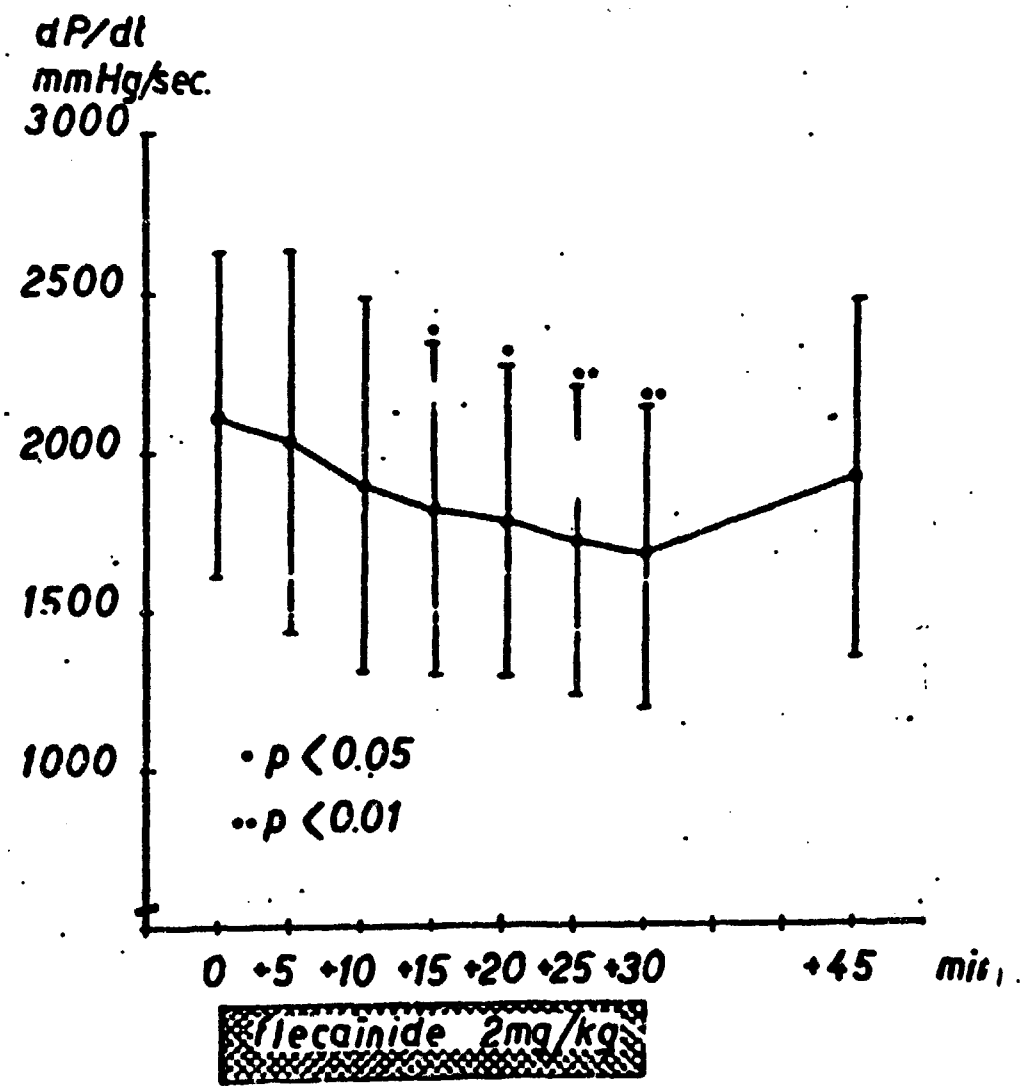


Figure 23: Hemodynamic data (V. Legrand)

Mean variations of dp/dt observed during flecainide infusion and 15 minutes after the end of injection.



The p value indicated is the level of significance of t test for paired data, comparison is made the basal value before flecainide infusion.

STUDY: R-818-015-01
INVESTIGATOR: RICHARD H. HELFANT, MD

TABLE 24

HIS BUNDLE ELECTROGRAM DATA FOR THE FIVE PATIENTS WITH UNDERLYING CONDUCTION ABNORMALITIES ON PRESTUDY ECG

Patient Number	ECG	PA Interval (msec) Minutes Postdose					A-H Interval (msec) Minutes Postdose					H-V Interval (msec) Minutes Postdose				
		Control	10	20	30	40	Control	10	20	30	40	Control	10	20	30	40
1	First degree heart block	30	[a]	25	30	20	160	[a]	175	155	160	40	[a]	40	40	40
3	Left anterior hemiblock	25	30	28	30		130	135	135	130		60	60	60	60	
5	Left bundle branch block	30	30	30	35		100	100	100	100		45	50	50	60	
7	Right bundle branch block and bifasicular block	10	20	20	20		80	80	80	80		60	80	80	75	
11	Right bundle branch block and bifasicular block	10	15	21	[a]		62	72	70	67		62	62	64.5	42	
Mean difference			5.00	3.80	5.00			3.75	5.60	0.00			6.25	7.60	2.00	
Standard deviation			4.08	6.76	4.08			4.79	6.27	3.54			9.46	9.29	14.40	
P-values:(t-test)			0.09	0.28	0.09			0.22	0.12	1.00			0.27	0.14	0.77	
Comparison of all 15 patients																
Mean difference			0.69	0.93	1.46			5.07	6.13	3.33			4.36	6.13	5.00	
Standard deviation			7.50	7.59	6.35			10.25	8.68	8.66			7.84	8.93	9.82	
P-values (t-test)			0.74	0.65	0.42			0.087	0.016	0.10			0.058	0.016	0.069	

[a] Not obtained.

Table 25: Electrophysiologic Effects of Flecainide in Man
Seipel et al.

. Wirkung von Flecainid 1 mg/kg auf die Sinusknotenfunktion bei Patienten mit normaler Ausgangssituation. A-A = spontane Periodendauer; SNRT = Sinusknotenerholungszeit; CSNRT = frequenzkorrigierte SNRT; SACT = kalkulierte sinu-atriale Leitungszeit.

	n	A-A ms	SNRT ms	CSNRT ms	SACT ms
Kontrolle	13	705,2 ± 94,2	1012,3 ± 122,3	307,1 ± 115,1	73,3 ± 17,2*)
1 mg/kg		727,1 ± 91,9	1036,9 ± 179,2	313,9 ± 137,8	75,0 ± 17,4*)
Kontrolle	8	862,5 ± 132,0	1165,0 ± 137,4	296,5 ± 105,8	-
2 mg/kg		831,6 ± 143,9	1238,3 ± 311,5	406,7 ± 267,2	-

*) n = 10

Effekt von Flecainid 1 mg/kg auf die intrakardialen Leitungszeiten bei 12 Patienten mit normaler Ausgangssituation. HRA-A = Leitungszeit vom hohen zum basalen rechten Vorhof; A-H = Leitungszeit vom basalen Vorhof zum Hisschen Bündel; H-V = Zeit von der His-Bündel-Aktivierung bis zur frühesten Ventrikelerregung; V-RVA = Zeit von der frühesten Ventrikelseptumaktivierung bis zur Depolarisation der rechten Ventrikelspitze; QRS = Breite des Kammerkomplexes; S-S 600 = konstante, stimulierte Vorhoffrequenz von 100/min.

		HRA-A	A-H	A-H (S-S 600)	H-V	V-RVA	QRS
Kontrolle	ms	26,0 ± 7,0	83,8 ± 8,1	99,5 ± 18,4	45,1 ± 8,2	21,3 ± 8,4*)	84,5 ± 6,0
1 mg/kg	ms	28,7 ± 8,1	95,1 ± 13,6	119,4 ± 35,0	52,5 ± 6,5	27,5 ± 12,0	91,3 ± 8,4
Differenz	%	+ 10,4	+ 13,5	+ 20,0	+ 15,7	+ 29,1	+ 8,1
Signifikanz	P	< 0,05	< 0,001	< 0,001	< 0,001	< 0,005	< 0,005

*) n = 9

Effekt von Flecainid 2 mg/kg auf die intrakardialen Leitungszeiten bei 6 Patienten mit normaler Ausgangssituation.

		HRA-A	A-H	A-H S-S 600	H-V	V-RVA	QRS
Kontrolle	ms	24,3 ± 6,7	76,5 ± 20,8	102,0 ± 42,1	48,3 ± 10,3	20,0 ± 5,0	84,4 ± 17,7
2 mg/kg	ms	26,5 ± 7,5	95,2 ± 19,5	142,2 ± 83,2	67,7 ± 7,4	23,3 ± 2,8	104,8 ± 21,6
Differenz	%	+ 9,0	+ 24,4	+ 39,4	+ 40,2	+ 16,5	+ 24,2
Signifikanz	p	ns	< 0,005	< 0,005	< 0,001	< 0,05	< 0,005

Wirkung von Flecainid 1 mg/kg auf die effektive (ERP) und funktionelle (FRP) Refraktärzeit von Vorhof (A), A-V Knoten (AVN) und Ventrikel (V) sowie auf den sog. Wenckebach-Punkt (WP) bei 12 Patienten mit normaler Ausgangssituation.

		ERP A	FRP AVN	ERP AVN	ERP V	WP
Kontrolle	ms	205,8 ± 17,8	396,0 ± 43,6*)	278,3 ± 37,6*)	218,9 ± 3,3	341,0 ± 66,6
1 mg/kg	ms	214,6 ± 22,6	427,8 ± 27,4	320,0 ± 43,8	231,1 ± 14,5	371,0 ± 69,6
Differenz	%	+ 4,3	+ 8,0	+ 15,0	+ 5,6	+ 8,0
Signifikanz	p	ns	< 0,05	ns	< 0,05	< 0,01

*) n = 9 (3 Pat. 1:1 Leitung bis ERP A).

Tab. 5. Wirkung von Flecainid 2 mg/kg iv. auf die Refraktärität der verschiedenen Herzabschnitte bei 6 Patienten mit normalen Ausgangsbedingungen.

		ERP A	FRP AVN	ERP AVN	ERP V	WP
Kontrolle	ms	212,0 ± 16,4	435,0 ± 49,5	310,0 ± 36,1*)	219,0 ± 8,9	340,0 ± 46,2
2 mg/kg	ms	246,0 ± 25,1	450,0 ± 14,1	348,3 ± 23,6*)	242,0 ± 16,4	397,0 ± 30,1
Differenz	%	+ 16,0	-	+ 12,4	+ 10,5	+ 16,8
Signifikanz	p	< 0,01	-	ns	< 0,01	< 0,05

*) n = 4 (2 Pat. mit 1:1 Leitung bis ERP A).

Table 26: Acute electrophysiologic effects of flecainide
Hellestrand et al.

Conduction intervals

Interval	*No.*	*Control (ms) (mean ± SD)*	*Flecainide (ms) (mean ± SD)*	*Statistical significance (p)*
Sinus cycle length	47	745 ± 198	734 ± 180	NS
PA	43	41 ± 13	50 ± 13	<0·001
AH (SR)	43	67 ± 21	81 ± 33	<0·001
AH (AP)	43	84 ± 38	101 ± 39	<0·001
HV	39	44 ± 9	61 ± 12	<0·001
QRS	47	96 ± 21	118 ± 30	<0·001
QT (SR)	39	368 ± 43	382 ± 44	<0·02
QT (AP)	39	342 ± 25	349 ± 30	<0·01
QTc	39	427 ± 34	446 ± 40	<0·001
JT	39	246 ± 27	232 ± 33	<0·001
WCL (AV)	19	371 ± 153	410 ± 178	<0·05
WCL (VA)	19	355 ± 91	496 ± 72	<0·001

PA, right intra-atrial conduction time; AH (SR), AV nodal conduction time in sinus rhythm; AH (AP), AV nodal conduction time during atrial pacing; HV, H to V conduction time; QRS, QRS duration; QT (SR), QT interval during sinus rhythm; QT (AP), QT interval during atrial pacing; QTc, the corrected QT interval; JT, the JT interval during atrial pacing (QT–QRS); WCL (AV), anterograde Wenckebach periodicity of the AV node; WCL (VA), retrograde Wenckebach periodicity of the AV node.

Refractory periods

Refractory period	*No.*	*Control (ms) (mean ± SD)*	*Flecainide (ms) (mean ± SD)*	*Statistical significance (p)*
A ERP	47	213 ± 32	219 ± 28	NS
AVN ERP	10	314 ± 66	287 ± 21	NS
V ERP	47	220 ± 22	229 ± 23	<0·01
AHfast (AV)	12	342 ± 59	364 ± 59	NS
AHfast (VA)	11	315 ± 99	450 ± 144	<0·01
AHslow (AV)	6	277 ± 40	293 ± 37	NS
AHslow (VA)	1	280	300	
AP (AV)	8	262 ± 47	361 ± 138	<0·05
AP (VA)	13	300 ± 49	453 ± 169	<0·01

A ERP, atrial effective refractory period; AVN ERP, AV nodal effective refractory period; V ERP, ventricular effective refractory period; AHfast (AV), anterograde refractoriness of "fast" AH pathway; AHfast (VA), retrograde refractoriness of "fast" AH pathway; AHslow (AV), anterograde refractoriness of "slow" AH pathway; AHslow (VA), retrograde refractoriness of "slow" AH pathway; AP (AV), anterograde refractoriness of accessory pathway; AP (VA), retrograde refractoriness of accessory pathway.

R-818-030-01
Investigator: Jeffrey Anderson, MD

TABLE 27

HOLTER ANALYSIS
PVCs/HOUR - 24-HOUR AVERAGES
(Percent Suppression of Baseline PVCs in Parentheses)

PTNO	Baseline Period	24-Hour Holter From Third Day Of Dose				Washout Day 1	Washout Day 3	Outpatient Day 7A	Outpatient Day 14A
		100 mg bid	200 mg bid	250 mg bid	300 mg bid				
1	147.3	26.1 (82.3%)	1.0 (99.3%)	--	--	239.1 (-62.3%)	602.9 (-309.2%)	0.7 (99.5%)	2.0 (98.6%)
2	2541.2	1060.5 (58.3%)	0.5 (100.0%)	--	--	587.7 (76.9%)	2110.5 (16.9%)	4.5 (99.8%)	0.0 (100.0%)
3	600.4	228.6 (61.9%)	505.1 (15.9%)	58.9 (90.2%)	--	368.0 (38.7%)	246.3 (59.0%)	6.1 (99.0%)	6.2 (99.0%)
4	948.6	447.1 (52.9%)	[a]	--	--	--	--	--	--
5	90.0	2.6 (97.1%)	--	--	--	2.3 (97.5%)	54.3 (39.7%)	17.2 (80.9%)	6.4 (92.9%)
6	363.4	18.5 (94.9%)	--	--	--	[b]	281.5 (22.5%)	51.6 (85.8%)	109.4 (69.9%)
7	1869.7[c]	504.5 (73.0%)	0.0 (100.0%)	--	--	20.9 (98.9%)	4711.7 (-152.0%)	0.0 (100.0%)	28.4 (98.5%)
8	152.8	371.3 (-143.1%)	[b]	0.3 (99.8%)	--	62.5 (59.1%)	281.4 (-84.2%)	0.1 (99.9%)	1.8 (98.8%)
9	1792.7	1533.3 (14.5%)	0.0 (100.0%)	--	--	930.7 (48.1%)	[b]	0.0 (100.0%)	0.0 (100.0%)
11	644.1	632.9 (1.7%)	520.7 (19.1%)	--	206.4 (68.0%)	[d]	--	--	--
13	1209.8	280.3 (76.8%)	1.0 (99.9%)	--	--	205.4 (83.0%)	1575.6 (-30.2%)	2.9 (99.8%)	3.7 (99.7%)
14	76.0	470.8 (-519.3%)	[a]	--	--	--	--	--	--

[a] Discontinued due to adverse experiences.
[b] No Holter tape available for analysis.
[c] Based on Holter taps from baseline day 2 only. No Holter tape available from baseline day 1.
[d] Discontinued due to lack of response. Holter indicated less than 80% suppression of baseline PVCs at 300 mg bid.

Figure 14
R-819-030-01 HOLTER ANALYSIS
PVCs/Hour - 24-Hour Averages

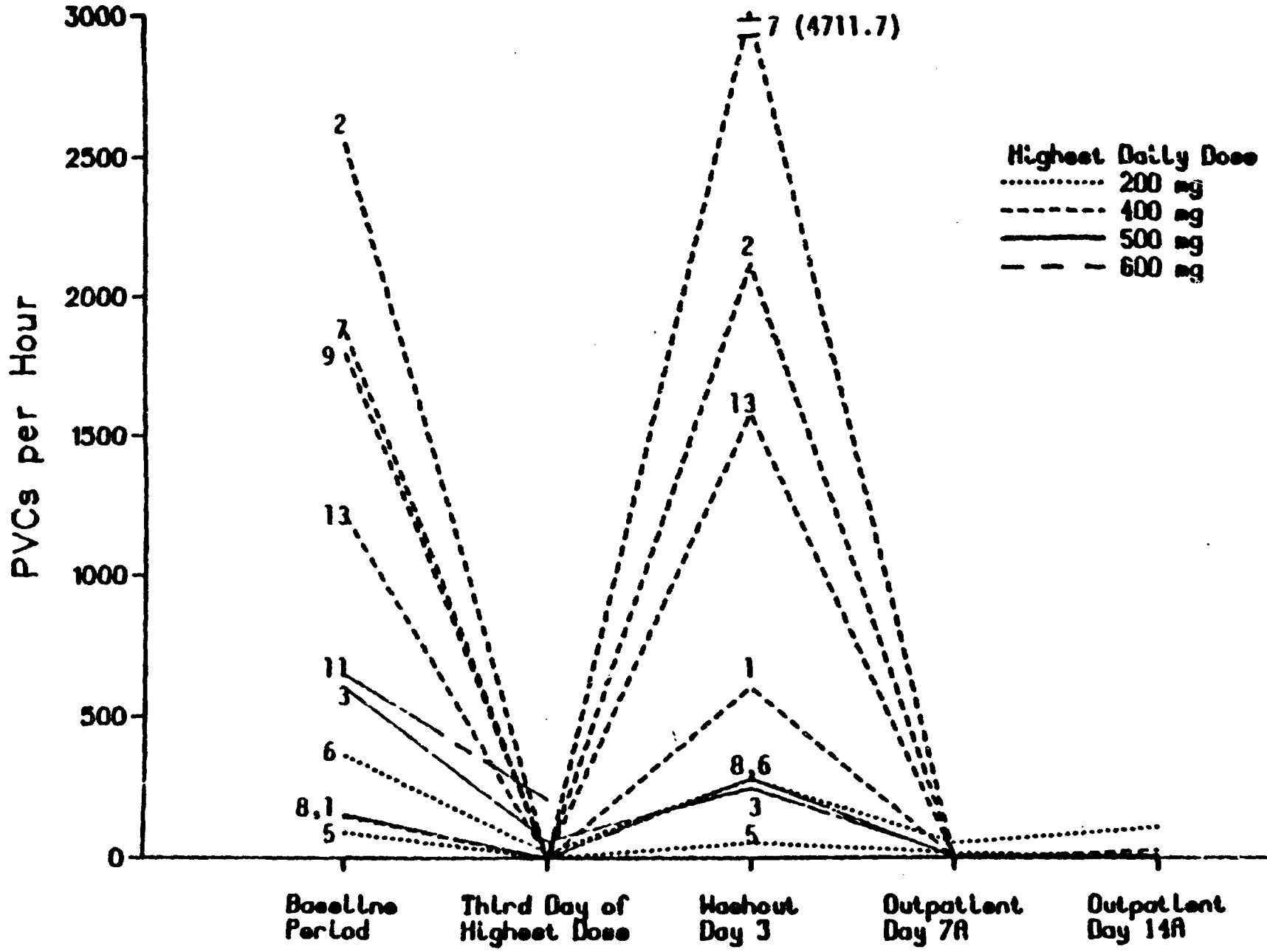


Figure 25
R-818-030-01 HOLTER ANALYSIS
Normalized Hourly PVC Counts
Patient 11

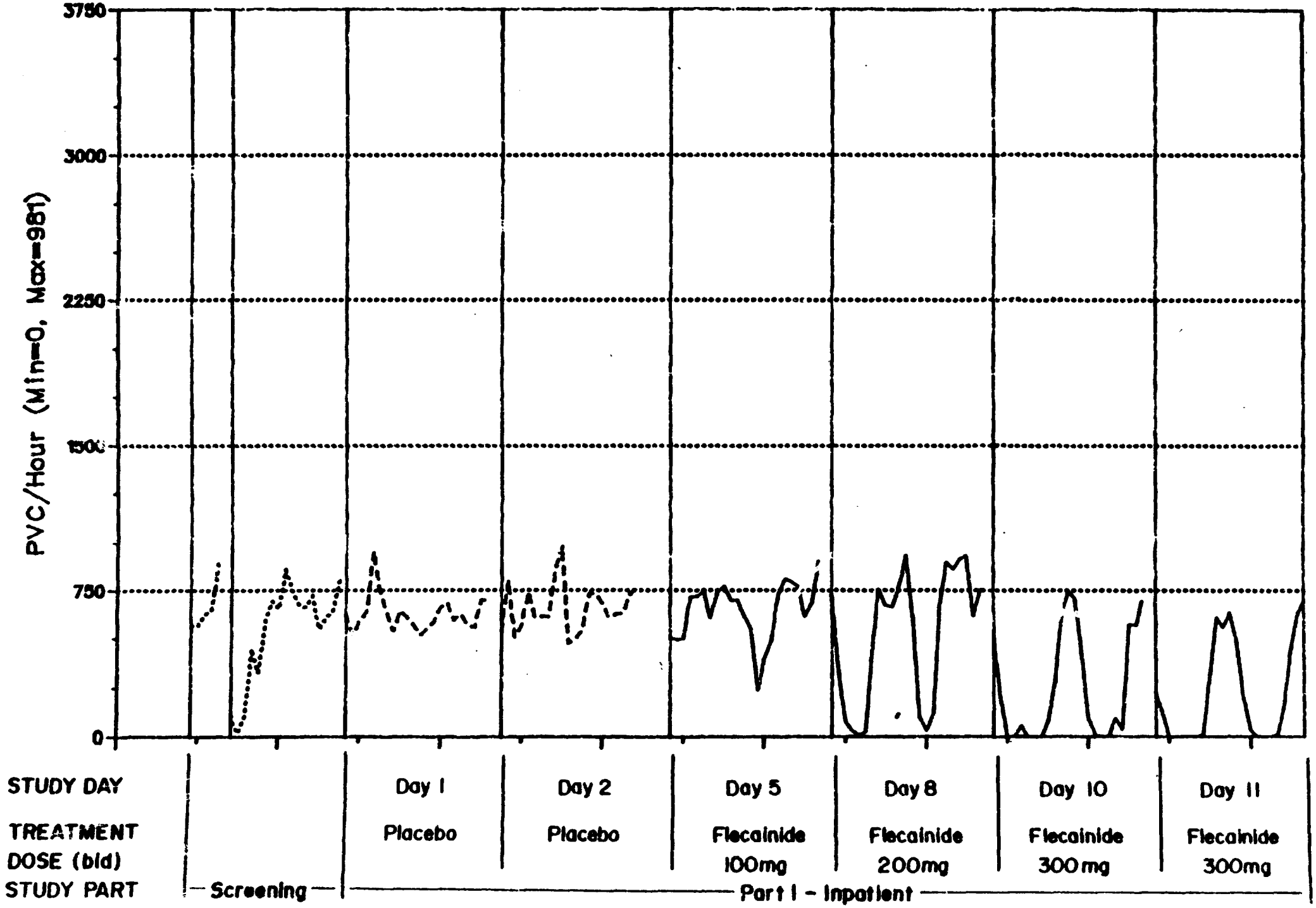


TABLE 28

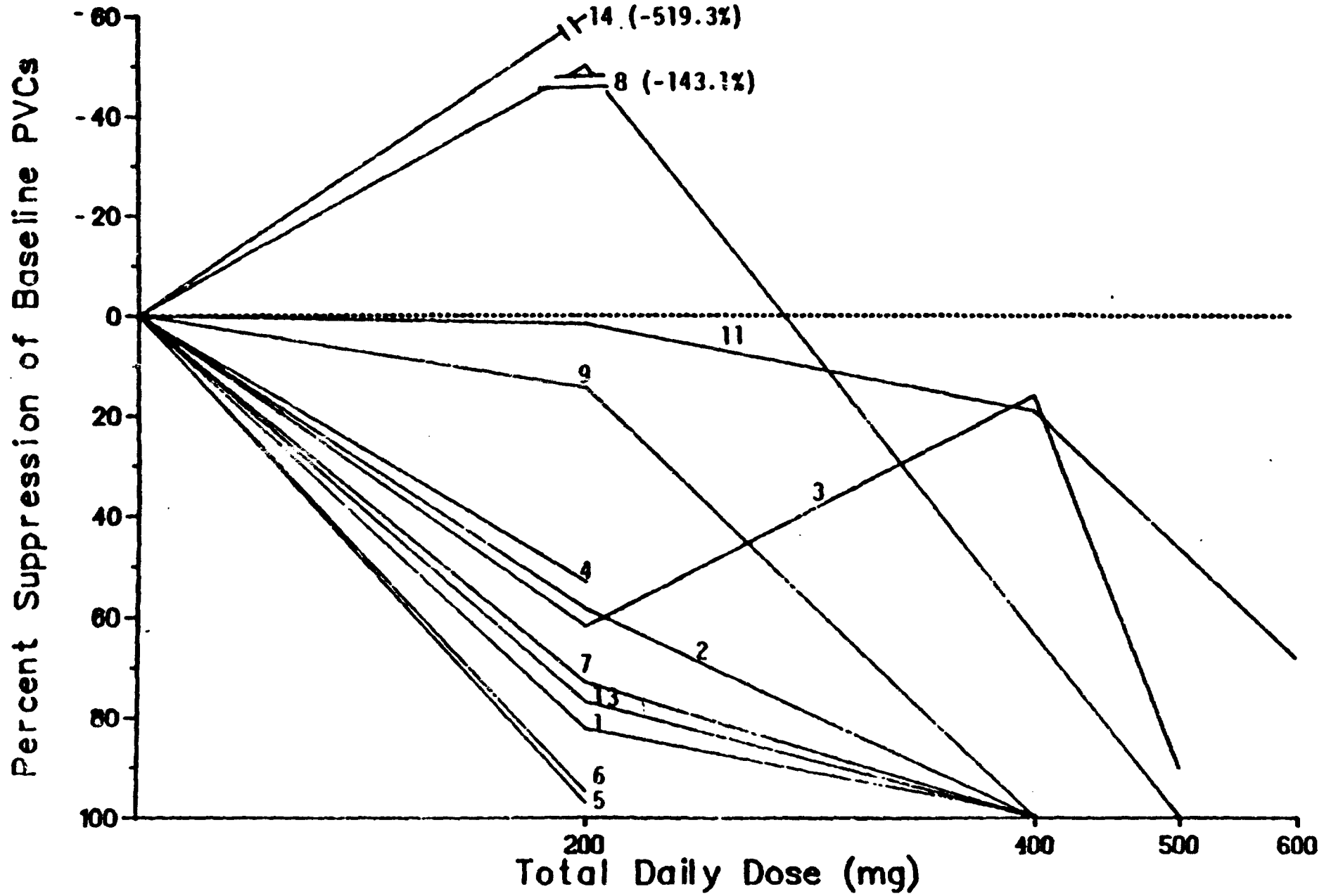
PVC PERCENT SUPPRESSION AT HIGHEST DOSE[a]

PTNO	HIGHEST DOSE (MG BID)	PERCENT SUPPRESSION of BASELINE PVCs DOSE RANGING: THIRD DAY OF HIGHEST DOSE	OUTPATIENT: DAY 7A	DAY 14A
1	200	99.3	99.5	98.6
2	200	100.0	99.8	100.0
3	250	90.2	99.0	99.0
5	100	97.1	80.9	92.9
6	100	94.9	85.8	69.9
7	200	100.0	100.0	98.5
8	250	99.8	99.9	98.8
9	200	100.0	100.0	100.0
11	300	68.0	[b]	[b]
13	200	99.9	99.8	99.7
Median	200	99.6	99.8	98.8
Average		94.9	96.1	95.3

[a]Patients 4 and 14 discontinued study during dose-ranging because of adverse experiences: not included in table.

[b]Patient discontinued due to lack of response. Holter indicated less than 80% suppression of baseline PVCs at 300 mg bid.

Figure 26
R-818-030-01
Relationship Between Dose and Percent Suppression of Baseline PVCs



R-818-030-01
Investigator: Jeffrey Anderson, MD

TABLE 29

HOLTER ANALYSIS
MULTIPLE PVCs/HOUR - 24-HOUR AVERAGES
PVCs Which Occur in Pairs, Triplets, or Runs of Four or More

(Percent Suppression of Baseline Multiple PVCs in Parentheses)

PTNO	Baseline Period	24-Hour Holter From Third Day Of Dose				Washout Day 1	Washout Day 3	Outpatient Day 7A	Outpatient Day 14A
		100 mg bid	200 mg bid	250 mg bid	300 mg bid				
1	16.9	0.9 (94.7%)	0.0 (100.0%)	--	--	13.0 (23.1%)	36.1 (-114.1%)	0.0 (100.0%)	0.0 (100.0%)
2	1603.6	193.0 (88.0%)	0.0 (100.0%)	--	--	29.5 (98.2%)	943.9 (41.1%)	0.0 (100.0%)	0.0 (100.0%)
3	0.3	0.0 (100.0%)	0.0 (100.0%)	0.0 (100.0%)	--	0.0 (100.0%)	0.0 (86.5%)	0.0 (100.0%)	0.0 (100.0%)
4	325.8	65.1 (80.0%)	[a]	--	--	--	--	--	--
5	0.4	0.0 (100.0%)	--	--	--	0.0 (100.0%)	0.0 (100.0%)	0.0 (100.0%)	0.0 (100.0%)
6	4.6	0.0 (100.0%)	--	--	--	[b]	3.7 (20.7%)	0.6 (87.3%)	2.4 (47.3%)
7	1366.9[c]	360.7 (73.6%)	0.0 (100.0%)	--	--	5.4 (99.6%)	4400.1 (-221.9%)	0.0 (100.0%)	2.0 (99.9%)
8	5.8	2.1 (63.9%)	[b]	0.0 (100.0%)	--	1.5 (73.5%)	9.0 (-54.2%)	0.0 (100.0%)	0.3 (95.4%)
9	0.0	89.2	0.0	--	--	4.5	[b]	0.0	0.0
11	2.0	0.3 (86.4%)	0.0 (100.0%)	--	0.3 (86.5%)	[d]	--	--	--
13	289.7	21.4 (92.6%)	0.2 (99.9%)	--	--	22.3 (92.3%)	484.4 (-67.2%)	1.2 (99.6%)	0.3 (99.9%)
14	0.5	0.6 (-38.6%)	[a]	--	--	--	--	--	--

[a] Discontinued due to adverse experiences.
[b] No Holter tape available for analysis.
[c] Based on Holter tape from baseline day 2 only. No Holter tape available from baseline day 1.
[d] Discontinued due to lack of response. Holter indicated less than 80% suppression of baseline PVCs at 300 mg bid.

Study: R-818-030-01
Investigator: JEFFREY L. ANDERSON, MD

NDA 18-830

TABLE 30

TROUGH PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE DURING THE DOSE-RANGING PORTION (PART 1) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Trough Plasma Flecainide Acetate Concentrations (ng/ml)[a]			
	Dose-Ranging[b] Day 5	Dose-Ranging[b] Day 8	Dose-Ranging[b] Day 11	Placebo Washout[b] Day 1
1	214	478	---[c]	506
2	155	350	---	390
3	133	427	623	753
5	294	---	---	314
6	249	---	---	295
7	208	534	---	618
8	235	733	1369	1387
9	254	592	---	641
13	275	661	---	814
Mean	224	539	996	635
Std. Dev.	53	134	528	337
N Patients	9	7	2	9

[a] Trough plasma flecainide level just prior to the morning (9 am) dose and at 12 hours following dosage on the previous evening (9 pm).

[b] Dosage regimens during the dose-ranging portion (part 1) of the study:
Days 3 thru 5 - 100 mg bid.
Days 6 thru 8 - 200 mg bid.
Days 9 thru 11 - 250 mg bid.
Placebo Washout Day 1 - placebo only.

[c] --- indicates that the patient did not require dosage increase to this level.

TABLE 31

APPROXIMATE PEAK PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE DURING THE DOSE-RANGING PORTION (PART 1) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Approximate Peak Plasma Flecainide Acetate Concentrations (ng/ml)[a] Dose-Ranging[b] Day 5	Dose-Ranging[b] Day 8	Dose-Ranging[b] Day 11
1	397	740	---[c]
2	273	674	---
3	213	679	743
5	517	---	---
6	384	---	---
7	336	828	---
8	251	1011	1639
9	446	1147	---
13	384	1044	---
Mean	356	875	1191
Std. Dev.	97	192	634
N Patients	9	7	2

[a] Approximate peak plasma flecainide level at three hours following the morning (9 am) dose.

[b] Dosage regimens during the dose-ranging portion (part 1) of the study:
Days 3 thru 5 - 100 mg bid.
Days 6 thru 8 - 200 mg bid.
Days 9 thru 11 - 250 mg bid.

[c] --- indicates that the patient did not require dosage increase to this level.

TABLE 32

TROUGH PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE DURING THE TWO-WEEK OUTPATIENT PORTION (PART 2) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Flecainide Dosage Regimen (mg bid)[b]	Trough Plasma Flecainide Acetate Concentrations (ng/ml)[a] Outpatient Day 7A Measured	Outpatient Day 7A Normalized[c]	Outpatient Day 14A Measured	Outpatient Day 14A Normalized[c]
1	200	790	790	921[d]	921
2	200	504	504	544	544
3	250	1056	845	1291	1033
5	100	400	800	452	904
6	100	397[e]	794	357[d]	714
7	200	663	663	777	777
8	250	1465	1172	1615	1292
9	200	717[f]	717	743[g]	743
13	200	1079[f]	1079	897[g]	897
Mean		786	818	844	869
Std. Dev.		357	203	403	213

[a] Trough plasma flecainide level just prior to the morning (9 am) dose and at about 12 hours following dosage on the previous evening (9 pm).
[b] Twice daily oral flecainide dosage regimen on an outpatient basis (at about 9 am and 9 pm).
[c] Plasma level data were normalized to a 200 mg bid dose of flecainide.
[d] Outpatient Day 13A.
[e] Outpatient Day 6A.
[f] Outpatient Day 8A.
[g] Outpatient Day 15A.

TABLE 33

PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE AT THE TIME OF INITIAL REAPPEARANCE OF PREMATURE VENTRICULAR CONTRACTIONS (PVCs) DURING THE PLACEBO WASHOUT PERIOD (PART 1) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Flecainide Dosage Regimen (mg bid)[a]	Baseline Arrhythmia Activity (PVCs/hr)[b]	Initial Reappearance of PVCs During Washout Period: To > 10% of Baseline Time[c] (hrs)	To > 10% of Baseline Plasma Level[d] (ng/ml)	To > 30 PVCs per hour Time[c] (hrs)	To > 30 PVCs per hour Plasma Level[d] (ng/ml)
1	200	147.3	21	327	23	297
2	200	2541.2	22	258	19	296
3	250	600.4	8	822	8	822
5	100	90.0	32	118	32	118
6	100	363.4	11	298	11	298
7	200	1869.7[e]	>35[f]	<269[g]	27	353
8	250	152.8	25	875	26	842
9	200	1792.7	21	480	19	514
13	200	1209.8	27	494	27	494
Median			22		23	
Mean				438		448
Std. Dev.				259		247

[a]Twice daily oral flecainide dosage regimen prior to the placebo washout period; the last dose was given at about 9 pm on the final dose-ranging day.
[b]Average PVC activity from the two baseline days of 24-hour Holter monitoring; data are from Table 6.
[c]Following the 9 pm dose of flecainide on the final dose-ranging day, the time of initial reappearance of PVCs to the defined degree of PVC activity.
[d]Plasma flecainide level at the time of initial reappearance of PVCs was estimated from the log-linear regression line for the terminal phase of flecainide elimination from plasma of individual patients.
[e]Average PVC activity from 24-hour Holter monitoring on baseline day 2 only; Holter tape from baseline day 1 was not available for analysis.
[f]Holter tape from placebo washout day 2 was not available for analysis.
[g]Plasma flecainide level at 35 hours following the last dose.

TABLE 34

COMPARISON OF TROUGH PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE TO THE PERCENT SUPPRESSION OF PREMATURE VENTRICULAR CONTRACTIONS (PVCs) DURING THE TWO-WEEK OUTPATIENT PORTION (PART 2) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Flecainide Dosage Regimen (mg bid)[a]	Outpatient Day 7A Percent Suppression of PVCs[b]	Outpatient Day 7A Trough Level (ng/ml)[c]	Outpatient Day 14A Percent Suppression of PVCs[b]	Outpatient Day 14A Trough Level (ng/ml)[c]
1	200	99.5	790	98.6	921
2	200	99.8	504	100.0	544
3	250	99.0	1056	99.0	1291
5	100	80.9	400	92.9	452
6	100	85.8	397	69.9	357
7	200	100.0	663	98.5	777
8	250	99.9	1465	98.8	1615
9	200	100.0	717	100.0	743
1_	200	99.8	1079	99.7	897
Mean		96.1	786	95.3	844
Std. Dev.		7.3	357	9.8	403

[a] Twice daily oral flecainide dosage regimen on an outpatient basis (at about 9 am and 9 pm).
[b] Percent suppression of baseline PVC activity from 24-hour Holter minitoring; data are from Table 6.
[c] Trough plasma flecainide level just prior to the morning (9 am) dose; data are from Table 23.

Figure 27
R-818-030-02 STUDY DESIGN

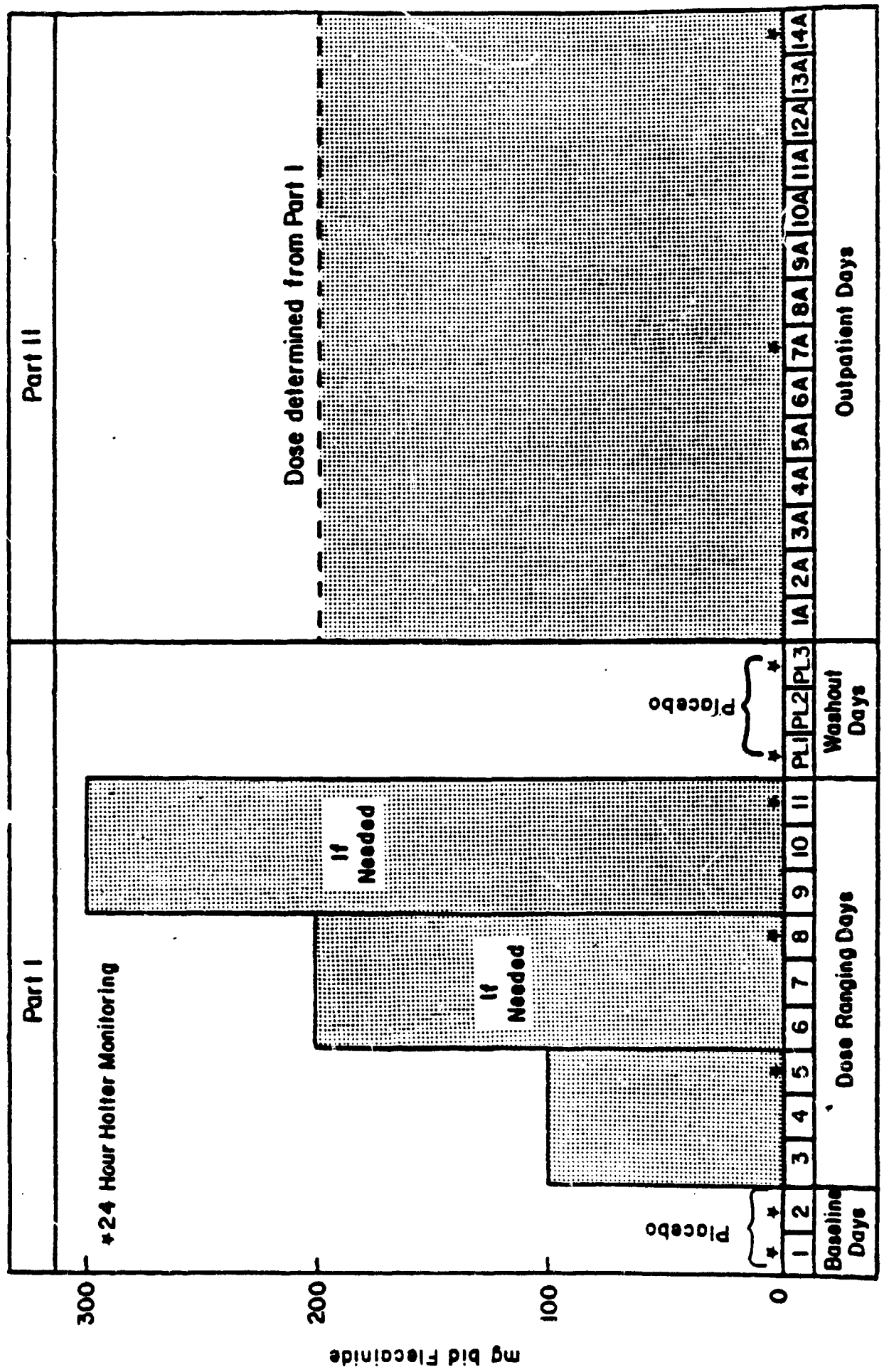


Figure 29
R-818-030-02 HOLTER ANALYSIS
Normalized Hourly PVC Counts
Patient 5

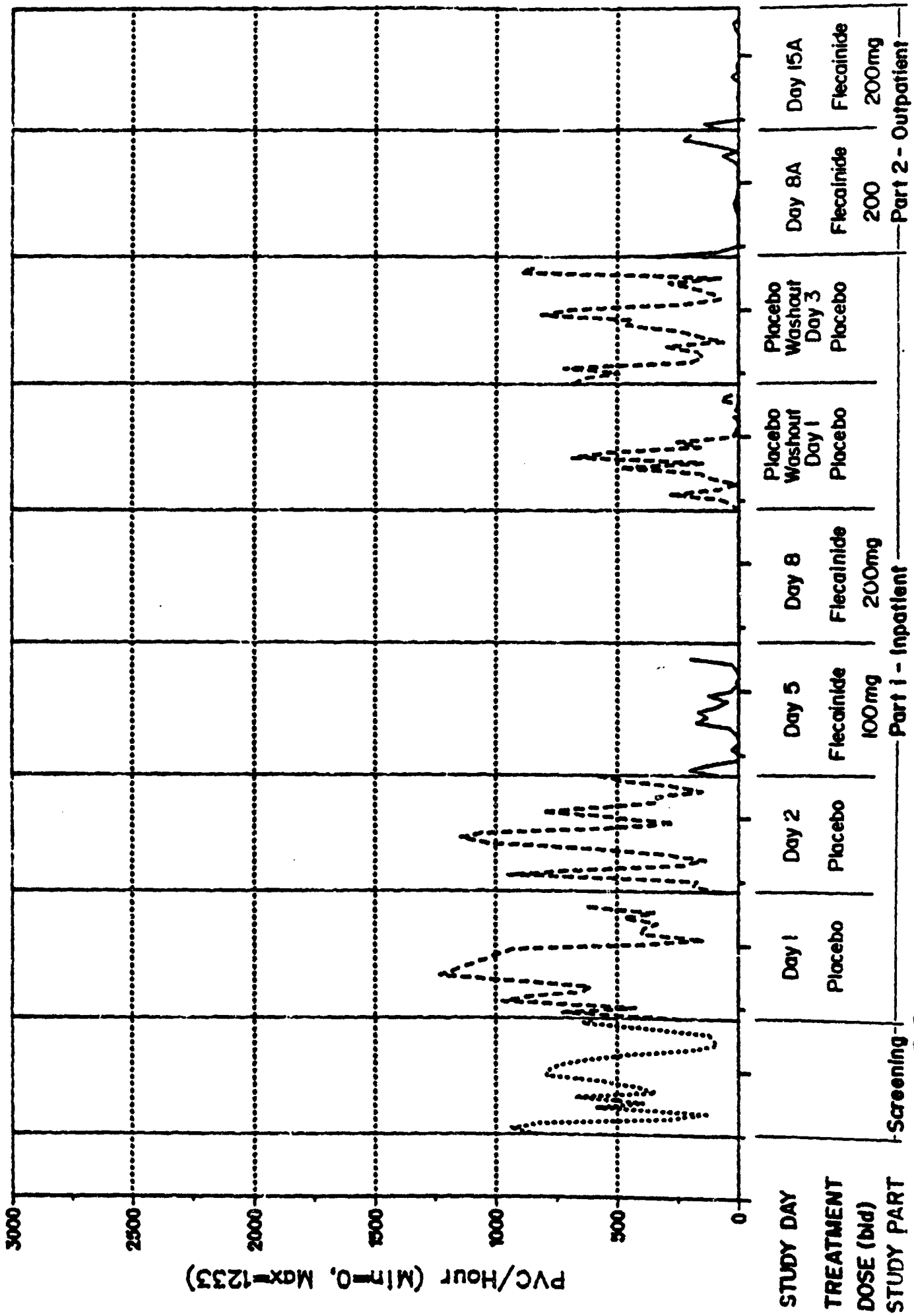


Figure 29

R-818-030-02 HOLTER ANALYSIS
Normalized Hourly PVC Counts
Patient 10

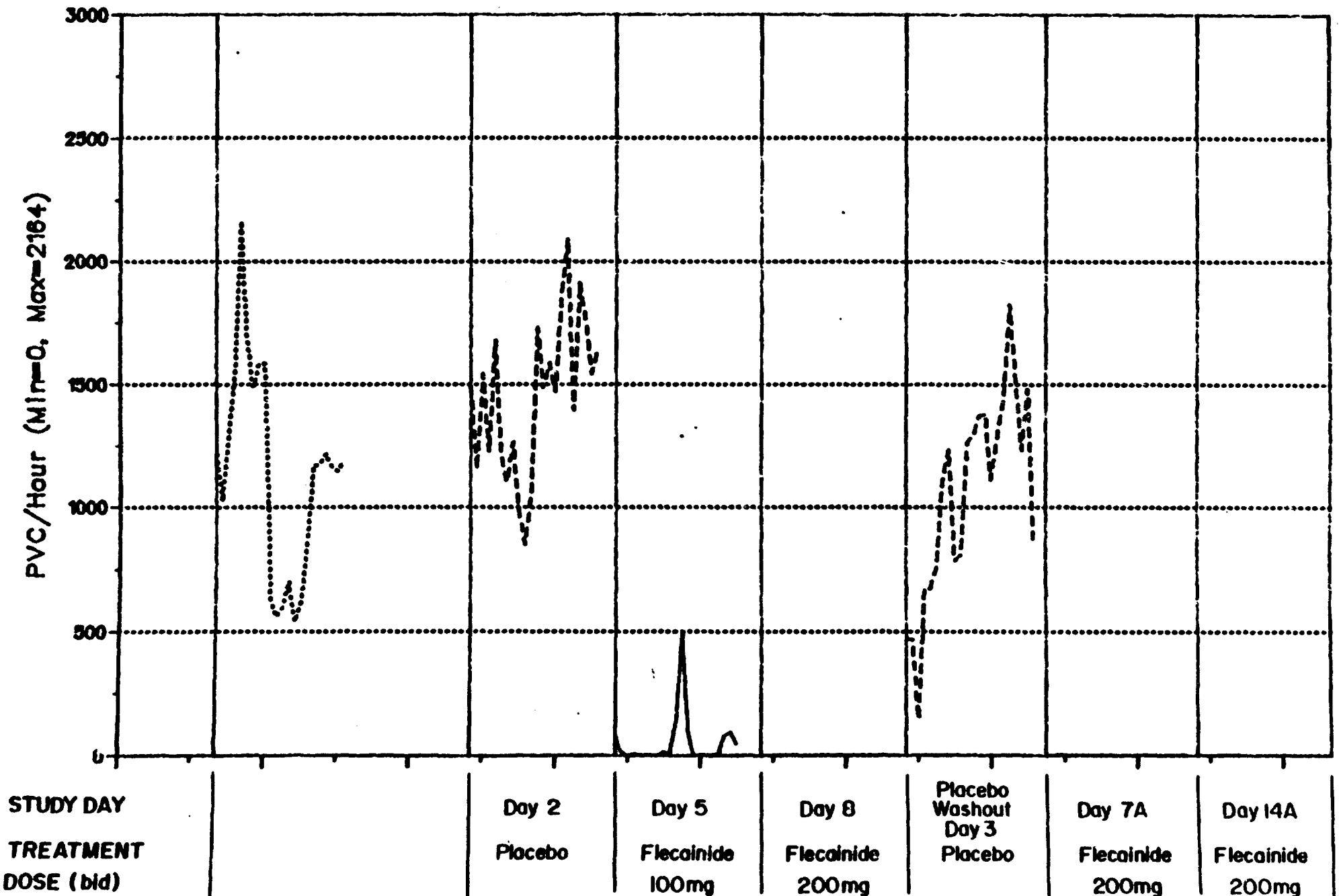
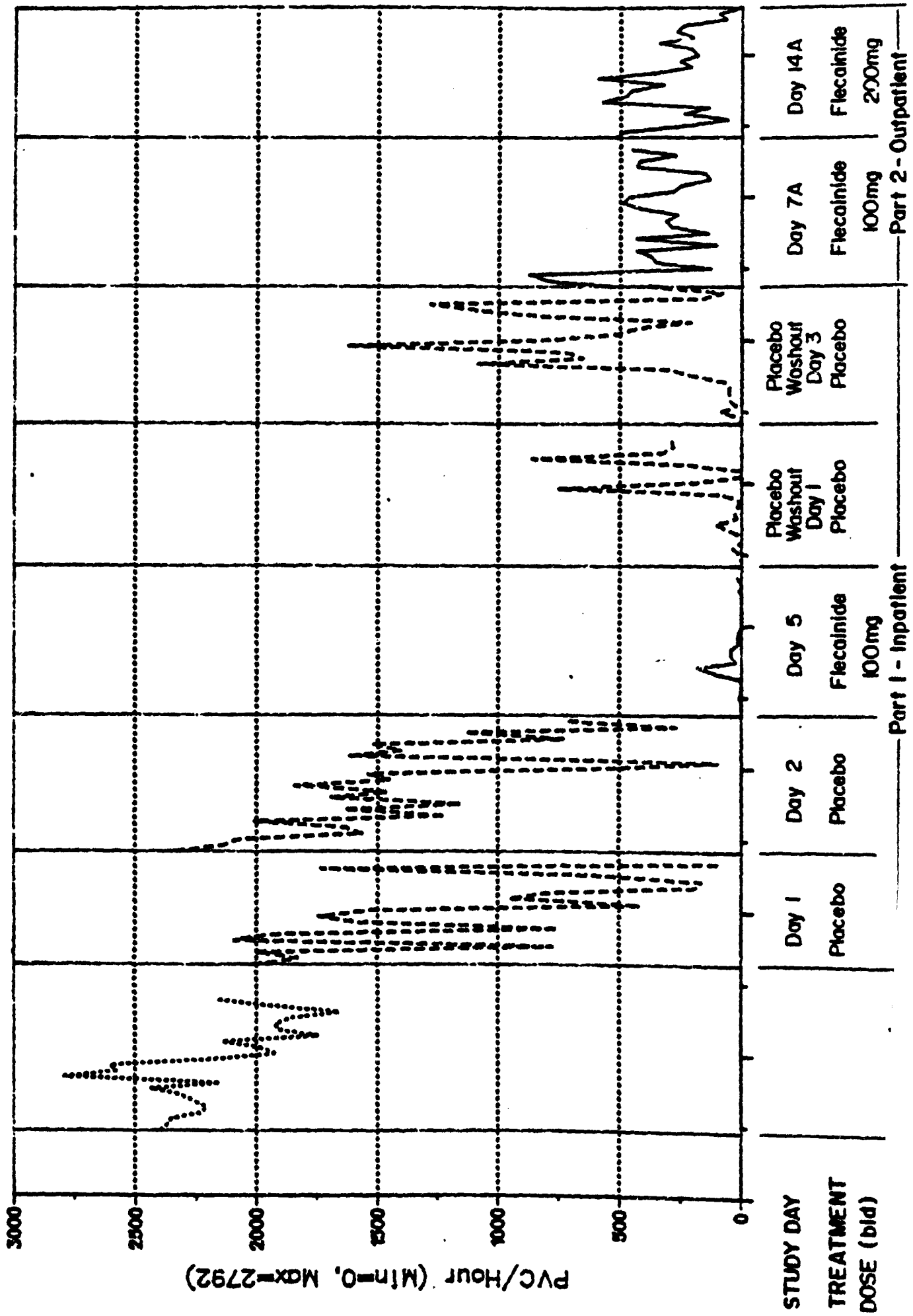


Figure 30.
R-818-030-02 HOLTER ANALYSIS
Normalized Hourly PVC Counts
Patient 15



STUDY R-818-030-02
INVESTIGATOR: Morrison Hodges, MD

TABLE 35

HOLTER ANALYSIS
PVCs/HOUR - 24-HOUR AVERAGES
(Percent Suppression of Baseline PVCs in Parantheses)

PTNO	Baseline Period	24-Hour Holter From Third Day Of Dose 100 mg bid	200 mg bid	300 mg bid	Washout Day 1	Washout Day 3	Outpatient Day 7A	Outpatient Day 14A
2	92.4	119.4 (-29.2%)	4.0 (95.6%)	--	66.9 (27.7%)	220.7 (-138.7%)	0.7 (99.3%)	0.4 (99.6%)
4	1477.1	124.8 (91.6%)	0.2 (100.0%)	--	0.8 (99.9%)	95.8 (93.5%)	1.5 (99.9%)	0.3 (100.0%)
5	529.0	64.4 (87.8%)	0.1 (100.0%)	--	141.8 (73.2%)	374.8 (29.1%)	27.2[a] (94.9%)	11.4[b] (97.8%)
7	102.2	41.8 (59.1%)	0.0 (100.0%)	--	4.3 (95.7%)	199.6 (-95.4%)	0.0 (100.0%)	[c]
8	2869.0[d]	955.8 (66.7%)	0.0 (100.0%)	--	554.3 (80.7%)	3408.5 (-18.8%)	0.0[e] (100.0%)	0.0[b] (100.0%)
9	734.5	[f]	301.0 (59.0%)	1.0 (99.9%)	255.0 (65.3%)	794.1 (-8.1%)	22.0 (97.0%)	0.0 (100.0%)
10	1446.1[g]	28.7 (98.0%)	0.0 (100.0%)	--	[f]	1055.2 (27.0%)	0.0 (100.0%)	0.0 (100.0%)
12	135.6	118.4 (12.7%)	26.1 (80.8%)	22.9 (83.1%)	67.4 (50.3%)	433.8 (-219.9%)	30.8 (77.3%)	50.0 (63.1%)
14	97.9	99.5 (-1.7%)	19.8 (79.7%)	17.5 (82.2%)	12.6 (87.2%)	[h]	[h]	[h]
15	1308.2	22.6 (98.3%)	--	--	148.8 (88.6%)	453.5 (65.3%)	356.7 (72.7%)	278.5 (78.7%)
16	700.0[g]	10.4 (98.5%)	0.0 (100.0%)	--	0.0 (100.0%)	524.6 (25.1%)	0.0 (100.0%)	0.0 (100.0%)

[a] Day 8A.
[b] Day 15A
[c] Holter tape recording technically unsatisfactory.
[d] Based on Holter tape from baseline day 1 only. No Holter tape available for analysis from baseline day 2.
[e] Day 9A.
[f] No Holter tape available for analysis.
[g] Based on Holter tape from baseline day 2 only. No Holter tape available for analysis from baseline day 1.
[h] Patient withdrawn, investigator's Trendscriber data indicated less than 80% suppression of PVCs at 300 mg bid

NDA 18-830

Figure 31

R-818-030-02 HOLTER ANALYSIS
PVCs/Hour - 24-Hour Averages

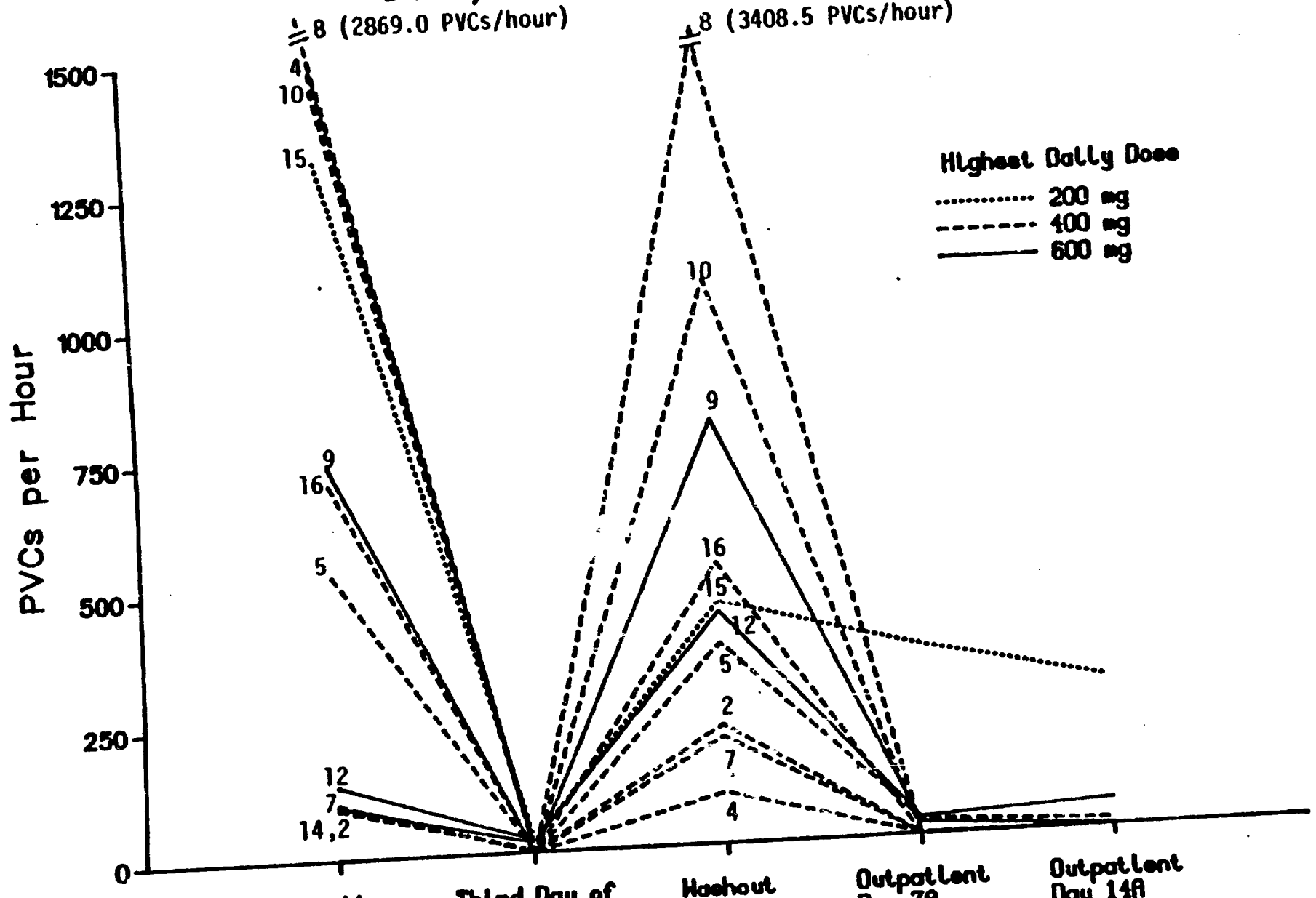


TABLE 36

PVC PERCENT SUPPRESSION AT HIGHEST DOSE

PTNO	HIGHEST DOSE (MG BID)	PERCENT SUPPRESSION OF BASELINE PVCs		
		DOSE RANGING THIRD DAY OF HIGHEST DOSE	OUTPATIENT DAY 7A	OUTPATIENT DAY 14A
2	200	95.6	99.3	99.6
4	200	100.0	99.9	100.0
5	200	100.0	94.9	97.8
7	200	100.0	100.0	[a]
8	200	100.0	100.0	100.0
9	300	99.9	97.0	100.0
10	200	100.0	100.0	100.0
12	300	83.1	77.3[b]	63.1[b]
14	300	82.2	[c]	[c]
15	100	98.3	72.7	78.7[d]
16	200	100.0	100.0	100.0
AVERAGE		96.3	94.1	93.2
MEDIAN	200	100.0	99.6	100.0

[a] Holter tape recording technically unsatisfactory.

[b] Patient received 200 mg bid during outpatient phase.

[c] Patient withdrawn, investigator's Trendscriber data indicated less than 80% suppression of PVCs at 300 mg bid.

[d] Patient received 200 mg bid on day 14A.

STUDY R-818-030-02
INVESTIGATOR: Morrison Hodges, MD

TABLE 37

HOLTER ANALYSIS
MULTIPLE PVCs/HOUR - 24-HOUR AVERAGES
(Percent Suppression of Baseline Multiple PVCs in Parentheses)

PTNO	Baseline Period	24-Hour Holter From Third Day Of Dose			Washout Day 1	Washout Day 3	Outpatient Day 7A	Outpatient Day 14A
		100 mg bid	200 mg bid	300 mg bid				
2	1.0	0.0 (100.0%)	0.0 (100.0%)	--	0.3 (72.9%)	1.4 (-35.5%)	0.0 (100.0%)	0.0 (100.0%)
4	150.0	5.4 (96.4%)	0.0 (100.0%)	--	0.1 (99.9%)	4.9 (96.7%)	0.0 (100.0%)	0.0 (100.0%)
5	70.9	6.1 (91.4%)	0.0 (100.0%)	--	0.3 (99.6%)	31.1 (56.1%)	0.1[a] (99.9%)	0.1[b] (99.9%
7	1.7	0.0 (100.0%)	0.0 (100.0%)	--	0.0 (100.0%)	0.0 (100.0%)	0.0 (100.0%)	[c]
8	771.7[d]	0.0 (100.0%)	0.0 (100.0%)	--	159.5 (79.3%)	2486.1 (-222.2%)	0.0[a] (100.0%)	0.0[b] (100.0%)
9	10.8	[f]	24.5 (-127.4%)	0.0 (100.0%)	15.4 (-43.1%)	79.3 (-635.5%)	0.2 (98.3%)	0.0 (100.0%)
10	10.2[g]	0.0 (100.0%)	0.0 (100.0%)	--	[f]	0.8 (92.4%)	0.0 (100.0%)	0.0 (100.0%)
12	3.7	3.0 (18.8%)	0.1 (97.5%)	0.2 (95.2%)	0.4 (90.3%)	41.7 (-1034.0%)	0.7 (80.5%)	0.8 (79.3%)
14	1.3	1.1 (15.3%)	1.2 (9.1%)	1.7 (-32.5%)	0.7 (44.0%)	[h]	[h]	[h]
15	81.5	3.1 (96.2%)	--	--	2.1 (97.5%)	5.5 (93.3%)	43.8 (46.3%)	12.1 (85.2%)
16	8.5[g]	0.0 (100.0%)	0.0 (100.0%)	--	0.0 (100.0%)	0.9 (89.7%)	0.0 (100.0%)	0.0 (100.0%)

[a] Day 8A.
[b] Day 15A.
[c] Holter tape recording technically unsatisfactory.
[d] Based on Holter tape from baseline day 1 only. No Holter tape available for analysis from baseline day 2.
[e] Day 9A.
[f] No Holter tape available for analysis.
[g] Based on Holter tape from baseline day 2 only. No Holter tape available for analysis from baseline day 1.
[h] Patient withdrawn, investigator's Trendscriber data indicated less than 80% suppression of PVCs at 300 mg bid.

TABLE 38

TROUGH PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE DURING THE DOSE-RANGING PORTION (PART 1) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Trough Plasma Flecainide Acetate Concentrations (ng/ml)[a]			
	Dose-Ranging[b] Day 5	Dose-Ranging[b] Day 8	Dose-Ranging[b] Day 11	Placebo Washout[b] Day 1
2	175	484	---[c]	545
4	266	754	---	804
5	315	874	---	863
7	249	605	---	822
8	337	661	--	681
9	89	223	362	412
10	323	792	---	914
12	123	412	718	690
15	243	---	---	332
16	210	652	---	842
Mean	233	606	540	691
Std. Dev.	84	204	252	200
N Patients	10	9	2	10

[a] Trough plasma flecainide level just prior to the morning (9 am) dose and at 12 hours following dosage on the previous evening (9 pm).

[b] Dosage regimens during the dose-ranging portion (part 1) of the study:
Days 3 thru 5 - 100 mg bid.
Days 6 thru 8 - 200 mg bid
Days 9 thru 11 - 300 mg bid
Placebo Washout Day 1 - placebo only.

[c] --- indicates that the patient did not require dosage increase to this level.

Study: R-818-030-02
Investigator: M. Hodges, MD

TABLE 39

NDA 18-830

PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE AT THE TIME OF INITIAL REAPPEARANCE OF PREMATURE VENTRICULAR CONTRACTIONS (PVCs) DURING THE PLACEBO WASHOUT PERIOD (PART 1) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Flecainide Dosage Regimen (mg bid)[a]	Baseline Arrhythmia Activity (PVCs/hr)[b]	Initial Reappearance of PVCs During Washout Period: To > 10% of Baseline Time[c] (hrs)	To > 10% of Baseline Plasma Level[d] (ng/ml)	To > 30 PVCs per hour Time[c] (hrs)	To > 30 PVCs per hour Plasma Level[d] (ng/ml)
2	200	92.4	17	452	25	336
4	200	1477.1	>35[e]	<415[f]	>35[e]	<415[f]
5	200	529.0	15	814	15	814
7	200	102.2	20	599	20	599
8	200	2869.0[g]	28	347	26	378
9	300	734.5	23	219	20	261
10	200	1446.1[h]	[i]	---	[i]	---
12	300	135.6	10	732	12	671
15	100	1308.2	26	184	16	274
	200	700.0[h]	>35[e]	<391[f]	>35[e]	<391[f]
Median			23	461	20	460
Mean				216		191
Std. Dev.						

[a] Twice daily oral flecainide dosage regimen prior to the placebo washout period; the last dose was given at about 9 pm on the final dose-ranging day.
[b] Average PVC activity from the two baseline days of 24-hour Holter monitoring; data are from Table 6.
[c] Following the 9 pm dose of flecainide on the final dose-ranging day, the time of initial reappearance of PVCs to the defined degree of PVC activity.
[d] Plasma flecainide level at the time of initial reappearance of PVCs was estimated from the log-linear regression line for the terminal phase of flecain elimination from plasma of individual patients.
[e] Holter tape was not recorded on placebo washout day 2.
[f] Plasma flecainide level at 35 hours following the last dose.
[g] Average PVC activity from 24-hour Holter monitoring on baseline day 1 only; Holter tape from baseline day 2 was not available for analysis.
[h] Average PVC activity from 24-hour Holter monitoring on baseline day 2 only; Holter tape from baseline day 1 was not available for analysis.
[i] Holter tape from placebo washout day 1 was not available for analysis.

TABLE 40

COMPARISON OF TROUGH PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE TO THE PERCENT SUPPRESSION OF PREMATURE VENTRICULAR CONTRACTIONS (PVCs) DURING THE TWO-WEEK OUTPATIENT PORTION (PART 2) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Flecainide Dosage Regimen (mg bid)[a]	Outpatient Day 7A Percent Suppression of PVCs[b]	Outpatient Day 7A Trough Level (ng/ml)[c]	Outpatient Day 14A Percent Suppression of PVCs[b]	Outpatient Day 14A Trough Level (ng/ml)[c]
2	200	99.3	770	99.6	818
4	200	99.9	1424	100.0	1203
5	200	94.9	1023	97.8	992
7	200	100.	1107	[d]	1381
8	200	100.0	759	100.0	687
9	300	97.0	585	100.0	710
10	200	100.0	715	100.0	1152
12	200	77.3	456	63.1	362
15	100	72.7	446	78.7	478
16	200	100.0	1010	100.0	1143
Mean		94.1	830	93.2	893
Std. Dev.		10.3	311	13.3	335
N Patients		10	10	9	10

[a] Twice daily oral flecainide dosage regimen on an outpatient basis (at about 9 am and 9 pm).
[b] Percent suppression of baseline PVC activity from 24-hour Holter minitoring; data are from Table 6.
[c] Trough plasma flecainide level just prior to the morning (9 am) dose; data are from Table 23.
[d] Holter tape from outpatient day 14A was technically unsatisfactory for analysis.

Study R-818-830-03
Investigator: Raymond L. Woosley, MD, PhD

TABLE 41

HOLTER ANALYSIS
PVCs/HOUR - 24-HOUR AVERAGES
(% Suppression From Baseline in Parentheses)

PTNO	Baseline Period	24-Hour Holter From Third Day Of Dose					Washout Day 3	Outpatient Day 7A	Outpatient Day 14A
		100 mg bid	200 mg bid	250 mg bid	300 mg bid	100 mg q8h			
1	2066	58 (97.2%)	—	—	—	—	1735 (16.0%)	281 (86.4%)	172 (91.7%)
2	131	670 (-413.1%)	6 (95.6%)	—	—	—	742 (-467.6%)	27 (79.2%)	19 (85.4%)
3	531	622 (-17.3%)	10 (98.0%)	—	—	—	1231 (-132.1%)	9 (98.4%)	46 (91.3%)
4	302	66 (78.3%)	5 (98.3%)	—	—	—	47 (84.5%)	12 (95.9%)	6 (97.9%)
5	843	1110 (-31.8%)	567 (32.7%)	[a]	33 (96.1%)	—	845 (0.0%)	0 (100.0%)	1 (99.8%)
6	926	1121 (-21.1%)	278 (70.0%)	113 (87.8%)	—	—	1481[b] (-51.3%)	87 (90.6%)	83 (91.1%)
7	69	116 (-68.5%)	51 (26.3%)	0 (99.7%)	—	—	187 (-172.7%)	2 (97.6%)	0 (99.7%)
8	1868[c]	1216 (34.9%)	368 (80.3%)	6 (99.7%)	—	—	1676[d] (10.3%)	3 (99.8%)	0 (100.0%)
9	227	65 (71.5%)	7 (97.1%)	—	—	—	168 (26.1%)	8 (96.4%)	1 (99.5%)
10	242	143 (40.8%)	[a]	—	—	8 (96.7%)	175[e] (27.6%)	11 (95.3%)	4 (98.2%)
11	311	184 (40.7%)	0 (99.9%)	—	—	—	260 (16.5%)	66 (78.9%)	4 (98.8%)

[a] No Holter tape available for analysis.
[b] Based on Holter tape from washout day 2, as patient received study drug on morning of placebo washout day 3.
[c] Based on Holter tape from baseline day 2 only. No Holter tape available for analysis from baseline day 1.
[d] Holter tape from fourth day of dose.

FIGURE 32

R-818-090-03 HOLTER ANALYSIS
PVCs/Hour - 24-Hour Averages

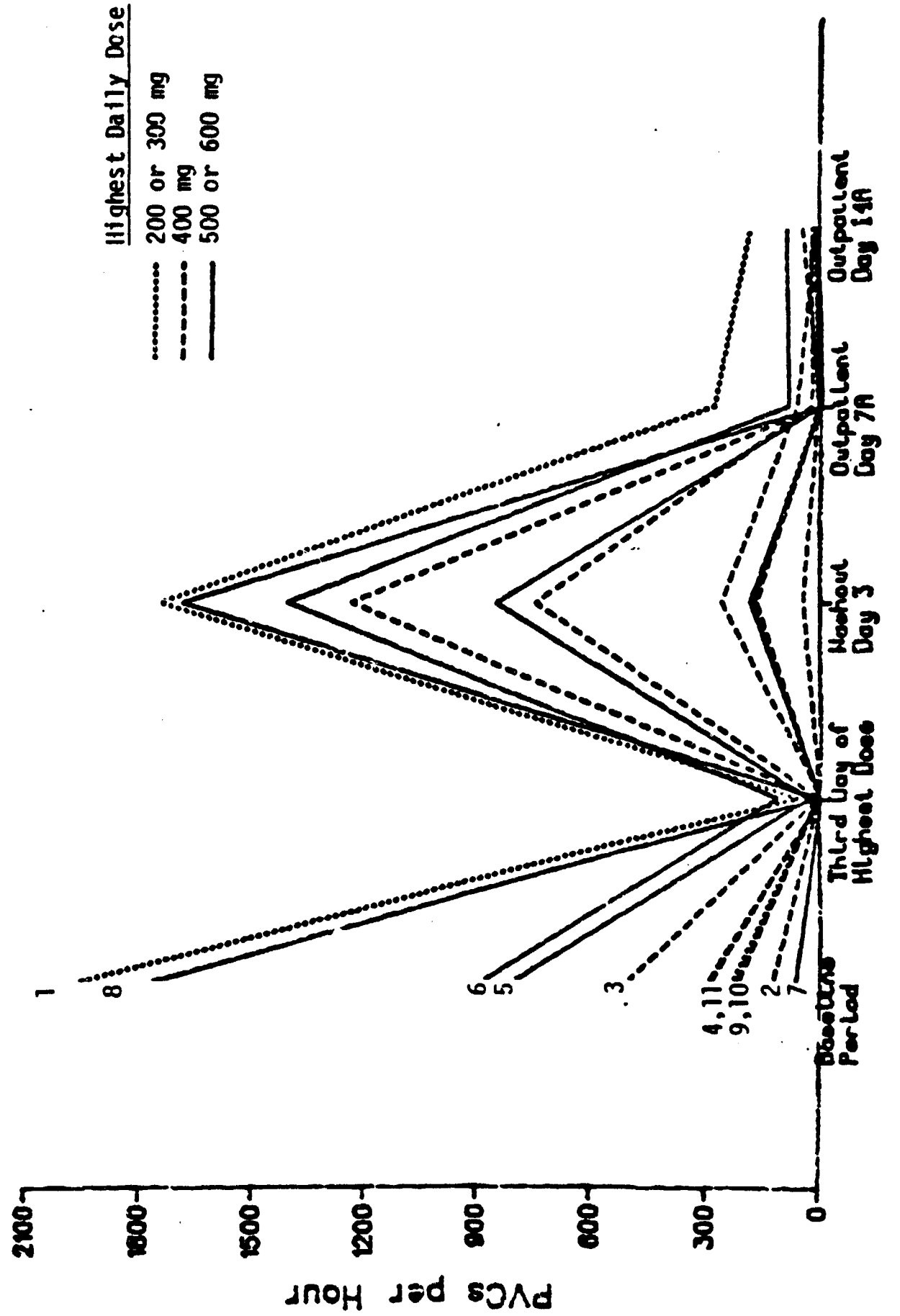
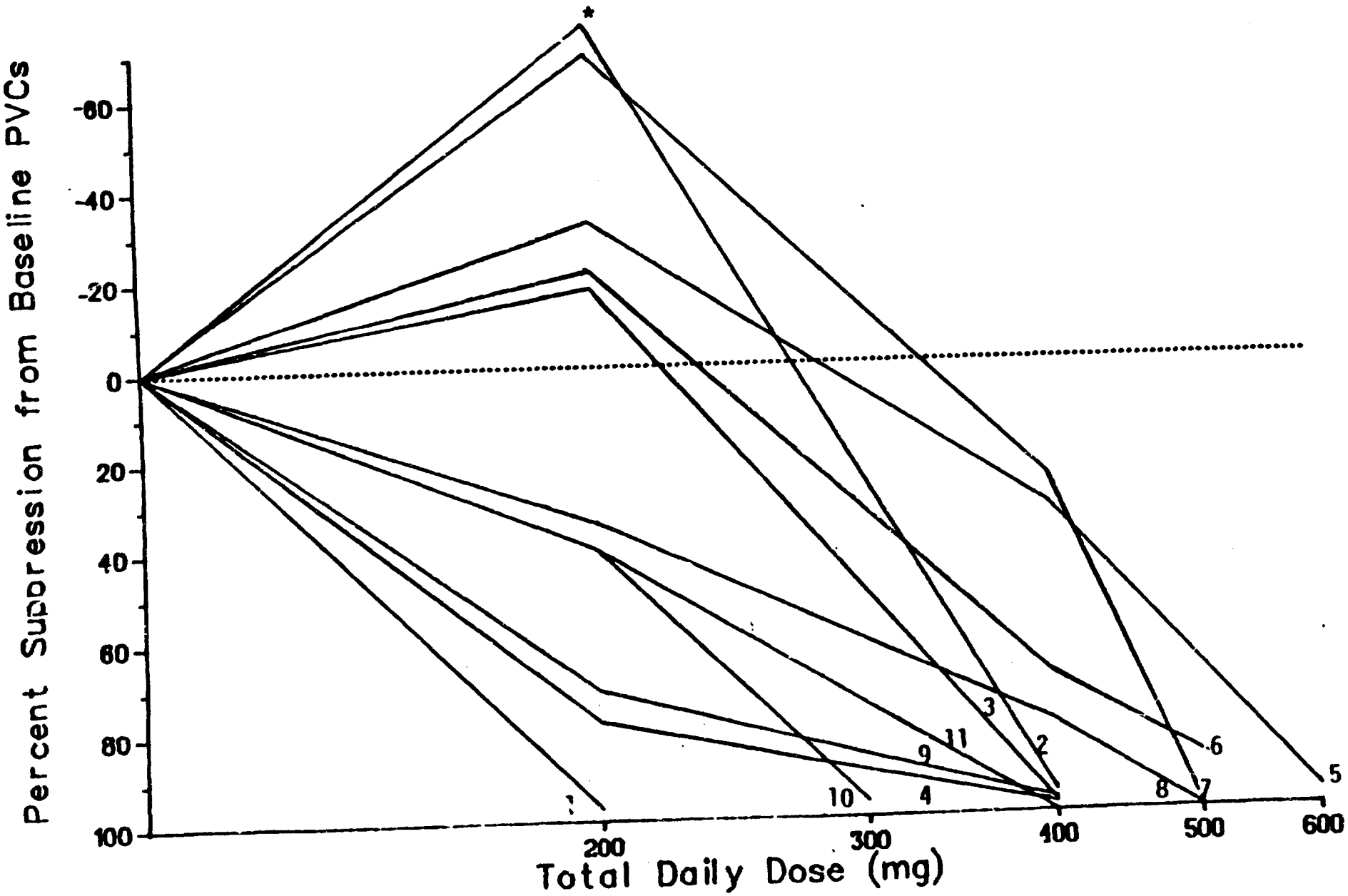


FIGURE 33

R-818-030-03
Relationship Between Dose and
Percent Suppression from Baseline PVCs



* Patient 2 had -413% suppression at 200 mg.

TABLE 44

Summary of Plasma Pharmacokinetic Data for Flecainide Acetate During Placebo Washout Period Following Multiple Oral Flecainide Dosage to 11 Patients

Patient Number	Last Dose of Flecainide (mg)[a]	Plasma Half-life of Flecainide (hours)[b]	Peak Time (hours)	Peak Level (ng/ml) Measured	Peak Level (ng/ml) Normalized[c]	Plasma AUC (ng.hours/ml)[d] Measured	Plasma AUC (ng.hours/ml)[d] Normalized[c]
1	100	17.4	4.0	376	752	4175	8350
2	200	22.9	2.9	1197	1197	11710	11710
3	200	17.2	6.0	1218	1218	12225	12225
4	200	12.7	2.5	486	486	4858	4858
5	250	18.6	4.0	771	617	7477	5982
6	250	17.8	3.0	401	321	3770	3016
7	250	25.8	2.0	1879	1503	17492	13994
8	250	21.4	4.5	1028	822	11036	8829
9	200	26.9	4.0	1277	1277	13989	13989
10	200	24.4	4.0	1251	1251	13242	13242
11	200	18.1	3.0	632	632	5955	5955
Mean		20.3	3.6		916		9286
Std. Dev.		4.3	1.1		388		3956

[a] Following multiple oral flecainide dosage, the last dose prior to the placebo washout period was given at about 9 am on placebo washout day 1.

[b] The terminal phase (post-absorptive) plasma half-life of flecainide acetate was estimated from the log plasma concentration versus time graph by calculation of the least squares line.

[c] Peak level and plasma AUC data were normalized to a 200 mg dose of flecainide.

[d] Area under the plasma flecainide level versus time curve (AUC) for one dosage interval (zero to 12 hours after last dose prior to the placebo washout period); plasma AUC values were calculated by the trapezoidal rule.

TABLE 45

NDA 18-830

Trough Plasma Concentrations of Unchanged Flecainide Acetate During the Dose-Ranging Portion (part 1) Following Multiple Oral Flecainide Dosage to 11 Patients

Patient Number	Trough Plasma Flecainide Acetate Concentration (ng/ml)[a]			
	Dose-Ranging[b] Day 5	Dose-Ranging[b] Day 8	Dose-Ranging[b] Day 11	Placebo Washout[b] Day 1
1	278	---[c]	---	291
2	248	734	---	907
3	245	713	---	952
4	143	382	---	331
5	119	304	480	459
6	74	223	320	[d]
7	230	581	1132	1286
8	192	564	796	514
9	337	852	---	1018
10	324	960[e]	---	960[e]
11	139	320	---	369
Mean	212	563	682	709
Std. Dev.	86	25[	359	353
N Patients	11	10	4	10

[a] Trough plasma flecainide level just prior to the morning (9 am) dose and at 12 hours following dosage on the previous evening (9 pm).

[b] Dosage regimens during the dose-ranging portion (part 1) of the study:
Days 3 thru 5 - 100 mg bid.
Days 6 thru 8 - 200 mg bid.
Days 9 thru 11 - 250 mg bid.
Placebo Washout Day 1 - highest dose required by each patient given at 9 am only.

[c] ---indicates that the patient did not require dosage increase to this level.

[d] Blood sample not available for analysis.

[e] Patient No. 10 went directly from dose-ranging day 7 to placebo washout day 1; since the trough level on placebo washout day 1 is from the third day of 200 mg bid dosage, the value is also shown under dose-ranging day 8.

TABLE 46

NDA 18-830

Trough Plasma Concentrations of Unchanged Flecainide Acetate During the Two-Week Outpatient Portion (part 2) Following Multiple Oral Flecainide Dosage to 11 Patients

Patient Number	Flecainide Dosage Regimen[b] (mg bid)	Trough Plasma Flecainide Acetate Concentration (ng/ml)[a] Outpatient Day 7A		Outpatient Day 14A	
		Measured	Normalized[c]	Measured	Normalized[c]
1	100	459	918	439	878
2	200	1194	1194	1198	1198
3	200	886	886	1086	1086
4	200	390	390	374	374
5	300	755	503	630	420
6	250	352	282	345	276
7	250	1020	816	1039	831
8	250	[d]	---	859	687
9	200	1137	1137	1226	1226
10	100 tid	750[e]	---	907[e]	---
11	200	292	292	269	269
Mean		724	713	761	725
Std. Dev.		336	354	361	375
N Patients		10	9	11	10

[a] Trough plasma flecainide level just prior to the morning (9 am) dose and at about 12 hours following dosage on the previous evening (9 pm), except for Patient No. 10.

[b] Twice daily oral flecainide dosage regimen on an outpatient basis at about 9 am and 9 pm, except for patient No. 10 (100 mg tid at about 6 am, 2 pm, and 10 pm).

[c] Plasma level data were normalized to a 200 mg bid dose of flecainide.

[d] Blood sample not available for analysis.

[e] Value not normalized to a 200 mg bid dose of flecainide.

TABLE 47

Plasma Concentrations of Unchanged Flecainide Acetate at the Time of Initial Reappearance of Premature Ventricular Contractions (PVCs) During the Placebo Washout Period (part 1 of the study) Following Multiple Oral Flecainide Dosage to 11 Patients

Patient Number	Flecainide Dosage Regimen (mg bid)[a]	Baseline Arrhythmia Activity (PVCs/hr)[b]	Initial Reappearance of PVCs During Washout Period: To > 10% of Baseline Time[c] (hrs)	To > 10% of Baseline Plasma Level[d] (ng/ml)	To > 30 PVCs per hour Time[c] (hrs)	To > 30 PVCs per hour Plasma Level[d] (ng/ml)
1	100	2066	14	280	8	356
2	200	131	7	1002	>24[e]	<599[f]
3	200	531	9	1039	9	1039
4	200	302	18	222	18	222
5	250	843	10	565	9	586
6	250	926	9	297	8	309
7	250	69	25	869	33	701
8	250	1868[g]	21	615	16	723
9	200	227	[h]	---	[h]	---
10	200	242	12	1002	12	1002
11	200	311	18	325	18	325
Median			13			
Mean				622		586
Std. Dev.				333		287
N Patients				10		10

[a] Twice daily oral flecainide dosage regimen prior to the placebo washout period; the last dose was given at about 9 am on placebo washout day 1.

[b] Average PVC activity from the two baseline days of 24-hour Holter monitoring; data are from Table 6.

[c] Following the 9 am dose of flecainide on placebo washout day 1, the time of initial reappearance of PVCs to the defined degree of PVC activity.

[d] Plasma flecainide level at the time of initial reappearance of PVCs was estimated from the log-linear regression line for the terminal phase of flecainide elimination from plasma of individual patients.

[e] Holter tape from placebo washout day 2 was not available for analysis.

[f] Plasma flecainide level at 24 hours following last dose.

[g] Average PVC activity from 24-hour Holter monitoring on baseline day 2 only; Holter tape from baseline day 1 was not available for analysis.

[h] Holter tapes from placebo washout days 1 and 2 were not available for analysis.

NDA 18-830

TABLE 48

Comparison of Trough Plasma Concentrations of Unchanged Flecainide Acetate to the Percent Suppression of Premature Ventricular Contractions (PVCs) During the Dose-Ranging Portion (part 1) Following Multiple Oral Flecainide Dosage to 11 Patients

Patient Number	Flecainide Dosage Regimen (mg bid)[a]	Dose-Ranging Day	Percent Suppression of PVCs[b]	Trough Plasma Level (ng/ml)[c]
1	100	5	97.2	278
2	200	8	95.6	734
3	200	8	98.0	713
4	200	8	98.3	382
5	300	[d]	96.1[d]	599
6	250	11	87.8	320
7	250	11	99.7	1132
8	250	11	99.7	796
9	200	8	97.1	852
10	200	8	[e]	---
11	200	8	99.9	320
Mean			96.9	613
Std. Dev.			3.5	283
N Patients			10	10

[a] Twice daily oral flecainide regimen (at about 9 am and 9 pm)

[b] Percent suppression of baseline PVC activity from 24-hour Holter monitoring; data are from Table 6.

[c] Trough plasma flecainide level just prior to the morning (9 am) dose; data are from Table 21.

[d] Data for 300 mg bid dose level in Patient 5 were obtained following the placebo washout period.

[e] Holter tape for dose-ranging day 8 was not available for analysis.

STUDY: R-818-041-01
INVESTIGATOR: Jordan L. Holtzman, MD, PhD

Table 49
Study Flow Chart

Flecainide-Propranolol Interaction Study
Overall Study Plan

Procedure	Study Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Propranolol, 80 mg, q8h	X	X	X	X	X	X	X	X	X	X	X[a]	Washout Period											X[a]
Flecainide, 200 mg, q12h								X	X	X	X[a]								X	X	X	X	X[a]
Pharmacodynamic Tests[b]	X			X				X			X								X			X	X
Placebo Capsules, q12h	X	X	X	X	X	X	X																
Placebo Tablets, q8h																			X	X	X	X	
Blood Samples for Plasma Drug Level Measurements	X[c]			X[d]				X[c]			X[e]								X[c]			X[c]	X[e]

Day 1 - Effect of propranolol, single dose
Day 5 - Effect of propranolol, multiple doses
Day 8 - Effect of flecainide, single dose, on propranolol, multiple doses
Day 11 - Effects of flecainide and propranolol under steady state conditions
Day 19 - Effect of flecainide, single dose
Day 22 - Effect of flecainide, multiple doses
Day 23 - Effect of propranolol, single dose, on flecainide, multiple doses

[a] AM dose only.
[b] Resting blood pressure, heart rate, respiration, systolic time intervals, echocardiography, exercise heart rate, effect on ECG rhythm strip.
[c] Pre 0900 hours dose.
[d] Pre 0900 hours dose and at 2,3,4,6, and 8 hours postdose.
[e] Pre 0900 hours dose and at 2,3,4,6, and 12 hours postdose.

FIGURE 34

R-818-041-01 HOLTZMAN
Means of Heart Rate

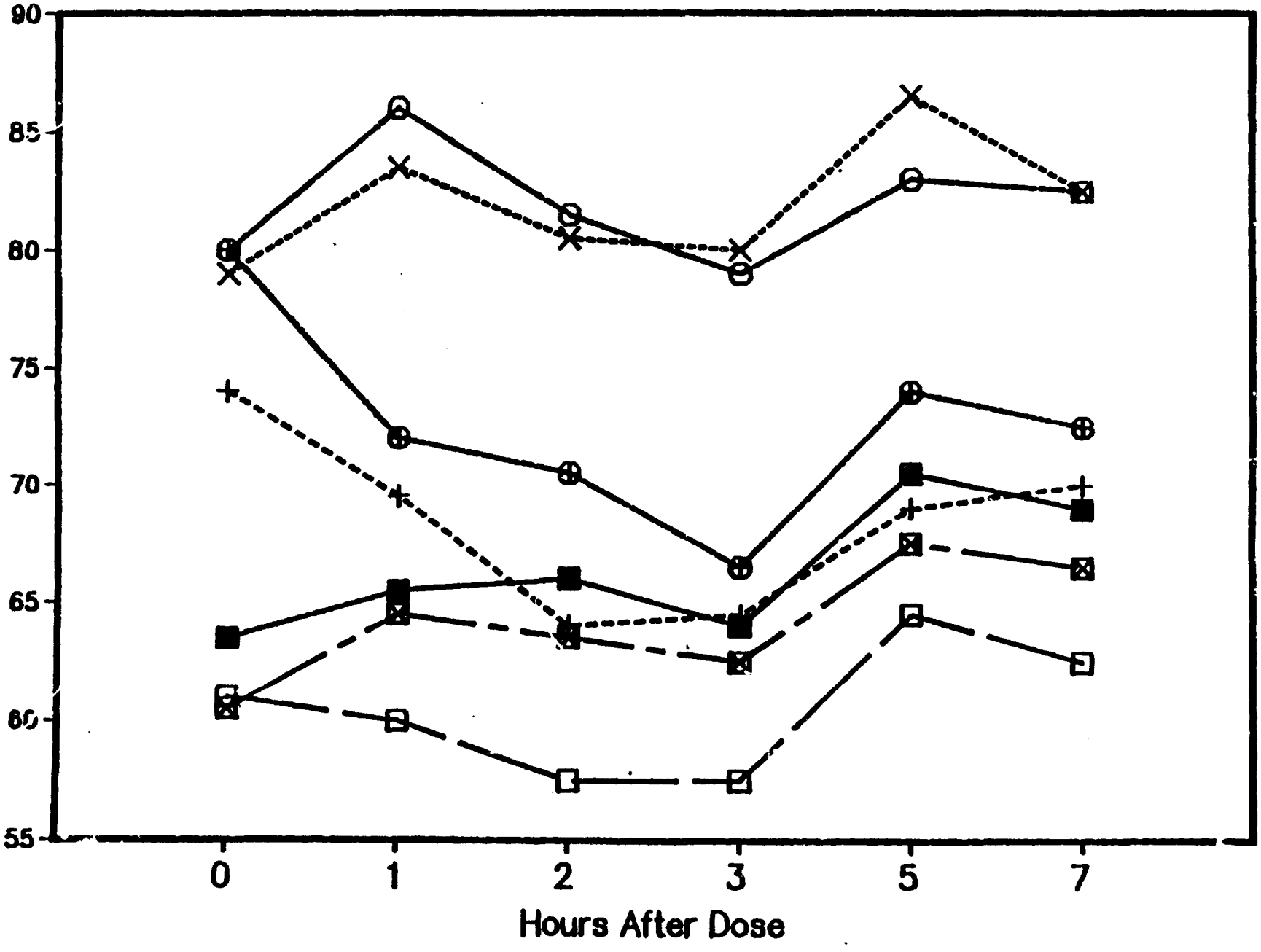


FIGURE 35

R-818-041-01 HOLTZMAN
Means of Post Exercise–Pre Exercise Heart Rate

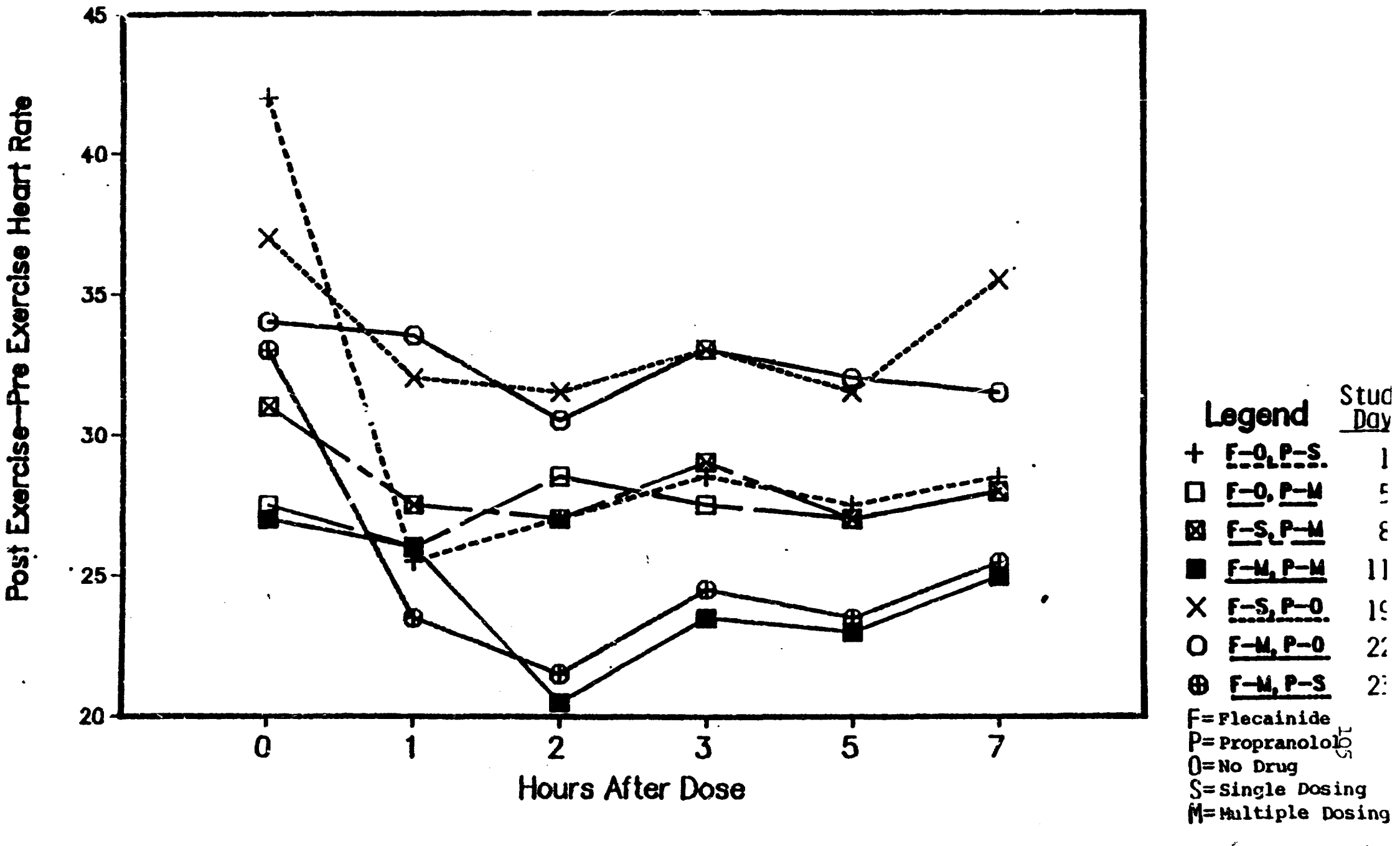


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FIGURE 36

R-818-041-01 HOLTZMAN
Means of PR Interval

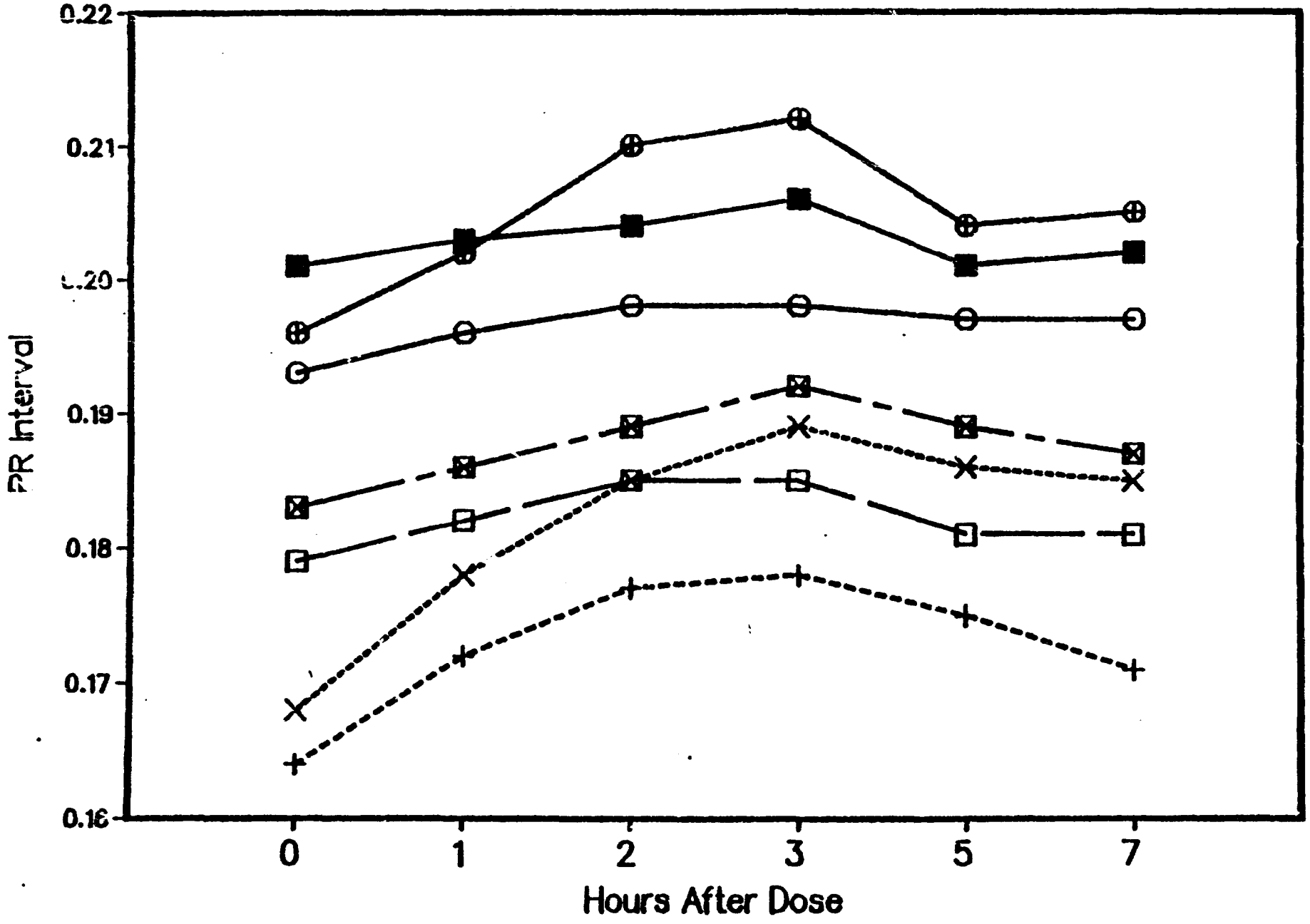


FIGURE 37

R-818-041-01 HOLTZMAN
Means of Corrected QT Interval

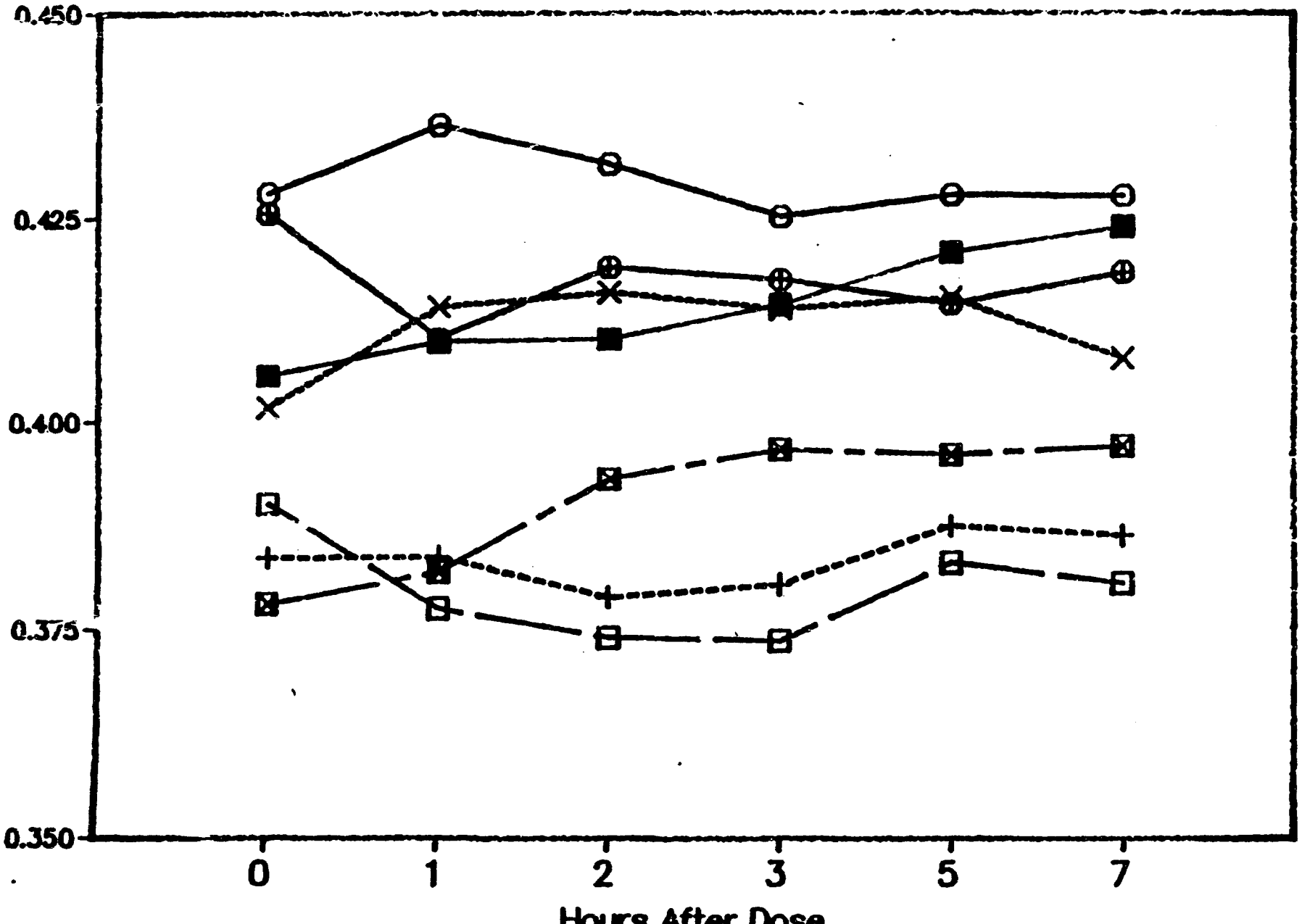


FIGURE 38

R-818-041-01 HOLTZMAN
Means of Systolic Blood Pressure

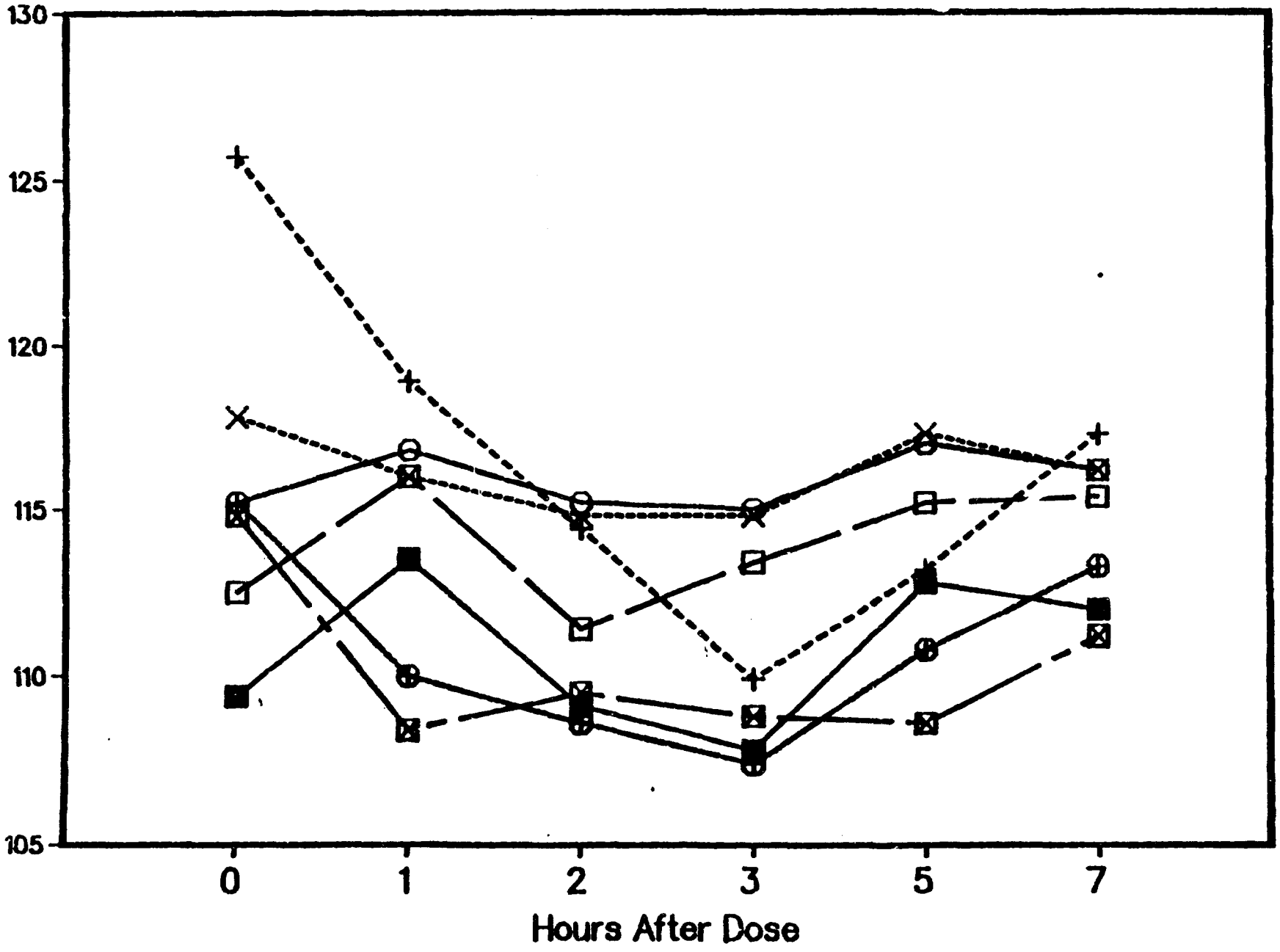


FIGURE 39

R-818-041-01 HOLTZMAN
Means of Diastolic Blood Pressure

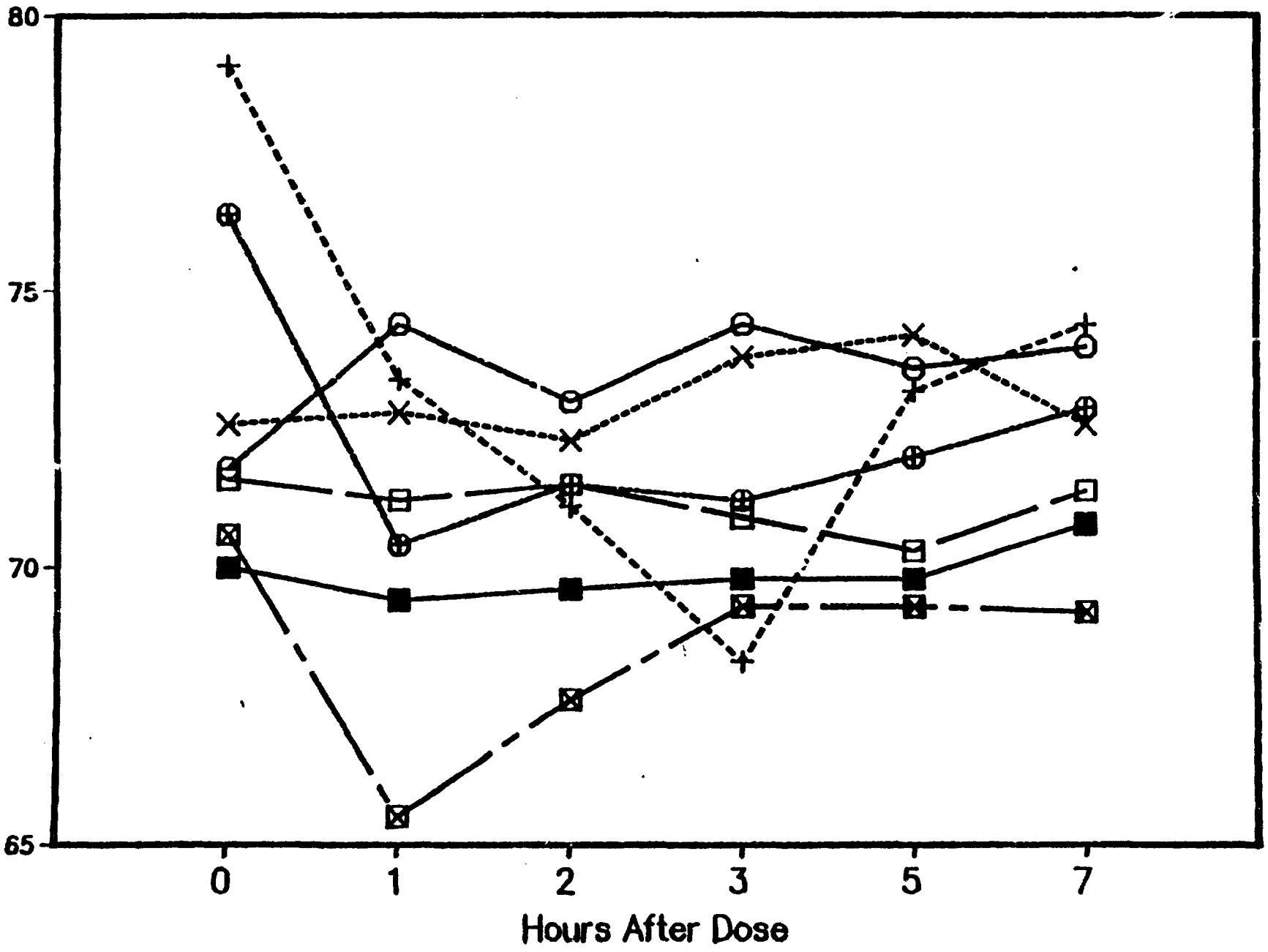


FIGURE 40

R-818-041-01 HOLTZMAN
Means of Left Ventricular End Systolic Volume

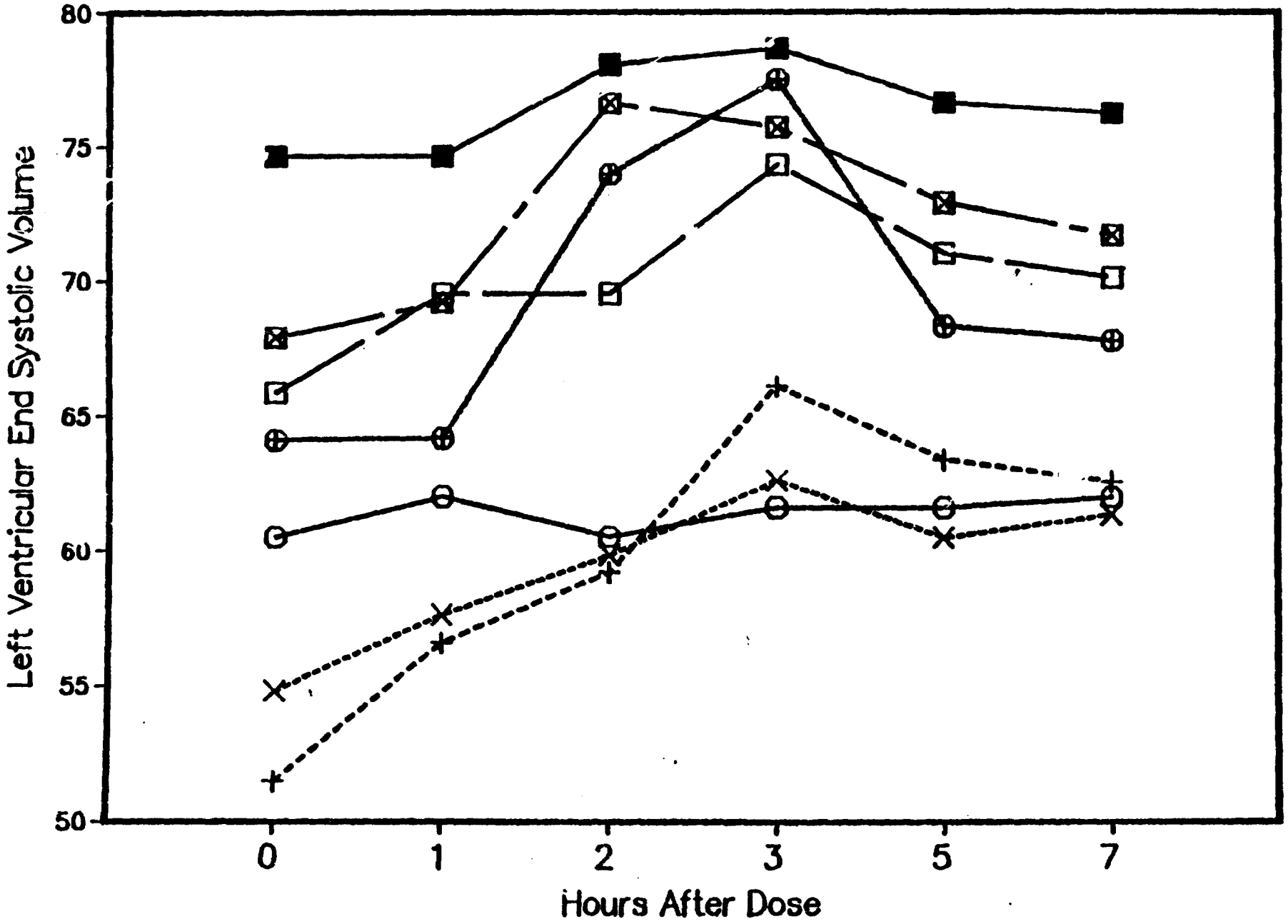


FIGURE 42

R-818-041-01 HOLTZMAN
Means of Mean VCF

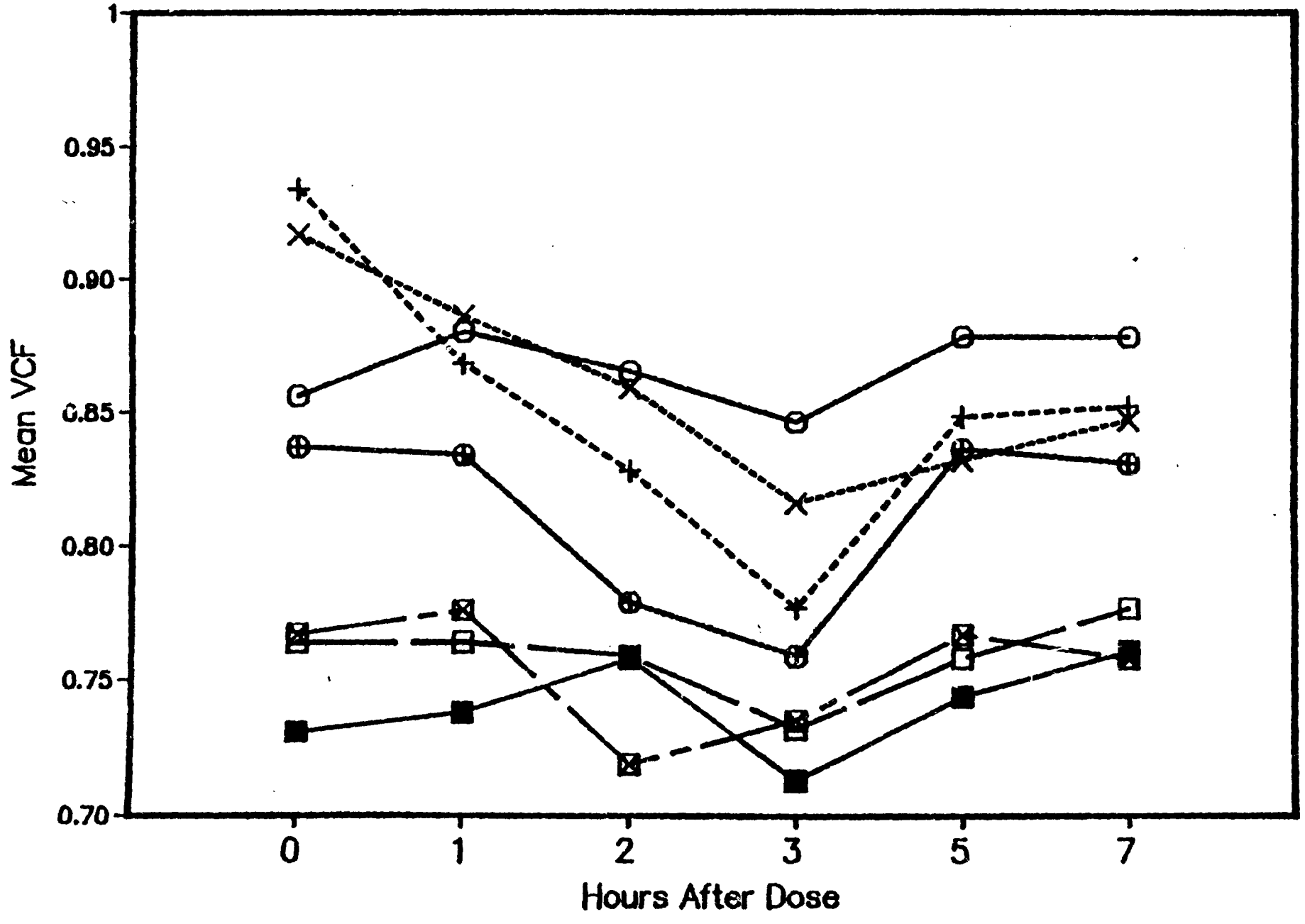


FIGURE 41

R-818-041-01 HOLTZMAN
Means of Left Ventricular End Diastolic Volume

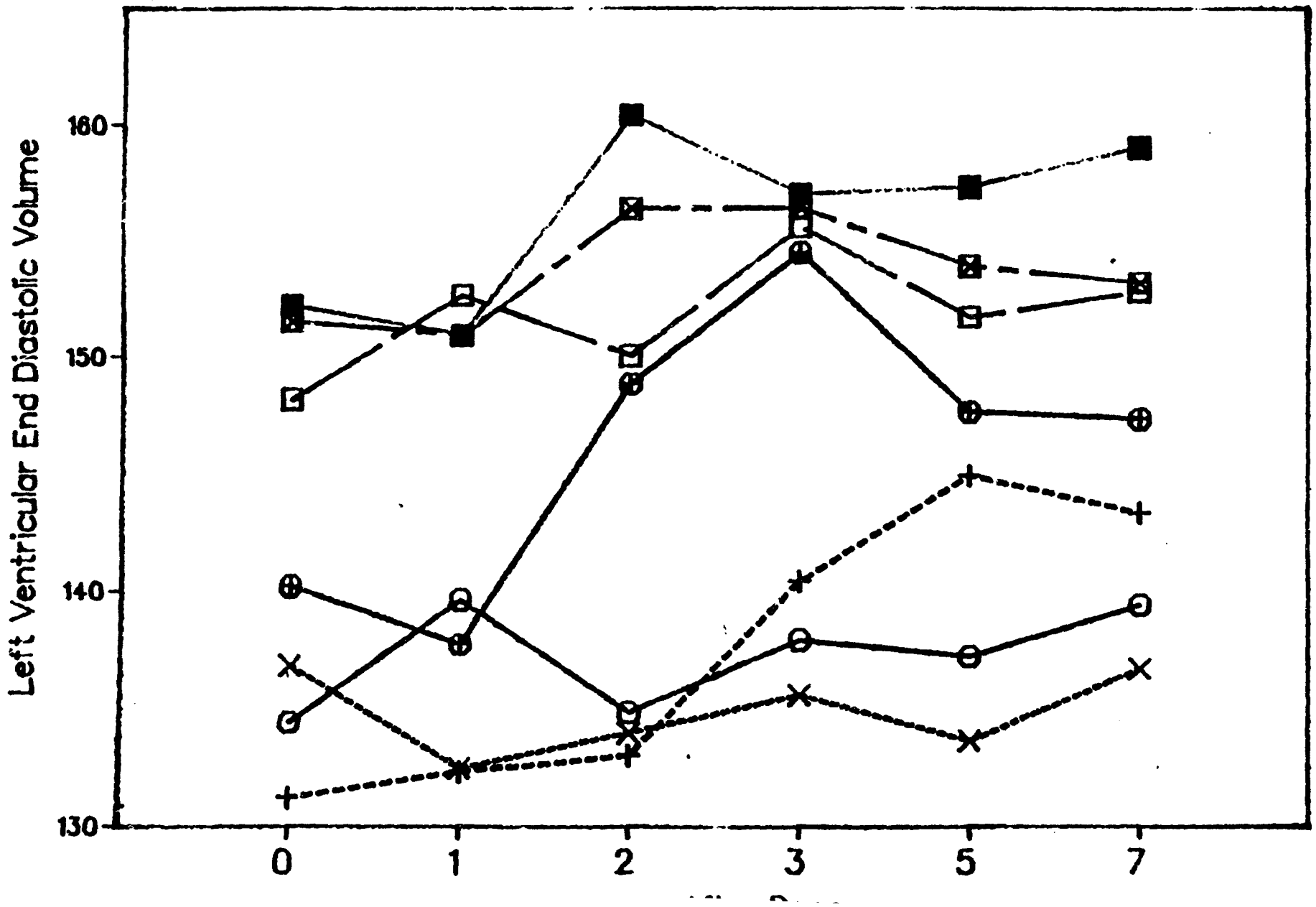


FIGURE 43

R-818-041-01 HOLTZMAN
Means of Percent Shortening of LV

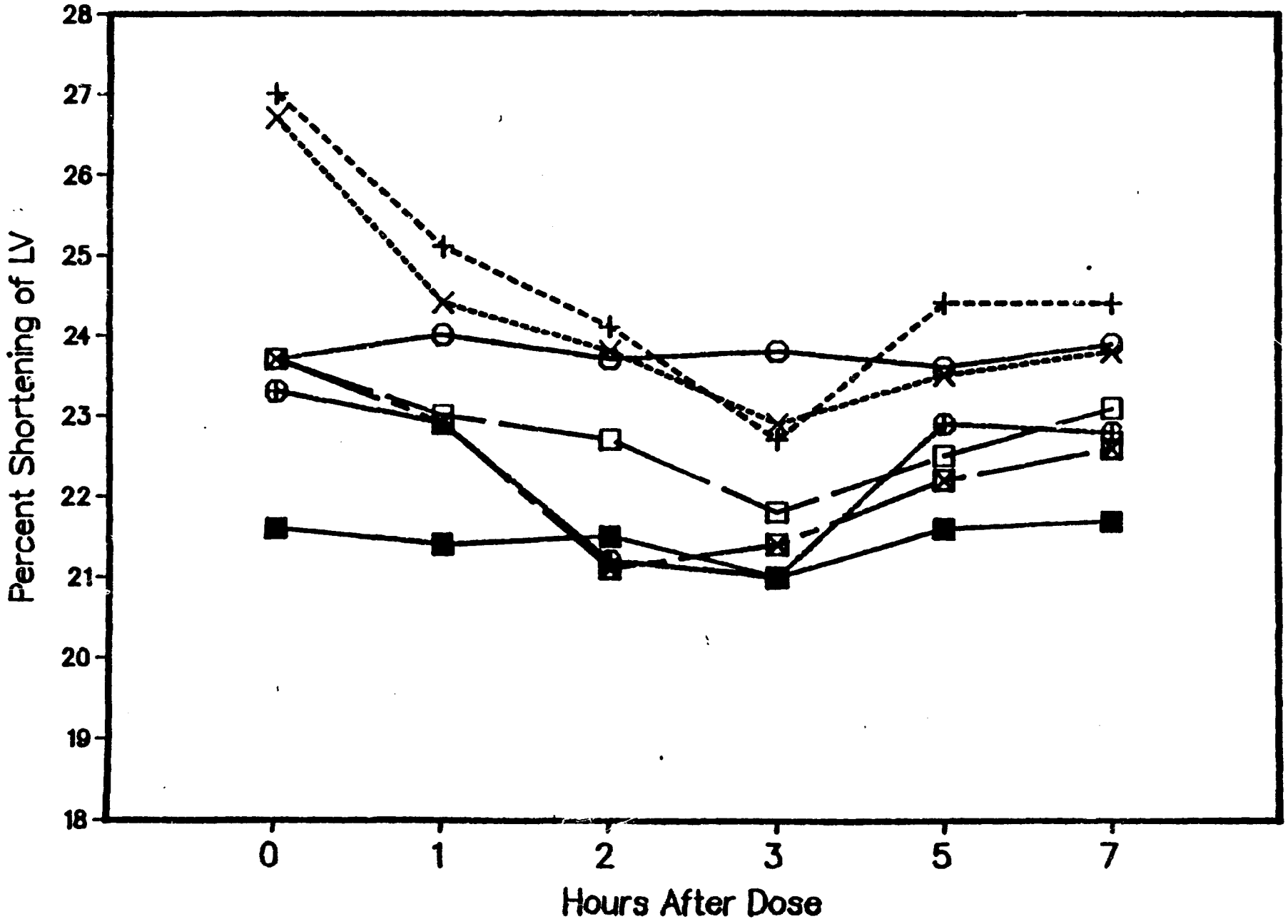
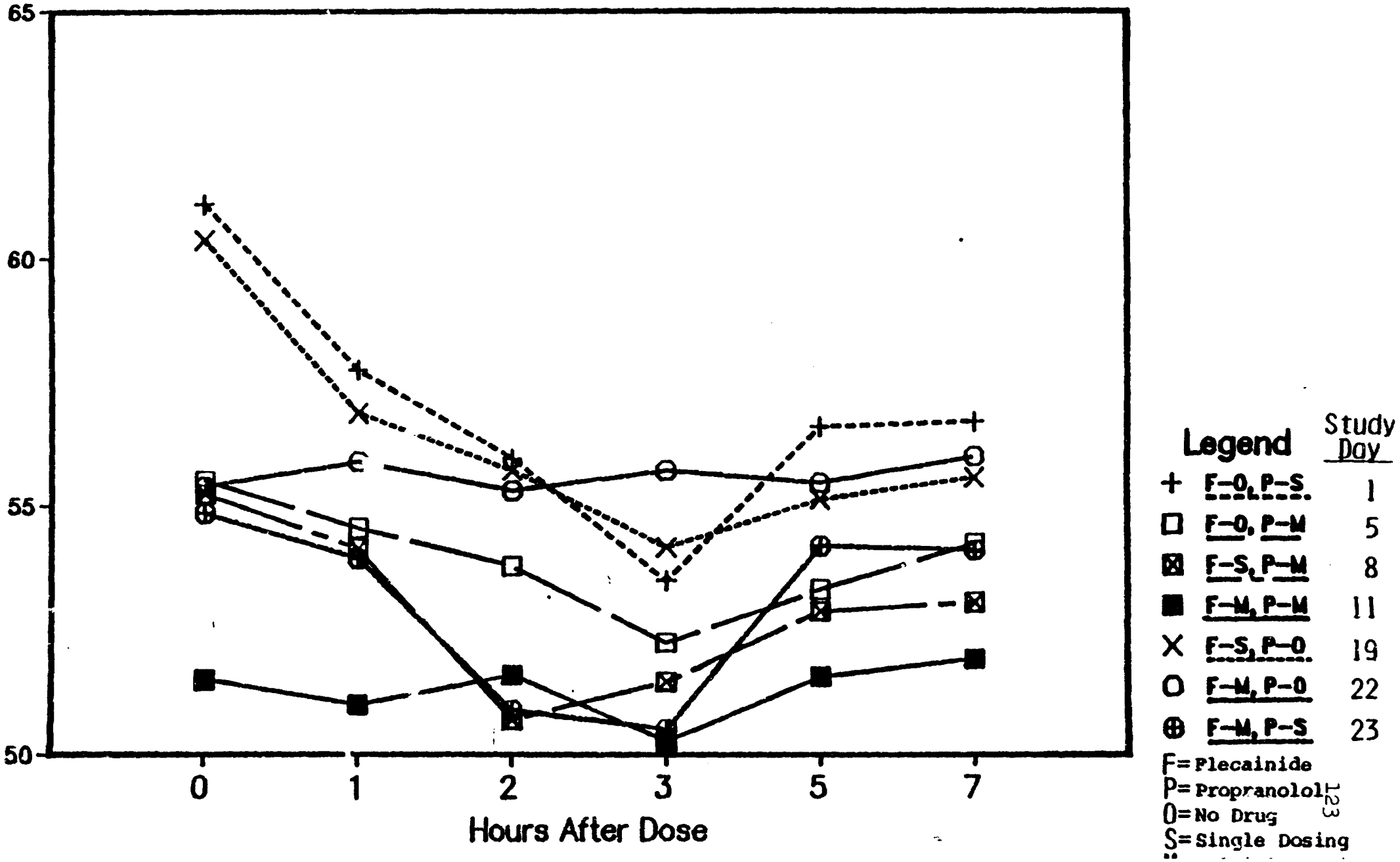


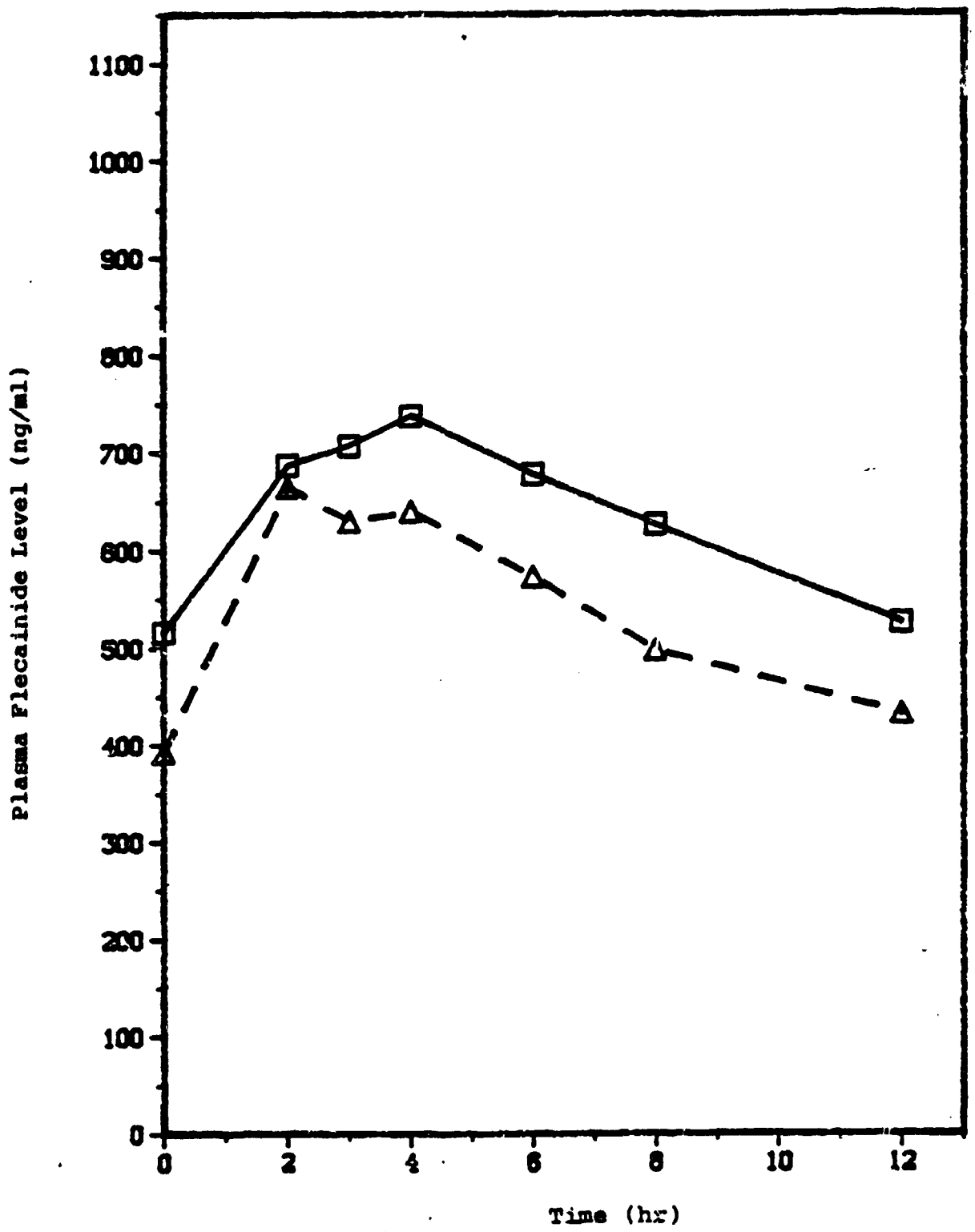
FIGURE 44

R-818-041-01 HOLTZMAN
Means of Ejection Fraction



STUDY: R-818-041-01
INVESTIGATOR: J. L. Holtzman, MD, PhD
NDA 18-830

Figure 45: Mean Plasma Flecainide Levels in 10 Subjects on Study Day 23 Following Administration of 200 mg Flecainide Every 12 Hours for Four Days (Days 19-22), Then Coadministration of One 200 mg Flecainide Capsule and a Single 80 mg Propranolol Tablet on Day 23 (△) Compared to Plasma Flecainide Levels on Day 11, the Fourth Day of Coadministration of One 200 mg Flecainide Capsule Every 12 Hours and One 80 mg Propranolol Tablet Every 8 Hours (□).



STUDY: R-818-045-01
INVESTIGATOR: GEORGE P. LEWIS, MD
NDA 18-830

TABLE 50

PREDOSE PLASMA DIGOXIN LEVELS FOLLOWING MULTIPLE (ONCE DAILY) ORAL ADMINISTRATION OF 0.25 MG[a]

SUBJECT NUMBER	STUDY DAY:	PLASMA DIGOXIN CONCENTRATION (NG/ML)[b]					
		PRE FLECAINIDE[c]		DURING FLECAINIDE		AFTER FLECAINIDE	
		9	10	13	15	19	22
1		0.34	0.40	0.56	0.45	1.17[d]	0.33[d]
2		0.67[d]	0.29[d]	0.44	0.49	0.38	0.37
3		0.31	0.49	0.52	0.58	0.41	0.23
5		0.40	0.22	0.38	0.25	0.29	0.32
6		1.39[d]	0.37[d]	0.57	0.51	0.49	0.46
7		0.54	0.58	0.59	0.43	0.41	0.35
8		0.31	0.48	0.65	0.53	0.44	0.30
9		0.52	0.61	0.70	0.62	0.61[d]	0.37[d]
10		0.51	0.63	0.76	0.50	0.38[d]	0.38[d]
11		0.21	0.36	0.56	0.40	0.39	0.38
12		0.42	0.38	0.68	0.52	0.55	0.51
13		0.32[d]	0.31[d]	0.36	0.40	0.31	0.40
14		0.51	0.47	0.47	0.38	0.46	0.31
16		0.32[d]	0.33[d]	0.61	0.67	0.86[d]	0.69[d]
17		0.52	0.43	0.73	0.56	0.56	0.44
MEAN		0.49	0.42	0.57	0.49	0.51	0.39
STD. DEV.		0.28	0.12	0.12	0.11	0.23	0.11

[a] PREDOSE LEVELS WERE DETERMINED ON THE INDICATED DAYS IMMEDIATELY PRIOR TO THE 0800 HOURS DAILY DOSE.
[b] ALL PLASMA DIGOXIN LEVELS ON STUDY DAY 1 (PREDOSE BLANK VALUE) WERE NOT QUANTIFIABLE (<0.15 NG/ML); SEE APPENDIX III.
[c] STUDY BASELINE DAYS.
[d] REPEAT ANALYSES PERFORMED: VALUE GIVEN IS THE MEAN OF ALL DETERMINATIONS EXCEPT WHEN A VALUE WAS ≤0.2 NG/ML (SEE APPENDIX III).

TABLE 48

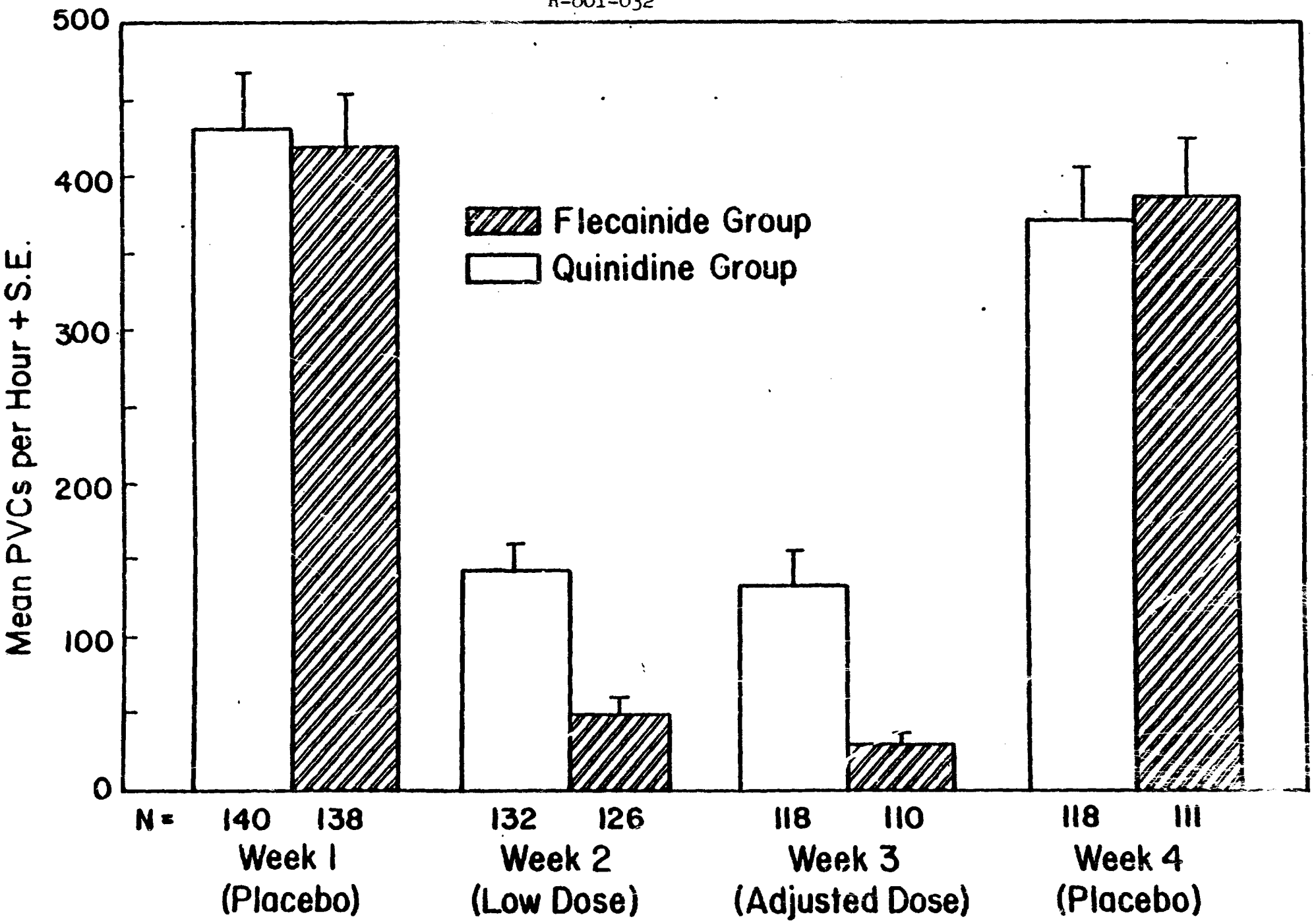
MEDIAN PERCENT SUPPRESSION OF PREMATURE VENTRICULAR CONTRACTIONS AND RANGE (MINIMUM, MAXIMUM) FOR EACH CENTER BY WEEK AND DRUG

	Week 2				Week 3			
Study Center	No. Pts	Flecainide Median % Suppression	No. Pts	Quinidine Median % Suppression	No. Pts	Flecainide Median % Suppression	No. Pts	Quinidine Median % Suppression
01	10	99.6 (-0.5,100)	9	89.3 (2.8,99.6)	10	99.1 (52.7,100)	8	86.0 (-0.6,95.9)
02	10	97.9 (43.7,100)	10	86.4 (-70.8,99.9)	9	98.5 (74.8,99.9)	10	79.2 (-57.8,99.1)
03	1	100 (100,100)	3	96.4 (40.8,100)	1	100 (100,100)	2	100 (100,100)
04	6	100 (96.8,100)	4	65.4 (-83.2,95.8)	4	99.9 (89.4,100)	3	79.6 (71.7,98.9)
05	12	99.6 (-33.7,100)	11	86.4 (-77.9,98.8)	10	99.9 (96.6,100)	10	83.8 (-29.8,99.4)
06	6	94.9 (80.4,100)	3	82.6 (-42.4,91.3)	5	99.5 (83.4,100)	4	76.6 (-17.0,99.5)
07	11	98.9 (-124.4,100)	10	93.5 (9.5,98.1)	11	98.2 (-11.9,100)	9	97.4 (-173.4,100)
08	12	98.5 (57.9,100)	10	62.5 (11.2,99.8)	11	100 (28.6,100)	9	80.6 (-2160.2,100)
09	8	97.3 (79.2,100)	9	87.6 (54.8,100)	8	94.4 (23.0,100)	8	84.4 (13.5,99.4)
10	4	99.2 (73.1,100)	1	-14.3 (-14.3,-14.3)	3	100 (77.9,100)	1	68.0 (68.0,68.0)
11	4	85.6 (79.2,99.7)	4	80.4 (37.7,99.5)	3	73.7 (72.7,100)	3	62.7 (47.2,99.5)
12	13	95.1 (-60.6,100)	13	66.2 (-104.4,100)	12	98.9 (51.4,100)	12	85.7 (-128.9,100)
13	11	99.8 (81.2,100)	14	81.0 (-759.7,99.5)	10	99.7 (85.1,100)	11	84.4 (-507.7,98.8)
14	9	99.8 (50.0,100)	9	78.4 (15.6,100)	9	98.3 (62.1,100)	5	92.0 (70.7,100)
16	4	100 (98.4,100)	4	81.6 (45.3,99.7)	4	100 (99.9,100)	4	41.5 (-126.9,99.9)
17	11	96.4 (-248.3,100)	12	76.9 (40.1,98.7)	8	99.9 (-0.5,100)	11	80.0 (30.5,99.7)

FIGURE 46

MEAN NUMBER OF PREMATURE VENTRICULAR CONTRACTIONS PER HOUR
FOR ALL PATIENTS WITH ANALYZABLE HOLTER MONITORING DATA

R-801-032



NDA 18-830

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FIGURE 47

PERCENT SUPPRESSION OF PREMATURE VENTRICULAR CONTRACTIONS BY DRUG
(WEEK 2) R-819-032

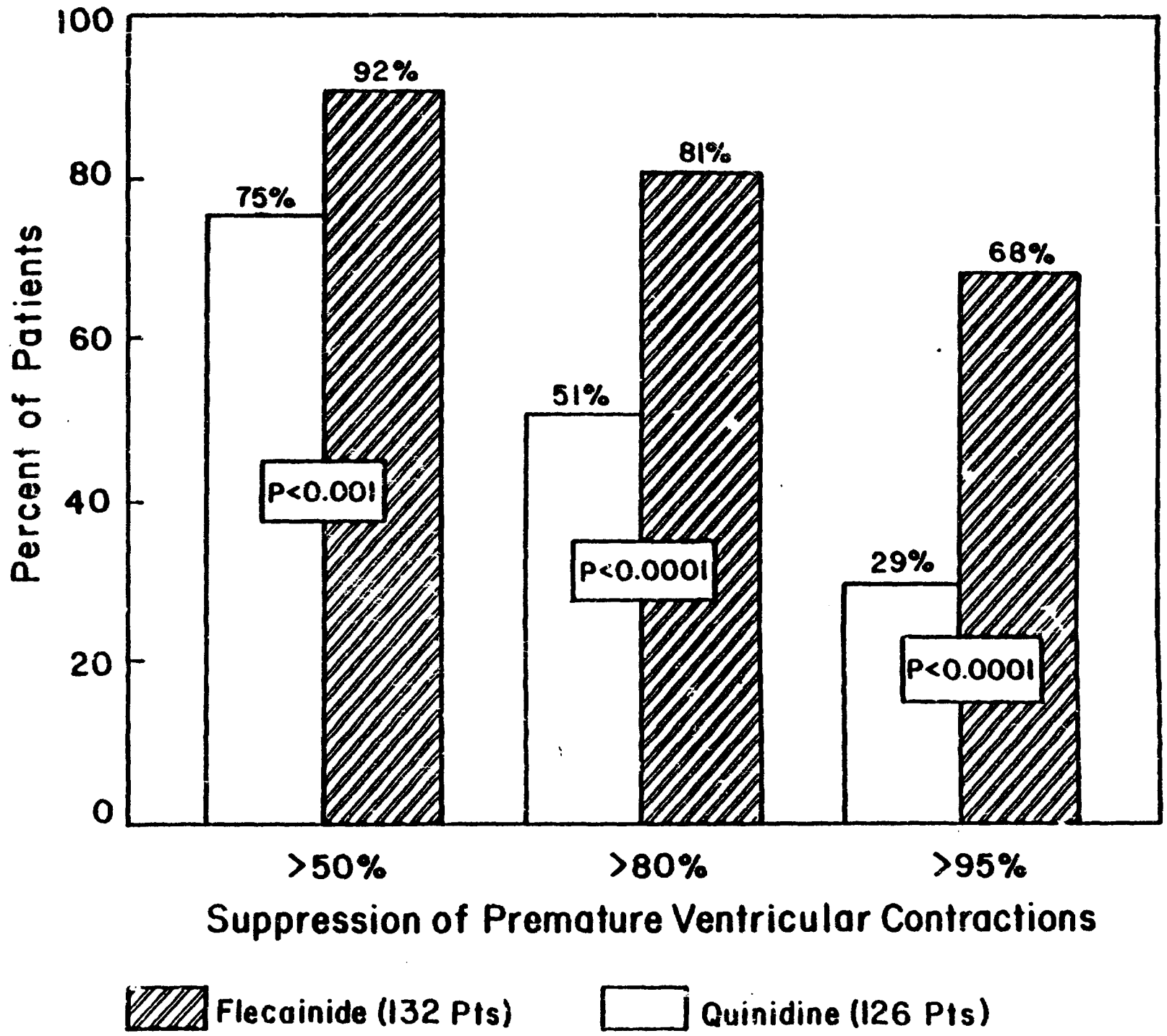

FIGURE 48

PERCENT SUPPRESSION OF PREMATURE VENTRICULAR CONTRACTIONS BY DRUG (WEEK 3) R-818-032

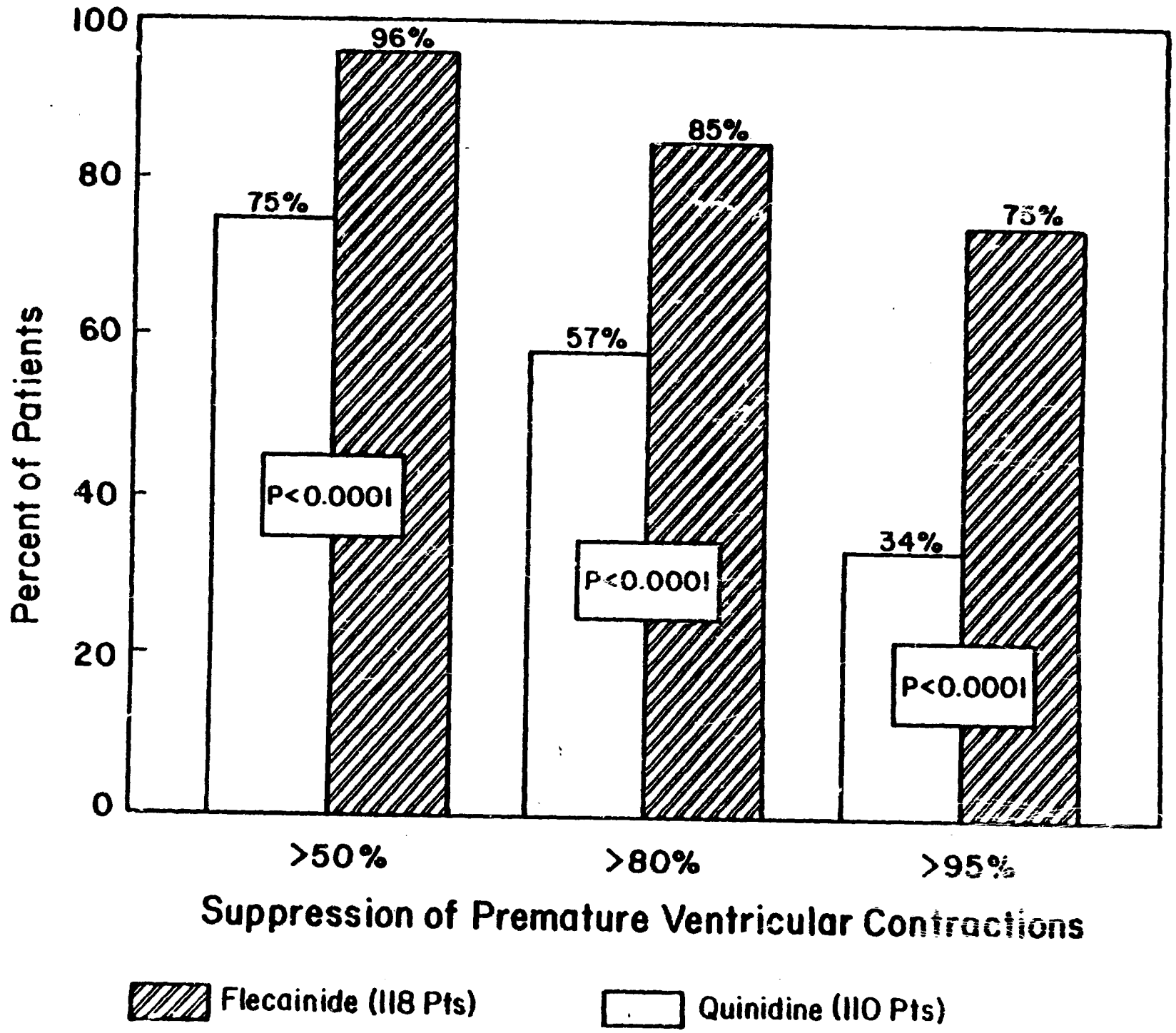

FIGURE 49
PERCENT SUPPRESSION OF PAIRED PREMATURE BEATS BY DRUG (WEEK 2) R-818-032

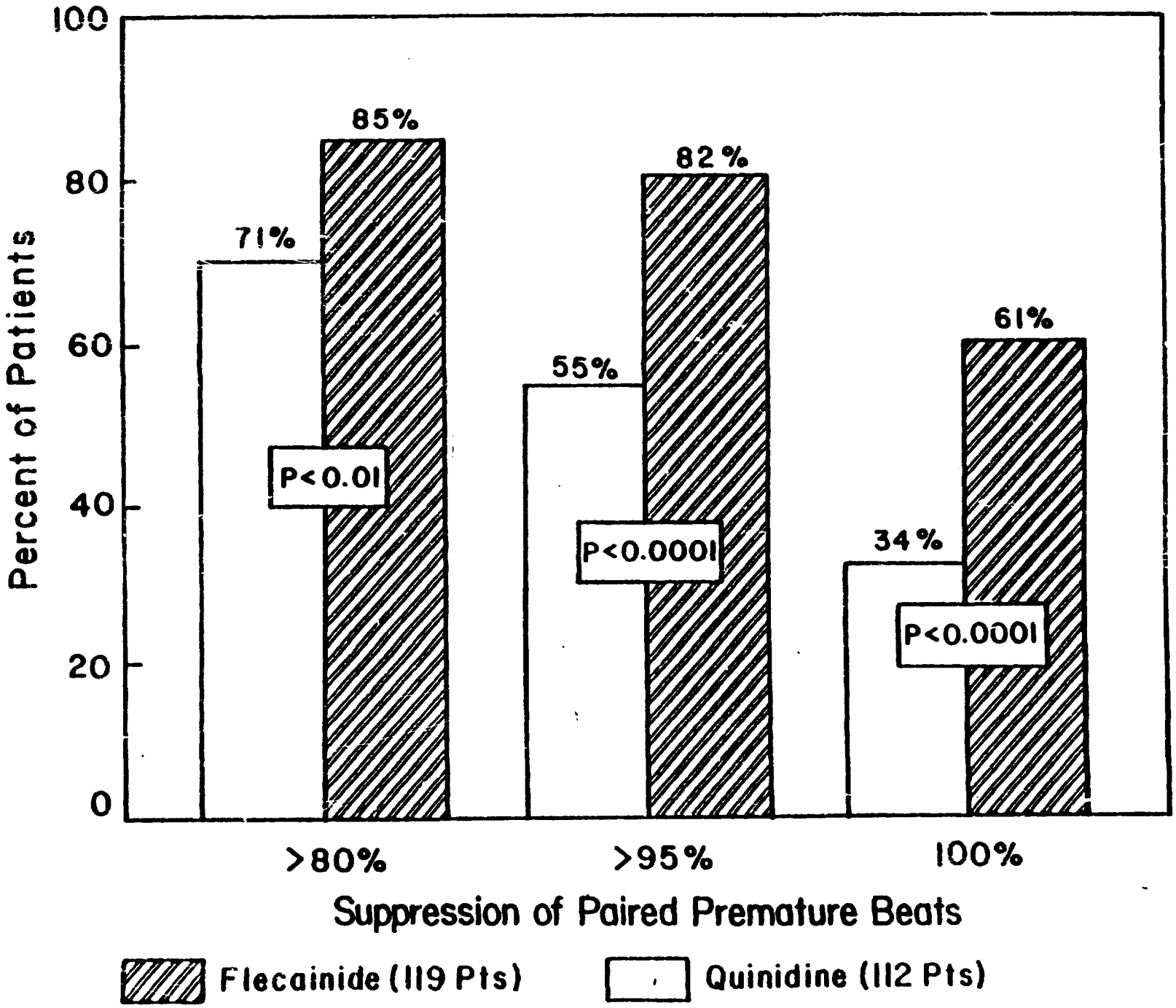

FIGURE 50

PERCENT SUPPRESSION OF PAIRED PREMATURE BEATS BY DRUG (WEEK 3) R-818-032

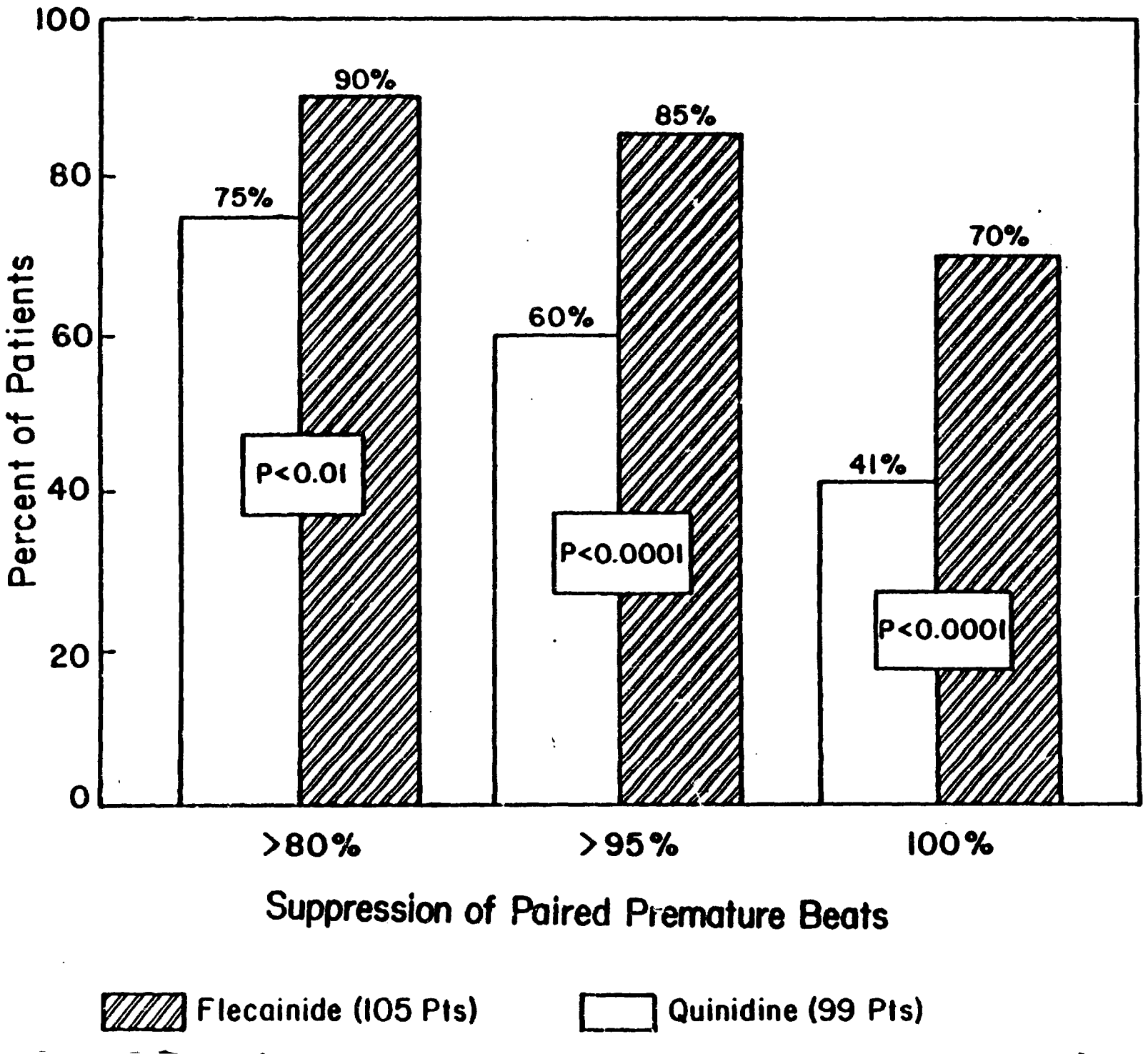

FIGURE 51

PERCENT SUPPRESSION OF BEATS OF VENTRICULAR TACHYCARDIA BY DRUG (WEEK 2)

N-818-032

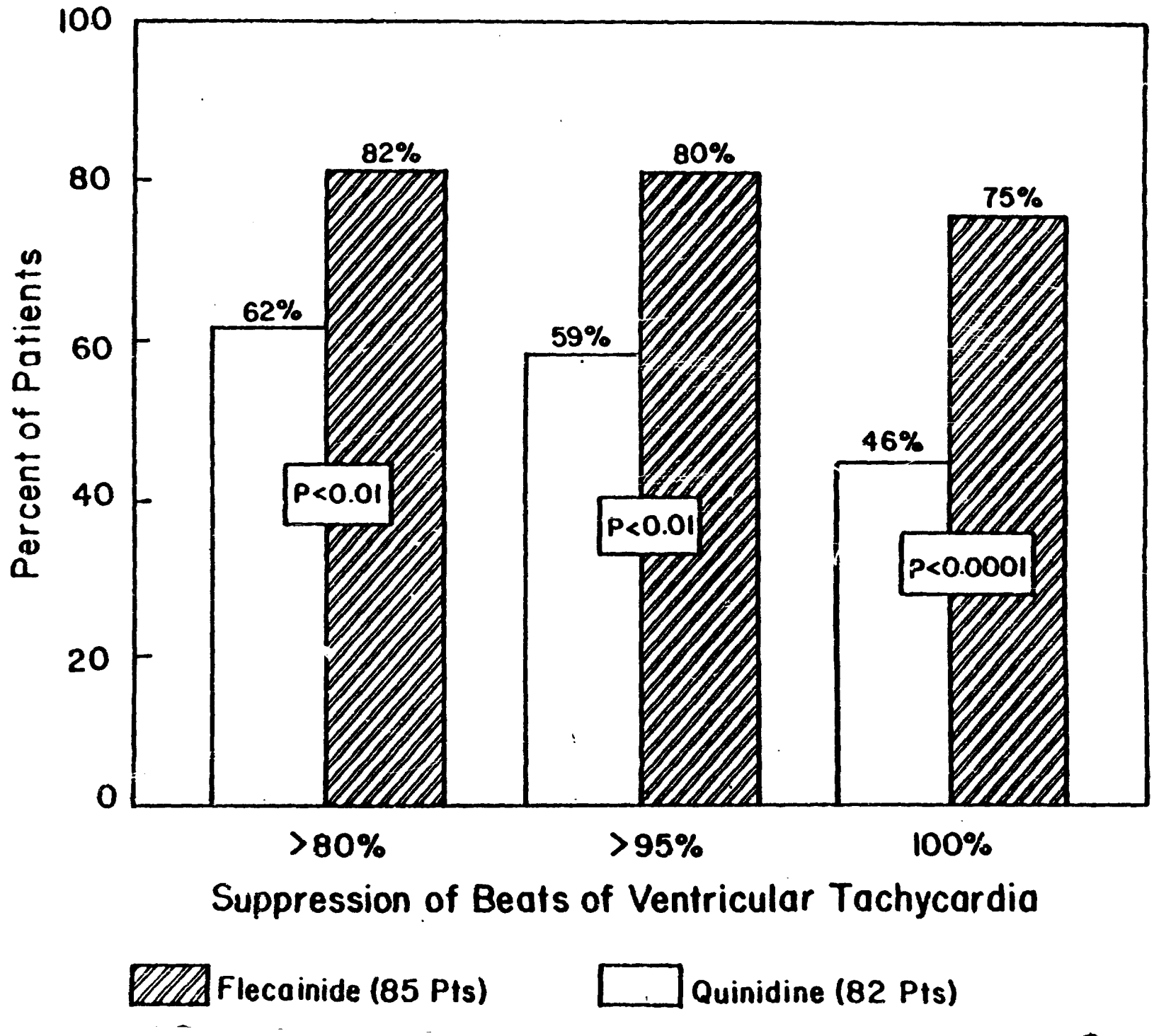

FIGURE 52

PERCENT SUPPRESSION OF BEATS OF VENTRICULAR TACHYCARDIA BY DRUG
(WEEK 3) R-818-032

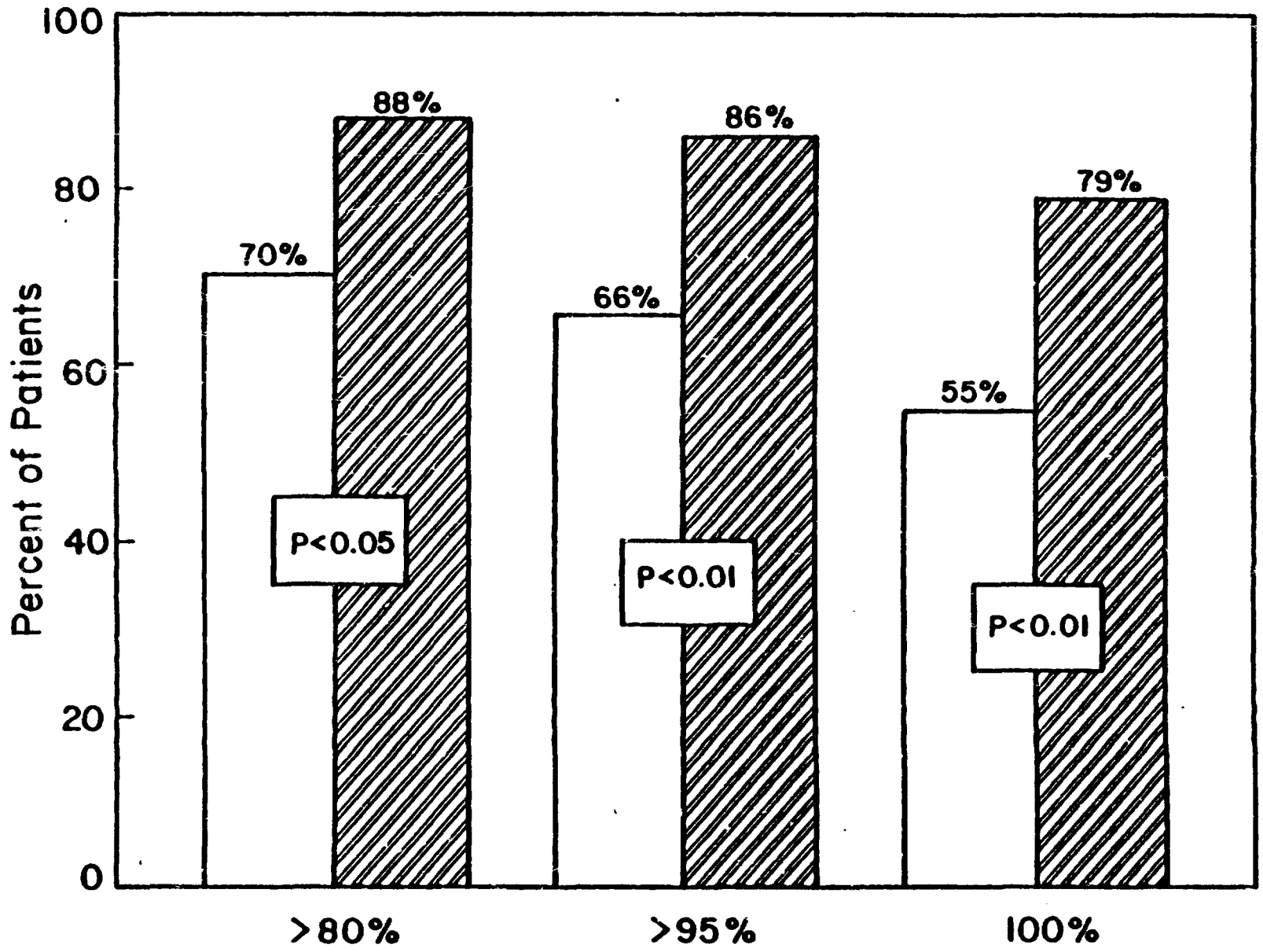

TABLE 52A

QUALIFYING PATIENTS WHO DISCONTINUED WHILE TAKING FLECAINIDE (WEEKS 2 AND 3)

Center	Pt No.	Dose mg bid	Last Study Day	Reasons
02 Hodges	7	200	W3D2	Congestive heart failure
	23	200	W2D2	Severe syncope, fatigue, weakness, and junctional bradycardia.
03 Cook	7	200	W2D2	Grand mal seizure - vasovagal episode
04 Farnhar	5	200	W3D3	Blurred vision, dizziness, first degree AV block worsened
	15	200	W2D7	First degree AV block, bradycardia
	20	200	W2D7	First degree AV block, dizziness
05 Hart	9	300	W3D5	Loss of equilibrium, dyspnea, fatigue
	10	200	W2D7	Severe weakness, diaphoresis, near syncope
06 Kalmansohn	10	200	W2D4	Palpitations and moderate dizziness
	14	200	W3D6	Severe fainting, nausea, dizziness, bradycardia, junctional rhythms
08 Lee	3	300	W3D7	Noncompliance
	6	300	W3D3	Ventricular tachycardia
	13	200	W2D4	Dizziness, peripheral blurring of vision, severe headache
10 Antlitz	3	200	W2D5	Congestive heart failure exacerbated
	4	200	W2D4	Dry mouth, nausea, numb hands and feet, disoriented
11 Marcus	2	200	W3D1	Widening of QRS and PR intervals
12 Morganroth	4	300	W3D2	Shortness of breath, nausea, junctional rhythm
	23	200	W2D3	Nervousness, dizziness, blurred vision, shortness of breath
13 Oshrain	19	200	W2D7	Blurred vision
17 Platt and Rosin	11	200	W3D1	Severe dizziness
	17	300	W3D6	Increase in PVCs

TABLE 52B

QUALIFYING PATIENTS WHO DISCONTINUED WHILE TAKING QUINIDINE (WEEKS 2 AND 3)

Center	Pt No.	Dose mg qid	Last Study Day	Reasons
01 Beller	6	400	W3D3	Vomiting, nausea, cramps
02 Hodges	28	300	W2D2	Acute thrombosis - patient died
03 Cook	3	300	W2D3	Severe diarrhea
	5	300	W3D5	Fever, diarrhea, tinnitus, rash, backache
	9	400	W3D2	Nausea, shortness of breath, rapid heart beat
04 Farnham	1	300	W2D2	Acute myocardial infarction - patient died two days later
	8	300	W2D6	Personal - noncompliance
	9	300	W2D2	Diarrhea, nausea, "sick"
05 Hart	8	300	W2D7	Gastric disturbances, ankle edema, precipitated CHF, increase in PVCs
07 Laidlaw	3	300	W2D4	Severe shortness of breath and wheezing, diarrhea
	15	300	W2D4	Acute myocardial infarction - patient died
	22	300	W3D4	Severe diarrhea
08 Lee	1	300	W2D3	Nausea, diarrhea
	5	400	W3D5	Severe nausea, vomiting, diarrhea, headache
	18	300	W2D5	Severe nausea and diarrhea
11 Marcus	1	300	W2D2	Diarrhea
	4	300	W2D7	Swelling, red hands; fatigue; peripheral edema; increased stools
12 Morganroth	13	400	W3D5	Severe nausea and dizziness
13 Oshrain	5	300	W3D4	Rash; axillary adenopathy, abnormal LF
14 Reid	5	300	W2D2	Tremor, fever, diarrhea, headache
	9	300	W2D6	Ventricular tachycardia, ventricular fibrillation
	12	300	W3D5	Vomiting, diarrhea, soft stools, tinnitus, fever, thrombocytopenia
	13	300	W3D1	Ventricular tachycardia
	18	300	W2D7	Cramps, sinus tachycardia, diarrhea, dehydration
17 Platt and Rosin	26	300	W2D7	Severe dizziness, nausea, vomiting, blurred vision

STUDY: R-818-019-04
INVESTIGATOR: PITAMBAR SOMANI, MD, ALAN B. MILLER, MD

TABLE 53

PVCs (FIRST 12 HOURS)[a] AND
PVC PERCENT SUPPRESSION FROM BASELINE

PT.NO.	TOTAL FLECAINIDE DOSE DAY 2	PVCs/MIN DAY 1	PVCs/MIN DAY 2	PERCENT SUPPRESSION DAY 2[a]	PVCs/MIN DAY 3	PERCENT SUPPRESSION DAY 3
2	180 mg	4.0	1.0	75.0	2.8	30.0
4	240 mg	4.8	0.5	89.6	2.1	56.3
7	120 mg	11.3	5.3	53.1	8.0	29.2
8	240 mg	13.9	8.2	41.0	7.5	46.0
9	240 mg	41.5	30.3	[illegible].0	43.5	-4.8
11	240 mg	4.2	2.2	47.6	1.8	57.1
12	240 mg	15.9	2.4	84.9	16.3	-2.5
13	120 mg	5.2	0.7	86.5	0.3	94.2
16	240 mg	18.0	12.0	33.3	26.4	-46.7
17	240 mg	20.7	16.2	21.7	No Dynagram[b]	No Dynagram[b]
18	120 mg	10.7	1.2	88.8	16.6	-55.1
19	240 mg	10.2	4.2	58.8	2.9	71.6
Average Percent Suppression				58.9		25.0

[a]Data for determining the percent suppression was calculated by using the PVCs per minute for the first 12 hours on days 1,2 and 3. It was felt that the data during this time period would better represent flecainide's actual activity.

[b]Analysis could not be completed because of technical problems.

TABLE 54

DAILY DOSAGE (MG/KG) vs: PLASMA DRUG CONCENTRATIONS

NDA 18-830 R-818-060-01

Centre/ Patient	FLECAINIDE - 400 mg/day			DISOPYRAMIDE - 600 mg/day		
	Daily Dose (mg/kg)	Plasma Levels (ng/ml) Week 1	Week 2	Daily Dose (mg/kg)	Plasma Levels (µg/ml) Week 1	Week 2
B/1	5.48	389	164	8.22	3.30	2.37
B/2	6.15	700	704	9.23	4 52	2.81
B/3	6.20	1983	1283	9.30	6.66	4.37
B/5	5.55	1067	1136	8.33	4.87	3.64
B/6	7.02	696	1532	10.53	2.71	2.14
B/7	5.41	400	355	8.11	3.21	2.05
B/10	6.66	1317	X	10.00	5.43	3.06
B/11	6.25	1083	673	9.38	5.18	4.97
B/12	5.33	619	155[a]	8.00	4.53	3.27
B/15	6.10	1658;1592	1871	9.10	X	X
T/1	6.67	1188	1189	10.00	3.74	3.96
T/2	5.41	1299	1423	8.11	4.58	3.71
T/4	6.56	1254	X	9.84	4.06	2.66
T/5	4.49	404	597	6.74	3.50	4.73
T/6	7.02	996	754	10.53	4.93	4.72
T/7	7.27	1328	948	10.91	[illegible]	2.74
T/8	5.63	796	787	8.45	[illegible]	3.96
T/9	6.67	1010	1259	10.00	[illegible]	3.76
T/10	4.82	594	668	7.23	3.68	3.27
T/11	5.41	1060	933	8.11	3.51	3.11
A/1	7.27	798	558	10.91	1.33[b]	0.82[b]
A/2	6.25	131[c]	868	9.38	3.33	3.89
A/3	4.21	543	570	6.32	0[d]	0[d]
A/4	4.82	404	449	7.23	2.90	2.88
R/1	5.80	170;160[b]	202[b]	8.70	2.04	1.83
R/2	5.00	300	X	7.50	2.06	X

X - Data missing
a) - Low, due to temporary suspension of the drug for administrative reasons
b) - Possible non compliance?
c) - Low, due to temporary suspension of the drug
d) - Drug discontinued

TABLE 55 : PREMATURE ABERRANT COMPLEXES PER 24 HOURS

R-818-060-01

Centre	Seq	Screen	Patient	Placebo	D	D	Placebo	R818	R818	Placebo	D	D	Placebo
BAERUM	1	929	B/1				0	2	5	5	6	6	0
	1	2883	B/2				1610	0	0	5976	0	2	154
	2	1532	B/3	573	1346	3640	866	453	47	(X)			
	1	..	B/5				(X)	2352	1557	6229	1527	2554	7603
	2	2414	B/6	(X)	1167	758	1133	372	(X)	2019			
	2	2033	B/7	4448	2682	(X)	2057	8216	1756	312			
	1	-	B/10				1180	4	144	5274	1	12	1162
	2	-	B/11	9930	13025	10714	(X)	(X)	(X)	158			
	1	-	B/12				153	(X)	22	41	0	1	0
	1	-	B/15				(X)	366	217	26300	13452	19943	37682
TRONDHEIM	1	X000s	T/1				2873	0	6	473	12	30	1005
	1	-	T/2				15008	741	222	23950	12759	11735	20040
	2	2-3000	T/4	674	17	138	649	1	7	1468			
	1	5000	T/5				2611	638	(X)	700	1201	14242	2792
(All screens	2	2000	T/6	16868	4663	41	6016	336	2108	7066			
approx	2	-	T/7	36274	19718	25881	18925	0	14	17747			
values)	2	2000	T/8	0	143	1	9	0	1	26			
	1	-	T/9				20702	0	0	2761	5	172	6570
	1	>1000	T/10				173	98	13	268	74	17	(X)
	2	X000s	T/11	624	8	2	820	0	0	271			
AKER	1	4977	A/1				1961	6	0	94	2075	68	(X)
	1	>>1000	A/2				63346	21262	2317	50579	49617	15932	83862
	2	29414	A/3	9534	(Xa)	(Xa)	45	12	740	1			
	2	-	A/4	3356	5050	4912	1014	12284	7648	1829			
RIKSHOSP	1	1778	R/1				160	11	913	(Xb)	466	2064	(X)
	1	20	R/2*				17	0	125	1125	0	2	289

COMMENTS:

* Patient excluded from efficiency evaluation due to insufficient PVCs.

X Data missing.

a Disopyramide discontinued for 2 weeks preceding this recording Treatment "none."

b Serum disopyramide level of 2.04 µg/ml detected within 3 hours of start of this tape.

Sequence 1 flecainide - disopyramide : Sequence 2 disopyramide - flecainide

TABLE 56: TOTAL EPISODES OF COMPLEX ARRHYTHMIC EVENTS DURING PERIODS:

R-818-060-01

ECG Abnormality	Screen	All Placebo	D1	D2	F1	F2
Multiform VES	8	51	19	16	8	10
Couplets	7	49	12	14	7	6
Bigeminy	5	36	9	10	4	5
Trigeminy	6	28	5	4	7	4
Quadrigeminy	2	0	1	1	0	0
Salvos	4	29	10	10	5	3
1° Heart block	0	1	3	2	5	4
2° Heart block	0	0	0	0	1	1
SVT	5	22	4	2	3	4
Bradycardia	4	43	17	16	13	15
TOTAL	41	86*	80	75	50	52

* Weekly average

D1, D2, and F1, F2 refer to first and second week of the respective drug treatment, regardless of the order in which they were received.

TABLE 57

ADVERSE EXPERIENCES

R-818-060-01

SYMPTOM:	NO OF PATIENTS REPORTING WHILST ON: FLECAINIDE	DISOPYR	PLACEBO	TOTAL NO EPISODES
Dry mouth	8	12	5	25
Dizziness	10	5	6	21
Blurred vision	11	2	3	16
Urinary nesitancy/retention	1	8	0	9
Urinary frequency/polyuria	0	2	0	2
Headache	3	2	3	8
Nausea	2	1	2	5
Constipation	1	1	1	3
Tremor	2	0	0	2
Pain around eyes	1	0	0	1
Nystagmus	1	0	0	1
Diarrhoea	0	1	1	2
Acid regurgitation	0	1	0	1
Anorexia	0	1	0	1
Malaise	0	1	1	2
Vertigo	1	0	1	2
Chest discomfort/pain	0	1	2	3
Dyspnoea	1	0	1	2
Syncope	0	0	2	2
Nervousness	0	0	1	1
Weakness	0	0	1	1
Epistaxis	0	1	0	1

Notes

1. Disopyramide was discontinued in 1 patient due to urinary frequency and nesitancy.

2. Flecainide was suspended for 3 days in 1 patient due to blurred visi and headache.
   Tolerance was better on re-institution of the drug

FIGURE 53

R-818-031 PATIENT EXPERIENCE

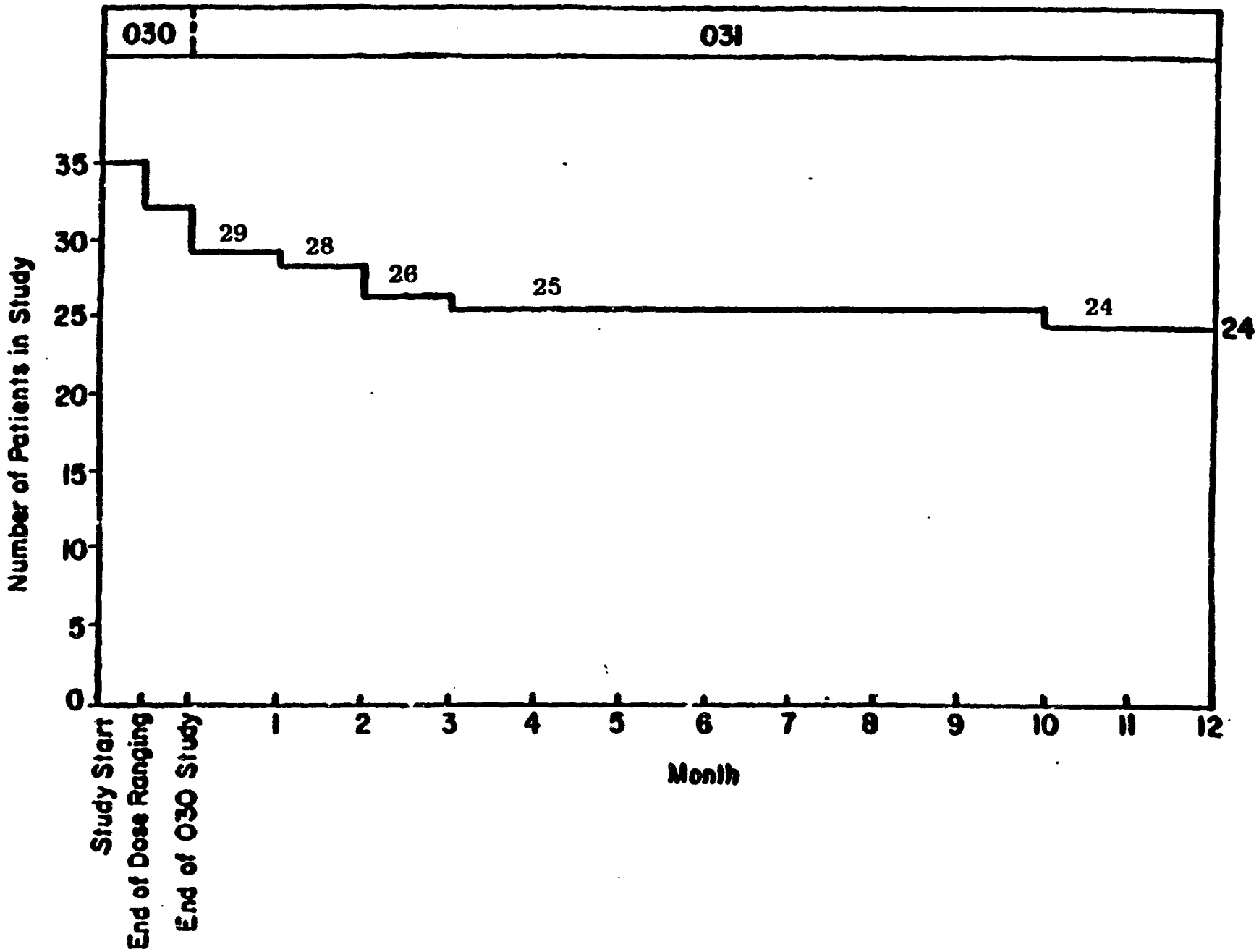

TABLE 58

EFFICACY RESULTS

Mean and Median Percent Suppression of Baseline PVCs and Multiple PVCs

	PVCs			Multiple PVCs*		
Visit[a]	No. Pts	Mean Percent Suppression	Median Percent Suppression	No. Pts	Mean Percent Suppression	Median Percent Suppression
End of R-818-030	29	95%	99%	28[b]	96%	100%
Month 1	14	95%	100%	14	97%	100%
Month 2	10	87%	100%	10	89%	100%
Month 3	10[c]	91%	100%	10[c]	94%	100%
Month 4	18	97%	100%	17[b]	100%	100%
Month 6	11[d]	99%	100%	11[d]	100%	100%
Month 8	16	97%	100%	15[b]	100%	100%
Month 10	15	85%	100%	15	96%	100%
Month 12	17	95%	99%	17	98%	100%

*Premature beats which occur in pairs, triplets or runs of four or more.

[a]Holters are taken periodically, but not routinely at every visit.
[b]One patient had no baseline multiple PVCs.
[c]Includes post visit from pt. #12, center 02.
[d]Includes month 5 Holter from pt. #1, center 03.

TABLE 59

ECG INTERVAL RESULTS

VISIT	NO. PTS.	MEAN TOTAL DAILY DOSE (MG)	PR		QRS		QT (Uncorrected)	
			MEAN (SEC)	MEDIAN PERCENT INCREASE FROM BASELINE	MEAN (SEC)	MEDIAN PERCENT INCREASE FROM BASELINE	MEAN (SEC)	MEDIAN PERCENT INCREASE FROM BASELINE
Baseline	29	-	0.168	-	0.081	-	0.378	-
End of 030	29	413.8	0.203	20.0%*	0.099	18.1%*	0.409	7.6%*
Month 1	29	410.3	0.202	20.0%*	0.101	25.0%*	0.405	5.1%*
Month 2	28	411.1	0.205	25.0%*	0.105	31.0%*	0.412	10.6%*
Month 3	27[a]	392.3	0.201	20.9%*	0.106	25.0%*	0.404	8.2%*
Month 4	25	392.0	0.205	25.0%*	0.111	31.3%*	0.406	10.0%*
Month 6	25	380.0	0.198	19.4%*	0.101	25.0%*	0.412	10.5%*
Month 8	24[b]	372.0	0.209	25.8%*	0.107	31.0%*	0.407	9.6%*
Month 10	25	363.5	0.202	23.8%*	0.105	25.0%*	0.398	5.0%*
Month 12	23[c]	358.3	0.211	25.7%*	0.107	27.5%*	0.408	11.1%*

* Statistically significant ($P \leq 0.05$) increase from baseline (Wilcoxon Signed-Rank Test).
[a] Includes poststudy visit from pt. #12, center 02.
[b] Pt. #2, center 03, missed ECGs during month 8 visit due to scheduling problems.
[c] Pt. #7, center 03, missed month 12 visit.

R-818-031 Update

TABLE 60

ADVERSE EXPERIENCES

	NUMBER OF PATIENTS REPORTING AT LEAST ONCE		
	Month 1-12	Month 13-24	Month 1-24
ABDOMINAL PAIN	3	0	3
ARRHYTHMIA	2	0	2
ARTHRALGIA	1	0	1
ASTHENIA	1	0	1
ATAXIA	2	0	2
BACK PAIN	1	0	1
BRADYCARDIA	1	0	1
BRONCHITIS	1	0	1
CARDIAC FAILURE	1	0	1
CHEST PAIN	5	1	6
CONFUSION	1	0	1
CONSTIPATION	2	0	2
COUGHING	1	1	1
CRAMPS LEGS	1	0	1
DIARRHEA	2	0	2
DIZZINESS	10	4	12
DYSPEPSIA	1	1	2
DYSPNEA	2	1	3
DYSURIA	2	0	2
EDEMA	2	0	2
FATIGUE	3	0	3
FEVER	3	0	3
FLUSHING	3	0	3
HEADACHE	7	2	8
HYPERTENSION	1	0	1
HYPOAESTHESIA	3	0	3
INFECTION	1	0	1
INSOMNIA	1	0	1
MICTURITION DISORDER	1	0	1
MICTURITION FREQUENCY	1	0	1
NAUSEA	6	1	7
NERVOUSNESS	4	0	4
PALPITATION	3	3	5
PARESTHESIA	2	1	2
PHARYNGITIS	1	1	2
PRURITUS	2	0	2
RASH	2	0	2
RENAL CALCULUS	1	0	1
RESPIRATORY DISORDER	1	0	1
RHINITIS	1	0	1
SINUSITIS	0	1	1
SKIN COLD CLAMMY	1	0	1
SWEATING INCREASED	1	0	1
SYNCOPE	2	0	2
TASTE PERVERSION	2	2	3
TINNITUS	1	0	1
TREMOR	2	2	3
UPPER RESPIRATORY TRACT INFECTION	2	0	2
VISION ABNORMAL	11	5	11
VOMITING	3	0	3
NUMBER OF PATIENTS REPORTING AT LEAST ONE ADVERSE EXPERIENCE	22	12	22
NUMBER OF PATIENTS	29	24	29

TABLE 61A

Summary of Flecainide Dosing

Total Daily Dose of Flecainide	Number of Patients at Total Daily Dose Month 6	Month 12
600 mg	3	4
500 mg	3	2
450 mg	1	1
400 mg	58	42
350 mg	0	1
300 mg	34	31
250 mg	1	0
200 mg	34	17
150 mg	4	2
100 mg	4	2
Total Patients	142	102
Median Daily Dose	300 mg	300 mg
Mean Daily Dose	318 mg	335 mg

TABLE 61B

Analysis of Dose Changes

	Number of Patients
Month 12 Dose < Month 6 Dose	5
Month 12 Dose = Month 6 Dose	85
Month 12 Dose > Month 6 Dose	12
Total	102

TABLE 62

24-Hour Holter Analyses

Frequency Distribution of Percent Suppression
of Baseline PVCs

Visit	No. Pts	Number of Patients (and Percentage) in Percent Suppression Categories			
		>50%	>80%	>95%	100%
Month 6 (Median Percent Supp=98.6%)	128	122 (95%)	101 (79%)	79 (62%)	23 (18%)
Month 12 (Median Percent Supp=98.9%)	90	81 (90%)	72 (80%)	61 (68%)	17 (19%)

Frequency Distribution of Percent Suppression
of Baseline Paired Premature Beats

Visit	No. Pts	Number of Patients (and Percentage) in Percent Suppression Categories			
		>50%	>80%	>95%	100%
Month 6 (Median Percent Supp=100%)	116	106 (91%)	98 (84%)	92 (79%)	73 (63%)
Month 12 (Median Percent Supp.=100%)	78	71 (91%)	69 (88%)	65 (83%)	57 (73%)

Frequency Distribution of Percent Suppression
of Baseline V-Tach Beats

Visit	No. Pts	Number of Patients (and Percentage) in Percent Suppression Categories			
		>50%	>80%	>95%	100%
Month 6 (Median Percent Supp.=100%)	79	72 (91%)	71 (90%)	70 (89%)	67 (85%)
Month 12 (Median Percent Supp.=100%)	50	48 (96%)	48 (96%)	47 (94%)	47 (94%)

Table 63

Interval Changes for Flecainide Patients Discontinued due to ECG Changes

R-818-033

Center	Pt. No.	Flecainide Dose at Time of Discontinuation	Length of Time on Drug	Interval Changes (seconds)	Reasons for Discontinuation
01	02	200 bid	3 months	PR: 0.28-[a] QRS 0.08-0.08	Sick sinus syndrome 1°AV block (not drug related)
03	03	200 bid	6 days	PR 0.16-0.22 QRS 0.08-0.14	1°AV block and complete right bundle branch block marked right axis deviation
03	08	200 bid	6 days	PR 0.18-0.24 QRS 0.12-0.15	1°AV block and complete left bundle branch block; (also severe dizziness)
04	09	150 bid	3 days	PR 0.18-0.22 QRS 0.08-0.08	NSR with sinus pauses, junctional escape beats, PAC's, 1°AV block
07	08	200 bid	1.5 months	PR 0.16-0.28 QRS 0.16-0.20	Supraventricular tachycardia (also weakness, diaphoresis and blurred vision)
12	24	300 bid	1 month	PR 0.16-0.26 QRS 0.09-0.15	Occasional 2° AV block, Wenkebach type (also blurred vision, lightheadedness, constipation and lack of therapeutic response

[a] atrial fibrillation

TABLE 64

Flow Chart, R-818-EN-03

Stage One Procedures	Days	1	2	3	4	5	6	7	8	or D/C
D/C Previous Antiarrhythmics		X								
Patient History		X								
Complete Physical Exam		X								
Ophthalmological Exam		X								
Chest X-Ray		X								
Laboratory Tests					X					
24-hour Holter monitor					X			X		
Vital signs		X	X	X	X	X	X	X	X	
Telemetry monitoring		X	X	X	X	X	X	X	X	
Record of Adverse Reactions		X	X	X	X	X	X	X		
Electrocardiogram					X				X	
Plasma for drug level					X			X		
Flecainide Administration						XX	XX	XX	(XX)	
Discharge to Stage Two									X	

Stage Two Procedures	Months	0	1	2	3	4	5	6	7	8	9	10	11	12	D/C
Drug Inventory and Concomitant Medication			X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam			X	X	X	X	X	X	X	X	X	X	X	X	X
Interim Medical History			X	X	X	X	X	X	X	X	X	X	X	X	
Ophthalmological Exam								X						X	X
Chest X-Ray														X	X
Laboratory Tests			X	X	X	X	X	X	X	X	X	X	X	X	X
LE Cells and ANF Titre					X			X			X			X	X
24-Hour Holter monitoring				X		X		X		X		X		X	
Vital Signs			X	X	X	X	X	X	X	X	X	X	X	X	X
Record of Adverse Reactions			X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram			X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma for drug level			X	X	X	X	X	X	X	X	X	X	X	X	X
Drug withdrawal (1/4 of the patients at months indicated)					X			X			X			X	

Withdrawal Procedures	Days	0	1	2	3	4	5	6
D/C Flecainide			X					
Telemetry monitoring			X	X	X	X	X	X
Vital Signs			X	X	X	X	X	X
Side Effects			X	X	X	X	X	
Plasma for drug level		X						X
24-Hour Holter monitor		X					X	
Flecainide Administration		X						X
Discharge or return to Stage Two								X

TABLE 65

PATIENT DISCONTINUATIONS

Center	Pt No.	Total Daily Dose at Time of D/C	Time on Drug	Reason for Discontinuation
01	3	400 mg	3 days	Inadequate response to therapy
	4	200 mg	2 weeks	Adverse experience (dizziness, headache)
	6	400 mg	8 months	Death
	11	400 mg	3 days	Adverse experience (dizziness)
	14	250 mg	16 months	Personal reasons
	15	200 mg	20 months	Personal reasons
	16	400 mg	1 day	Death
	21	400 mg	8 months	Ventricular fibrillation
	24	400 mg	1 week	Death
	30	200 mg	16 months	Death
	39	400 mg	3 days	Inadequate response to therapy
02	103	400 mg	4 days	Inadequate response to therapy
	105	400 mg	1 month	Death
	106	400 mg	4 days	Inadequate response to therapy

TABLE 65(CONCLUDED)

PATIENT DISCONTINUATIONS

Center	Pt No.	Total Daily Dose at Time of D/C	Time on Drug	Reason for Discontinuation
03	202	400 mg	14 months	Adverse experience (eye complaints)
	203	400 mg	3 days	Death
	209	300 mg	16 months	Death
	213	400 mg	3 days	Inadequate response to therapy
	214	400 mg	12 months	End of study
	215	200 mg	12 months	End of study
	217	400 mg	3 days	Inadequate response to therapy
	221	400 mg	6 months	Inadequate response to therapy
	222	200 mg	7 months	Acute anterior MI
	223	200 mg	12 months	Lack of return of arrhythmia during placebo withdrawal
	225	400 mg	3 days	Inadequate response to therapy
04	301	400 mg	3 days	Inadequate response to therapy
	305	400 mg	6 months	Inadequate response to therapy
	306	400 mg	5 months	Questionable compliance
	308	400 mg	3 days	Inadequate response to therapy

TABLE 66
HOLTER RESULTS --SUPPRESSION OF PVCS
AVERAGE PVCS / HOUR
PERCENT SUPPRESSION OF BASELINE PVCS

PTNO	BASELINE	DAY 7	MONTH 2	MONTH 4	MONTH 6	MONTH 8	MONTH 10	MONTH 12
1	895.0	10.8 98.8%	32.8 96.3%	131.5 85.3%	151.0 83.1%	62.9 93.0%	57.1 93.6%	26.2 97.1%
2	297.1	4.3 98.5%	24.5 91.8%	136.5 54.1%	20.3 93.2%	3.5 98.8%	3.5 98.8%	83.5 71.9%
3	36.2	18.5 49.0%	A	A	A	A	A	A
4	730.6	35.5 95.1%	A	A	A	A	A	A
5	1099.5	150.8 86.3%	16.2 98.5%	109.1 90.1%	43.4 96.1%	4.6 99.6%	12.0 98.9%	10.3 99.1%
6	435.1	29.9 93.1%	0.7 99.8%	0.1 100.0%	0.3 99.9%	0.2 100.0%	A	A
7	435.1	23.5 94.6%	0.1 100.0%	0.0 100.0%	2.5 99.4%	0.5 99.9%	B 7.3 98.3%	C 0.7 99.8%
8	647.1	7.3 98.9%	0.1 100.0%	1.5 99.8%	1.8 99.7%	4.8 99.3%	3.2 99.5%	2.9 99.5%
9	480.4	0.0 100.0%	0.0 100.0%	0.6 99.9%	0.3 99.9%	0.2 100.0%	0.0 100.0%	0.4 99.9%
10	334.5	0.0 100.0%	0.0 100.0%	0.0 100.0%	0.0 100.0%	6.0 98.2%	377.4 -12.8%	0.0 100.0%
11	394.1	0.1 100.0%	A	A	A	A	A	A
12	500.0	0.2 100.0%	0.0 100.0%	0.2 100.0%	3.6 99.3%	1.2 99.8%	24.6 95.1%	12.5 97.5%

NOTE: A = WITHDRAWN FROM STUDY
B = HOLTER ACTUALLY TAKEN ON MONTH 11
C = HOLTER ACTUALLY TAKEN ON MONTH 13

TABLE 66
(CONTINUED)
HOLTER RESULTS --SUPPRESSION OF PVCS
AVERAGE PVCS / HOUR
PERCENT SUPPRESSION OF BASELINE PVCS

PTNO	BASELINE	DAY 7	MONTH 2	MONTH 4	MONTH 6	MONTH 8	MONTH 10	MONTH 12
28	1051.3	0.5 100.0%	7.8 99.3%	724.5 31.1%	4.6 99.6%	1.5 99.9%	8.0 99.2%	A
29	294.2	0.0 100.0%	0.0 100.0%	0.0 100.0%	0.0 100.0%	0.0 100.0%	A	A
30	19.9	0.5 97.5%	1.6 91.8%	0.3 98.7%	2.4 88.1%	2.0 90.0%	A	A
31	158.0	3.4 97.9%	1.7 98.9%	2.0 98.7%	2.5 98.4%	A	A	A
32	21.8	0.0 100.0%	0.0 100.0%	0.0 100.0%	0.0 99.8%	A	A	A
33	677.1	23.8 96.5%	3.7 99.5%	114.7 83.1%	79.2 88.3%	A	A	A
34	1162.0	117.0 89.9%	212.0 81.8%	6.5 99.4%	1.0 99.9%	A	A	A
35	200.5	0.0 100.0%	0.0 100.0%	0.0 100.0%	A	A	A	A
36	86.5	1.5 98.3%	3.2 96.3%	5.0 94.2%	A	A	A	A
37	445.1	2.5 99.4%	595.6 -33.8%	0.0 100.0%	A	A	A	A
38	1083.0	58.5 94.6%	B 24.3 97.8%	10.5 99.0%	A	A	A	A
39	606.3	526.3 13.2%	C	C	C	C	C	C

NOTE: A = NO HOLTER TAKEN OR DATA NOT RECEIVED
B = HOLTER ACTUALLY TAKEN ON MONTH 3A
C = WITHDRAWN FROM STUDY

TABLE 66 (CONTINUED)
HOLTER RESULTS --SUPPRESSION OF PVCS
AVERAGE PVCS / HOUR
PERCENT SUPPRESSION OF BASELINE PVCS

PTNO	BASELINE	DAY 7	MONTH 2	MONTH 4	MONTH 6	MONTH 8	MONTH 10	MONTH 12
101	78.-	9.0 88.5%	0.0 100.0%	13.2 83.2%	64.7 17.5%	7.7 90.2%	35.5 54.8%	35.8 54.3%
103	25.4	41.7 -63.9%	A	A	A	A	A	A
105	B	0.4 %	A	A	A	A	A	A
106	38.5	13.3 65.6%	A	A	A	A	A	A
107	330.9	0.0 100.0%	0.0 100.0%	1.3 99.6%	1.5 99.5%	1.0 99.7%	0.0 100.0%	AB
201	22.5	0.7 97.0%	0.0 100.0%	0.0 100.0%	0.0 99.8%	0.1 99.6%	0.5 97.8%	1.0 95.6%
202	204.9	18.9 90.8%	4.3 97.9%	6.7 96.7%	3.3 98.4%	3.5 98.3%	1.7 99.2%	0.5 99.8%
203	268.7	0.5 99.8%	A	A	A	A	A	A
205	102.5	13.1 87.2%	238.4 -132.6%	99.8 2.7%	142.4 -38.9%	60.0 41.4%	111.5 -8.7%	40.0 61.0%
207	625.0	89.4 85.7%	157.4 74.8%	167.3 73.2%	177.6 71.6%	100.8 83.9%	61.0 90.2%	256.8 58.9%
208	671.9	16.1 97.6%	189.6 71.8%	71.0 [illegible]%	22.3 96.7%	17.5 97.4%	17.0 97.5%	56.0 91.7%
209	446.4	129.6 71.0%	83.6 81.3%	59.7 86.6%	47.8 89.3%	11.7 97.4%	51.9 88.4%	26.2 94.1%

NOTE: A = WITHDRAWN FROM STUDY
B = NO HOLTER TAKEN OR DATA NOT RECEIVED

TABLE 66 (CONTINUED)
HOLTER RESULTS --SUPPRESSION OF PVCS
AVERAGE PVCS / HOUR
PERCENT SUPPRESSION OF BASELINE PVCS

PTNO	BASELINE	DAY 7	MONTH 2	MONTH 4	MONTH 6	MONTH 8	MONTH 10	MONTH 12
14	272.5	0.0 100.0%	15.0 94.5%	35.7 86.9%	0.1 100.0%	18.3 93.3%	3.6 98.7%	2.0 99.2%
15	1541.9	18.8 98.8%	0.0 100.0%	0.1 100.0%	0.1 100.0%	0.1 100.0%	0.1 100.0%	0.0 100.0%
16	446.8	A	A	A	A	A	A	A
17	36.8	0.1 99.8%	0.0 100.0%	0.2 99.5%	2.4 93.6%	0.2 99.4%	0.6 98.3%	0.4 98.9%
18	1275.9	1.0 99.9%	14.7 98.8%	3.1 99.8%	2.6 99.8%	0.7 99.9%	0.7 99.9%	3.0 99.8%
19	522.8	38.3 92.7%	27.4 94.8%	8.0 98.5%	B 0.7 99.9%	5.2 99.0%	26.0 95.0%	C
21	533.0 D	54.2 89.8%	256.8 51.8%	98.6 81.5%	34.3 93.6%	193.3 63.7%	A	A
22	728.3	66.4 90.9%	54.8 92.5%	4.0 99.5%	0.0 100.0%	0.5 99.9%	0.0 100.0%	0.3 100.0%
23	692.4	0.1 100.0%	0.0 100.0%	0.0 100.0%	0.0 100.0%	0.1 100.0%	0.0 100.0%	0.0 100.0%
24	219.9	1.6 99.3%	A	A	A	A	A	A
25	643.3	0.0 100.0%	0.0 100.0%	0.0 100.0%	0.0 100.0%	0.0 100.0%	6.1 99.1%	0.1 100.0%
26	198.2	0.0 100.0%	0.0 100.0%	0.0 100.0%	0.0 100.0%	0.1 100.0%	0.0 100.0%	0.0 100.0%

NOTE: A = WITHDRAWN FROM STUDY
B = HOLTER ACTUALLY TAKEN ON MONTH 7
C = NO HOLTER TAKEN OR DATA NOT RECEIVED
D = PATIENT STARTED FLECAINIDE THERAPY PRIOR TO BASELINE HOLTER

TABLE 66
(CONCLUDED)
HOLTER RESULTS --SUPPRESSION OF PVCS
AVERAGE PVCS / HOUR
PERCENT SUPPRESSION OF BASELINE PVCS

PTNO	BASELINE	DAY 7	MONTH 2	MONTH 4	MONTH 6	MONTH 8	MONTH 10	MONTH 12
210	130.6	2.2 98.3%	10.6 91.9%	64.5 50.6%	25.5 80.5%	21.2 83.8%	56.5 56.8%	24.0 81.6%
211	72.9	1.8 97.6%	0.0 99.9%	165.0 -126.3%	102.1 -40.0%	123.6 -69.5%	0.0 99.9%	0.1 99.8%
212	663.0	16.5 97.5%	82.4 87.6%	94.8 85.7%	12.3 98.2%	1.8 99.7%	0.8 99.9%	1.8 99.7%
213	116.0	605.7 -422.3%	A	A	A	A	A	A
214	224.3	17.7 92.1%	0.0 100.0%	15.7 93.0%	1.3 99.4%	6.7 97.0%	0.1 99.9%	0.2 99.9%
215	92.2	91.8 0.4%	1.2 98.7%	3.5 96.2%	0.1 99.9%	0.4 99.6%	B	B
217	43.9	36.0 17.9%	A	A	A	A	A	A
220	28.5	0.2 99.3%	0.6 98.0%	3.6 87.3%	B	B	B	B
221	302.1	206.5 31.7%	352.5 -16.7%	347.6 -15.1%	B	B	B	B
MED % SUPPRES		97.6%	98.8%	98.7%	99.4%	99.4%	98.9%	99.5%

NOTE: A = WITHDRAWN FROM STUDY
B = NO HOLTER TAKEN OR DATA NOT RECEIVED

TABLE 66

UPDATED 24-HOUR HOLTER RESULTS
AVERAGE PVCS / HOUR
PERCENT SUPPRESSION OF BASELINE PVCS

PTNO	BASELINE	DAY 7	MONTH 2	MONTH 4	MONTH 6	MONTH 8	MONTH 10	MONTH 12
28	1051.3	0.5 100.0%	7.8 99.3%	724.5 31.1%	4.6 99.6%	1.5 99.9%	8.0 99.2%	* 10.2 99.0%
29	294.2	0.0 100.0%	0.0 100.0%	0.0 100.0%	0.0 100.0%	0.0 100.0%	A	* 0.1 100.0%
30	19.9	0.5 97.5%	1.6 91.8%	0.3 98.7%	2.4 88.1%	2.0 90.0%	* 1.5 92.3%	B
31	158.0	3.4 97.9%	1.7 98.9%	2.0 98.7%	2.5 98.4%	* 10.5 93.4%	* 1.6 99.0%	* 1.4 99.1%
32	21.8	0.0 100.0%	0.0 100.0%	0.0 100.0%	0.0 99.8%	* 0.0 100.0%	* 0.3 98.9%	* 1.2 94.4%
33	677.1	23.8 96.5%	3.7 99.5%	114.7 83.1%	79.2 88.3%	* 33.0 95.1%	* 6.8 99.0%	* 0.8 99.9%
34	1162.0	117.0 89.9%	212.0 81.8%	6.5 99.4%	1.0 99.9%	* 0.2 100.0%	* 0.1 100.0%	* 0.0 100.0%
35	200.5	0.0 100.0%	0.0 100.0%	0.0 100.0%	* 0.0 100.0%	* 0.0 100.0%	A	* 0.1 99.9%
36	86.5	1.5 98.3%	3.2 96.3%	5.0 94.2%	* 2.6 97.0%	* 3.8 95.6%	* 0.7 99.2%	* 1.1 98.7%
37	445.1	2.5 99.4%	595.6 -33.8%	0.0 100.0%	* 0.0 100.0%	* 0.0 100.0%	* 0.0 100.0%	* 0.0 100.0%
38	1083.0	58.5 94.6%	24.3 97.8%	10.5 99.0%	* 26.9 97.5%	* 262.2 75.8%	* 23.9 97.8%	* 10.0 99.1%
107	330.9	0.0 100.0%	0.0 100.0%	1.3 99.6%	1.5 99.5%	1.0 99.7%	0.0 100.0%	* 0.7 99.8%

NOTE: * = HOLTER RESULTS RECEIVED SINCE PREVIOUS REPORT.
A = HOLTER NOT DONE.
B = PATIENT NOT ON FLECAINIDE AT TIME OF HOLTER.

TABLE 66
(CONCLUDED)
UPDATED 24-HOUR HOLTER RESULTS
AVERAGE PVCS / HOUR
PERCENT SUPPRESSION OF BASELINE PVCS

PT#O	BASELINE	DAY 7	MONTH 2	MONTH 4	MONTH 6	MONTH 8	MONTH 10	MONTH 12
215	92.2	91.8 0.4%	1.2 98.7%	3.5 96.2%	0.1 99.9%	0.4 99.6%	* 15.4 83.3%	* 16.3 82.3%
220	28.5	0.2 99.3%	0.6 98.0%	3.6 87.3%	* 0.0 99.9%	* 0.0 100.0%	* 0.1 99.7%	* 0.2 99.3%
221	302.1	206.5 31.7%	352.5 -16.7%	347.6 -15.1%	* 165.1 45.3%	B	B	B
222	* 7.2	* 0.0 99.4%	B	* 0.0 100.0%	* 0.0 100.0%	B	B	B
223	* 2.9	* 0.0 100.0%	* 0.0 100.0%	* 0.2 92.8%	** 10.8 -275.4%	* 0.2 94.2%	* 0.8 71.0%	* 0.6 79.1%
225	* 9.0	* 32.0 -253.9%	B	B	B	B	B	B
301	* 343.9	* 325.0 5.5%	B	B	B	B	B	B
302	* 252.9	* 0.3 99.9%	* 0.3 99.9%	* 0.0 100.0%	* 0.2 99.9%	* 0.1 100.0%	* 0.2 99.9%	* 0.0 100.0%
305	* 96.0	* 49.4 48.6%	* 551.9 -474.9%	* 295.0 -207.3%	B	B	B	B
306	* 976.4	* 0.1 100.0%	* 0.2 100.0%	* 0.0 100.0%	B	B	B	B
307	* 223.4	* 0.1 100.0%	* 0.0 100.0%	A	* 0.0 100.0%	* 0.0 100.0%	* 1.1 99.5%	* 0.0 100.0%
308	* 110.1	* 119.5 -8.5%	B	B	B	B	B	B

NOTE: * = HOLTER RESULTS RECEIVED SINCE PREVIOUS REPORT.
A = HOLTER NOT DONE.
B = WITHDRAWN FROM STUDY

TABLE 67
HOLTER RESULTS -- RETURN OF PVCS
FOR PATIENTS AT WASHOUT
AVERAGE PVCS / HOUR
PERCENT SUPPRESSION OF BASELINE PVCS

PTNO	WASHOUT MONTH	BASELINE	PREWASHOUT	WASHOUT
1	9	895.0	152.6 82.9%	1728.7 -93.2%
2	6	297.1	20.3 93.2%	142.9 51.9%
5	3	1099.5	33.5 96.9%	1994.6 -81.4%
6	4	435.1	0.1 100.0%	615.4 -41.4%
7	13	435.1	0.7 99.8%	644.6 -48.2%
8	9	647.1	0.5 99.9%	64.7 90.0%
9	12	480.4	0.4 99.9%	30.1 93.7%
10	6	334.5	0.0 100.0%	167.7 50.0%
12	8	500.0	1.2 99.8%	449.0 10.2%
14	6	272.5	0.1 100.0%	136.7 49.8%
15	12	1541.9	0.0 100.0%	7.3 99.5%
17	9	36.8	1.2 96.7%	199.3 -441.2%
18	12	1275.9	3.0 99.8%	84.5 93.4%

TABLE 67 (CONTINUED)
HOLTER RESULTS -- RETURN OF PVCS
FOR PATIENTS AT WASHOUT
AVERAGE PVCS / HOUR
PERCENT SUPPRESSION OF BASELINE PVCS

PTNO	WASHOUT MONTH	BASELINE	PREWASHOUT	WASHOUT
19	3	522.8	3.3 99.4%	704.0 -34.7%
21	3	533.0	34.5 93.5%	191.5 64.1%
22	6	728.3	0.0 100.0%	966.8 -32.8%
23	12	692.4	0.0 100.0%	24.3 96.5%
25	6	643.3	0.0 100.0%	528.2 17.9%
26	3	198.2	0.1 100.0%	202.5 -2.1%
29	12	294.2	0.0 100.0%	0.1 100.0%
30	3	19.9	2.7 86.6%	36.1 -81.2%
31	6	158.0	2.5 98.4%	892.3 -464.6%
34	3	1162.0	128.0 89.0%	396.5 65.9%
35	3	200.5	0.0 100.0%	0.1 100.0%
101	6	78.4	64.7 17.5%	10.4 86.7%
107	6	330.9	1.5 99.5%	152.0 54.0%

TABLE 67 (CONCLUDED)
HOLTER RESULTS -- RETURN OF PVCS
FOR PATIENTS AT WASHOUT
AVERAGE PVCS / HOUR
PERCENT SUPPRESSION OF BASELINE PVCS

PTNO	WASHOUT MONTH	BASELINE	PREWASHOUT	WASHOUT
201	12	22.5	1.0 95.6%	32.7 -44.9%
202	6	204.9	3.3 98.4%	301.3 -47.0%
205	3	102.5	18.8 81.7%	284.0 -177.1%
207	9	625.0	94.9 84.8%	522.6 16.4%
208	9	671.9	77.5 88.5%	1742.8 -159.4%
209	12	446.4	26.2 94.1%	48.8 89.1%
210	12	130.6	24.0 81.6%	152.5 -16.8%
211	6	72.9	102.1 -40.0%	423.3 -480.6%
212	3	663.0	17.6 97.3%	3.4 99.5%
214	9	224.3	1.3 99.4%	5.2 97.7%
215	3	92.2	1.1 98.8%	13.5 85.3%
MEDIAN % SUPPRESSION			98.8%	17.9%

TABLE 68

UPDATED 24-HOUR HOLTER RESULTS FOR PATIENTS AT WASHOUT
AVERAGE PVCS / HOUR
PERCENT SUPPRESSION OF BASELINE PVCS

PTNO	MONTH	BASELINE	PREWASHOUT	WASHOUT
28	12	1051.3	10.2 99.0%	33.7 96.8%
32	9	21.8	0.1 99.6%	159.6 -633.7%
33	9	677.1	1.3 99.8%	468.4 30.8%
36	12	86.5	1.1 98.7%	26.3 69.6%
37	6	445.1	0.0 100.0%	0.1 100.0%
38	6	1083.0	26.9 97.5%	516.4 52.3%
220	12	28.5	0.2 99.3%	11.1 61.0%
221	6	302.1	165.1 45.3%	186.7 38.2%
222	6	7.2	0.0 100.0%	1.8 75.1%
223	12	2.9	0.6 79.1%	2.5 13.0%
302	3	252.9	0.3 99.9%	13.1 94.8%
306	3	970.4	0.2 100.0%	701.1 28.2%

TABLE 69 R-818-035

ADVERSE EXPERIENCES
NUMBER OF PATIENTS REPORTING AT LEAST ONCE

	ORIGINAL REPORT VISITS	NEW VISITS	ALL VISITS
ABDOMINAL PAIN	1	1	2
ANGINA PECTORIS	2	1	3
ANXIETY	1	0	1
ARRHYTHMIA	2	1	3
ARTHRALGIA	1	0	1
ASTHENIA	2	0	2
ATAXIA	2	0	2
BLINDNESS	0	1	1
BRADYCARDIA	1	0	1
CARDIAC FAILURE	1	0	1
CHEST PAIN	1	1	2
CONSTIPATION	0	1	1
CONVULSIONS	1	0	1
DIARRHEA	1	0	1
DIPLOPIA	2	0	2
DIZZINESS	31	10	34
DYSPNEA	2	0	2
ECG ABNORMAL	1	0	1
EDEMA	1	0	1
EYE ABNORMALITY	1	0	1
EYE PAIN	0	1	1
FATIGUE	3	2	5
FLUSHING	0	1	1
HEADACHE	11	3	13
HYPERTONIA	1	0	1
HYPOAESTHESIA	1	2	3
IMPOTENCE	2	2	2
INFECTION	1	0	1
INSOMNIA	1	0	1
MALAISE	2	1	3
MENSTRUAL DISORDER	1	1	1
NAUSEA	6	3	9
NERVOUSNESS	1	0	1
NOCTURIA	1	0	1
PAIN	4	1	5
PALPITATION	3	2	4
PRURITUS	1	0	1
RASH	1	0	1
RASH ERYTHEMATOUS	1	0	1
SKIN DISORDER	1	0	1
SOMNOLENCE	0	2	2
THINKING ABNORMAL	1	2	2
TINNITUS	1	0	1
TREMOR	1	1	2
TWITCHING	1	0	1
VERTIGO	2	0	2
VISION ABNORMAL	10	4	12
VOMITING	2	0	2
NUMBER OF PATIENTS REPORTING AT LEAST ONE ADVERSE EXPERIENCE	41	23	48
NUMBER OF PATIENTS AT RISK	57	49	66
PERCENT OF PATIENTS REPORTING AT LEAST ONE ADVERSE EXPERIENCE	72%	47%	73%

TABLE 70

Long-term European Experience

Number and Percent of Patients Who Discontinued Flecainide Therapy by Reason and Duration of Treatment

Reason	Duration of Treatment (Weeks) 0-2	3-12	13-26	27-52	52-104	>104	Total
Death	0 0.0%	0 0.0%	1 0.5%	2 1.0%	1 0.5%	0 0.0%	4 2.0%
ECG Abnormalities	1 0.5%	1 0.5%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	2 1.0%
* Adverse Experiences	4 2.0%	2 1.0%	1 0.5%	0 0.0%	0 0.0%	0 0.0%	7 3.5%
Inadequate Efficacy	4 2.0%	5 2.5%	2 1.0%	0 0.0%	0 0.0%	0 0.0%	11 5.5%
Other	2 1.0%	3 1.5%	6 3.0%	1 0.5%	3 1.5%	0 0.0%	15 7.5%
Continuing Therapy	2 1.0%	15 7.5%	30 14.9%	50 24.9%	53 26.4%	12 6.0%	162 80.6%
Total No. at Risk	13 6.5%	26 12.9%	40 19.9%	53 26.4%	57 28.4%	12 6.0%	201 100.0%

* Adverse Experience	No. of Patients
Pressure in head (especially eyes); feeling of abdominal fullness with nausea. (Flecainide for two days only)	1
Heart failure - possibly caused by flecainide, Grade IV CHF History. (Flecainide for six days)	1
Heart Failure - Noted an increase in heart failure at baseline; flecainide was discontinued and CHF therapy was changed. (Flecainide for four months)	1
Vomiting and severe dizziness (Flecainide for seven days)	1
Chest pain, nausea, dizziness, difficulty concentrating severe. (Flecainide for five days)	1
Vertigo, visual disturbance - also not effective. (Flecainide for four weeks)	1
Visual disturbance (also psychological disorder of memory). (Flecainide for four weeks)	1
Total	7

TABLE 71

Summary of Reasons for Discontinuation[a]

Reason	Number of Patients N=228	(%)
Lack of response	45[b]	(19.7)
Adverse experience	41[c]	(18.0)
Death	27	(11.8)
Lack of response and adverse experience	5	(2.2)
Riker's decision to stop enrollment led physician to decide to discontinue patient	4	(1.7)
Patient no longer needed antiarrhythmic therapy	3	(1.3)
Lost to followup	3	(1.3)
Non-compliance	2	(0.9)
Transferred to another flecainide study	2	(0.9)
Intercurrent disease	2	(0.9)
Lack of response and lost to followup	1	(0.5)
Protocol requirements not met	1	(0.5)
Equal efficacy of flecainide and disopyramide	1	(0.5)
Personal	1	(0.5)
Total	139	(61.0%)

[a]According to the investigator.
[b]Twenty-five patients were discontinued because they failed EPS.
[c]In 11 instances, adverse experiences listed as reasons for discontinuation are actually indicative of lack of response (eg, VT).

TABLE 72

Patients Who Discontinued Due to Cardiac Side Effects

Patient ID	VT	Widened QRS	Widened PR	Bundle Branch Block	Complete Heart Block	Sinus Pauses	Brady-cardia	Worsened CHF	Proarrhythmic Event	Other/Comments
020-02-103	+	-	-	-	-	-	-	-	-	
020-04-101	-	+	-	-	-	-	-	-	-	Excessively dry mouth
020-08-111	+	-	-	-	-	-	-	-	-	Torsades de pointes
020-13-001[a]	+	+	+	-	-	-	-	-	+	Torsades de pointes
020-14-102	-	-	-	-	-	-	+	-	-	Sinus exit block
122	+	-	-	-	-	-	-	-	-	Positive PES
129	-	-	-	-	+	-	+	-	-	Dizziness, nausea
130	+	-	+	+	-	-	-	-	-	
020-19-101	+	-	-	-	-	-	-	-	-	"Non-responder or adv exp"
020-20-102	-	+	+	-	-	-	-	-	-	Prolonged QT
103	-	-	-	-	-	+	-	-	-	
020-26-003	-	-	-	-	-	-	-	+	-	
020-26-004[a]	+	-	-	-	-	-	-	-	+	V-fib
007[a]	+	-	-	-	-	-	-	-	-	"Increased ectopy" swollen lips, tongue, mouth
010[a]	+	+	-	-	-	-	-	-	+	
020-28-003	-	-	-	+	-	-	-	-	-	
004[a]	+	-	-	-	-	-	-	+[a]	(+)	Adverse experience recorded as CHF only, proarrhythmic event recorded later.
014	-	-	-	-	-	+	-	-	-	
020-44-104[a]	+	-	-	-	-	-	-	-	+	Prolonged QT
105[a]	+	-	-	-	-	-	-	-	+	
020-54-102	-	-	-	-	+	-	-	-	-	Hypotension, polyuria
020-59-104	+	-	-	-	-	-	-	-	-	
020-68-102	-	-	-	-	-	-	-	+	-	
020-78-101	-	-	-	-	-	-	-	+	-	
020-87-101[a]	+	-	-	-	-	-	-	+	+	Polymorphic, junctional VT
TOTAL	14	4	3	2	2	2	2	5	6	

[a]Patient reported to have experienced a proarrhythmic event

TABLE 72A

Reasons for Discontinuation R-818-028

Patient ID		No. Days on Drug	
028-01	102	213	Intercurrent disease (severe cerebral degenerative disease with Parkinsonian features)
028-02	101	210	Non-responder, adverse experience (lightheadedness)
	102	334	Adverse experience (peripheral vision problems)
	103	233	Adverse experience (sustained VT requiring cardioversion)
	104	412	Death
028-04	101	25	Adverse experience (excessively dry mouth, wide QRS)
028-05	105	49	Adverse experience (diplopia, dizziness, nausea, headache, loss of appetite)
028-07	101	2	Death
	102	218	Adverse experience (dizziness, visual disturbances, forgetfulness, intolerance to heat)
	105	209	Death
	106	161	Death
	107	16	Adverse experience (weakness, fatigue, visual disturbances, dizziness, nervousness, shortness of breath)
028-08	102	248	Non-compliance
	103	29	Non-responder, lost to followup
	105	253	Lost to followup
	110	239	Lost to followup
	111	81	Adverse experience (torsades de pointes)
	112	269	Non-responder at lower dose which was required because of adverse experience (CHF)
	113	3	Non-responder
	115	336	Death
	116	80	Adverse experience (exfoliative dermatitis)
	120	33	Flecainide no longer required
	121	29	Non-compliance
028-10	007	8	Physician decided to discontinue patient based on Riker's decision to stop enrollment because of the risk of difficult resuscitation in some patients
	012	15	Physician decided to discontinue patient based on Riker's decision to stop enrollment because of the risk of difficult resuscitation in some patients
028-11	101	18	Adverse experience (visual disturbances, abdominal cramps)
	102	6	Non-responder (sustained VT after exercise test)
	103	336	Flecainide no longer required following endocardial remapping and tissue resection
	104	113	Transferred to another (R-818-057) flecainide study
	105	10	Transferred to another (R-818-057) flecainide study
	108	0	Based on results of exercise testing, patient had equally good response on disopyramide, so patient put on disopyramide (only one 300 mg dose of flecainide given)

TABLE 72A (Continued)

Reasons for Discontinuation R-818-028

Patient ID		No. Days on Drug	
028-11	109	155	Adverse experience (weakness in legs and hand tremors, possibly due to concomitant amiodarone treatment)
	110	42	Non-responder
028-12	101	6	Death
028-13	001	83	Adverse experience (proarrhythmic events, prolongation of PR, QRS, QT, torsades de pointes
	003	4	Non-responder (failed PES)
	005	81	Adverse experience (fatigue, visual disturbances, malaise)
	008	26	Non-responder
	009	6	Non-responder
	010	1	Non-responder
028-14	102	3	Adverse experience (bradycardia)
	103	11	Non-responder (failed PES)
	104	7	Non-responder (failed PES)
	105	20	Non-responder (failed PES)
	106	9	Non-responder (failed PES)
	108	3	Death
	109	7	Non-responder (Failed PES)
	112	5	Death
	114	196	Death
	115	365	Personal ("vague, non-specific sense of ill being")
	116	16	Non-responder (failed PES)
	117	6	Non-responder (failed PES)
	118	6	Adverse experience (tingling, nervousness, numbness)
	120	62	Death
	121	2	Protocol requirements not met (patient had LBBB associated with 1°AVB at baseline)
	122	12	Non-responder (failed PES), adverse experience (sustained VT in PES lab and spontaneous VT requiring overdrive pacing)
	123	5	Death
	124	8	Non-responder
	125	8	Non-responder, adverse experience (visual disturbances, dizziness, ataxia)
	126	6	Non-responder (failed PES)
	128	9	Non-responder (failed PES)
	129	1	Adverse experience (dizziness, nausea, 3° AV block, bradycardia)
	130	4	Adverse experience (tachycardia, 1°AVB, LBBB)
	131	10	Death
	132	3	Death
	133	2	Death
	134	12	Non-responder (failed exercise test)

TABLE 72A (Continued)

Reasons for Discontinuation R-818-028

Patient ID		No. Days on Drug	
028-17	006	180	Lost to followup
028-19	101	7	Non-responder or adverse experience (VT)
028-20	102	1	Adverse experience (1° AV block, IVCD, prolonged QT)
	103	1	Adverse experience (episode of sinus pauses)
028-21	101	15	Non-responder (failed EPS). Patient later reported by investigator to have experienced a proarrhythmic event
028-22	101	90	Adverse experience (syncopal episodes)
	102	2	Adverse experience (photosensitivity rash, pruritic)
028-25	101	5	Non-responder (patient later reported by investigator to have experienced a proarrhythmic event)
028-26	003	559	Adverse experience (CHF)
	004	0	Adverse experience (proarrhythmic event)
	005	6	Non-responder (failed PES)
	006	7	Non-responder (failed PES)
	007	3	Non-responder (failed PES) and adverse experience (swollen lips, tongue and increased ectopy)
	008	6	Non-responder
	009	3	Non-responder
	010	14	Adverse experience and non-responder (proarrhythmic event VT, IVCD)
	011	7	Non-responder (patient later reported by investigator to have experienced a proarrhythmic event)
028-27	002	8	Non-responder (patient later reported by investigator to have experienced a proarrhythmic event)
	004	126	Non-compliance and intercurrent disease (patient had possible multiple sclerosis or amyotrophic lateral sclerosis and was discontinued to eliminate any chance of drug effect; symptoms continued after flecainide was discontinued)
	011	127	Non-responder
028-28	002	100	Adverse experience (fatigue, ataxia, dizziness)
	003	2	Adverse experience (dizziness associated with LBBB)
	004	3	Adverse experience (CHF, patient later reported by investigator to have experienced a proarrhythmic event)
	014	2	Adverse experience (sinus pauses)
	015	11	Adverse experience (dizziness, hand tremor, perioral paresthesia, flushed face)
	017	9	Non-responder
028-33	102	282	Lack of response
	103	8	Non-responder (failed PES, patient later reported by investigator to have experienced a proarrhythmic event)

TABLE 72A (Continued)

Reasons for Discontinuation R-818-028

Patient ID		No. Days on Drug	
028-34	101	19	Death
	102	141	Adverse experienc: (ataxia, dizziness, numbness and tingling, nausea, dysconjugate ocular movement, tremor, headache)
	103	11	Death
028-37	001	6	Non-responder (patient later reported by investigator to have experienced a proarrhythmic event)
	002	27	Adverse experience (dizziness, diplopia, urinary incontinence)
	003	9	Non-responder (failed PES, patient later reported by investigator to have experienced a proarrhythmic event)
	004	2	Non-responder (failed PES)
028-42	101	2	Death
028-43	002	4	Lack of response (failed PES)
	003	4	Death
	004	20	Adverse experience (Visual disturbances)
	005	4	Death
	006	41	Adverse experience (patient felt sick and nauseous on flecainide and discontinued without consulting physician)
	007	275	Lack of response
028-44	101	5	Non-responder (failed PES)
	102	240	Death
	103	5	Non-responder (failed PES, patient later reported by investigator to have experienced a proarrhythmic event)
	104	2	Adverse experience (increased VT, prolonged QT)
	105	5	Adverse experience (proarrhythmic event)
028-45	101	6	Non-responder
028-51	102	12	Adverse experience (dyspnea on exertion)
028-54	101	4	Lack of response
	102	2	Adverse experience (polyuria, hypotension, 3rd ° AV block)
	103	180	Adverse experience (dizziness)
028-55	001	41	Death
	002	18	Physician decided to discontinue patient based on Riker's decision to stop enrollment because of the risk of difficult resuscitation in some patients
028-59	101	3	Death
	103	120	Non-responder (arrhythmia worse with exercise testing)
	104	1	Adverse experience (Sust. VT requiring cardioversion)
028-60	101	201	Death
028-62	001	183	Flecainide no longer required following spontaneous improvement in post-partum cardiomyopathy

TABLE 72A (Concluded)

Reasons for Discontinuation R-818-028

Patient ID		No. Days on Drug	
028-62	003	282	Non-responder
028-63	101	37	Death
	103	104	Death
028-68	101	202	Non-responder
	102	2	Adverse experience (worsened CHF)
028-72	101	0	Non-responder (failed (PES)
	103	5	Death
028-74	102	160	Death
028-78	101	160	Adverse experience (CHF)
028-84	101	2	Phone contact from Riker regarding risk of difficult resuscitation in some patients; physician felt that this patient carried a significant risk of ventricular arrhythmia on flecainide.
028-85	101	5	Non-responder (failed PES)
028-87	101	1	Adverse experience (CHF, proarrhythmic effect)
028-88	101	88	Intercurrent disease
		5371	total

TABLE 73

Adverse Experiences

Number of Patients Reporting at Least Once

	No. of Patients
ABDOMINAL PAIN	2
ALLERGIC REACTION[a]	1
ALOPECIA	1
AMNESIA	2
ANGINA PECTORIS	2
ANOREXIA	2
ARRHYTHMIA	1
ARTHRALGIA	2
ASTHENIA	5
ATAXIA	3
BRADYCARDIA	2
CARDIAC FAILURE	7
CHEST PAIN	4
CONFUSION	1
CONSTIPATION	4
CONVULSIONS	1
CRAMPS LEGS	1
DEPERSONALIZATION	1
DEPRESSION	1
DERMATITIS	1
DIARRHEA	1
DIPLOPIA	3
DIZZINESS	52
DYSPNEA	7
EDEMA	2
EYE ABNORMALITY	2
FATIGUE	6
FEVER	3
FLUSHING	3
HEADACHE	11
HEART DISORDER[b]	1
HICCUP	2
HYPOESTHESIA	6
HYPOTENSION	2
IMPOTENCE	2
INSOMNIA	1
MALAISE	2
MICTURITION FREQUENCY	1
MOUTH DRY	1
MYALGIA	2
NAUSEA	11
NERVOUSNESS	4
PAIN	4
PALPITATION	5
PARESIS	4
PARESTHESIA	4
PHOTOPHOBIA	1
POLYURIA	3
PRURITUS	1
PULMONARY EDEMA	1
RASH	6
SKIN DEPIGMENTATION	1
SKIN DISCOLORATION	1
SOMNOLENCE	1
SPEECH DISORDER	1
STUPOR	2
SWEATING INCREASED	2
SYNCOPE	5
TACHYCARDIA	4
TASTE PERVERSION	1
THINKING ABNORMAL	1
TREMOR	11
TWITCHING	1
URINARY INCONTINENCE	1
VERTIGO	1
VISION ABNORMAL	49
VOMITING	2

Number of Patients Reporting at Least One Adverse Experience = 109

Number of Patients at Risk = 197

Percent of Patients Reporting at least One Adverse Experience = 55%

[a] swollen lips, tongue and mouth
[b] gallop rhythm

TABLE 4

Adverse Experiences

A Comparison of the Most Common Adverse Experiences (≥ 3%) in Compassionate-use Patients and Patients from Other Longterm Flecainide Studies

Adverse Experience	Percent (%) of Patients Reporting: Other longterm studies[a] (N=280)	Compassionate-use Study (N=97)
Dizziness	32%	26%
Vision Abnormal	30%	25%
Headache	10%	6%
Nausea	10%	6%
Tremor	4%	6%
Asthenia	6%	3%
Palpitations	6%	3%
Fatigue	6%	3%
Dyspnea	5%	4%
Nervousness	5%	2%
Chest Pain	4%	2%
Constipation	4%	2%
Rash	4%	3%
Hypoesthesia	3%	3%
Tinnitus	3%	0%
Diarrhea	%	0.5%
Abdominal Pain	%	1%
Syncope	%	3%
Cardiac Failure	1%	4%

[a] Patients with chronic ventricular arrhythmias[13]

TABLE 74

Adverse Experiences

A Comparison of the Most Common Adverse Experiences (≥ 3%) in Compassionate-use Patients and Patients from Other Longterm Flecainide Studies

	Percent (%) of Patients Reporting	
Adverse Experience	Other longterm studies[a] (N=280)	Compassionate-use Study (N=197)
Dizziness	32%	26%
Vision Abnormal	30%	25%
Headache	10%	6%
Nausea	10%	6%
Tremor	4%	6%
Asthenia	6%	3%
Palpitations	6%	3%
Fatigue	6%	3%
Dyspnea	5%	4%
Nervousness	5%	2%
Chest Pain	4%	2%
Constipation	4%	2%
Rash	4%	3%
Hypoesthesia	3%	3%
Tinnitus	3%	0%
Diarrhea	3%	0.5%
Abdominal Pain	3%	1%
Syncope	3%	3%
Cardiac Failure	1%	4%

[a] Patients with chronic ventricular arrhythmias[13]

TABLE 75

Proarrhythmic Events

Demographics, Cardiac Diagnoses, and Outcome for Patients Who Experienced a Proarrhythmic Event

Patient ID	Age	Sex	ASHD	Old MI	CHF hx	VT	VT + CHF	Documented Prior Arrest	Base-line LVEF	Death
028-12-101	44	M	+	+	+	+	+	+	17	+
028-13-001	55	M	-	-	+	+	+	+	-	-
028-14-112	75	M	+	+	+	+	+	+	30	+
028-14-132	61	M	+	+	+	+	+	+	25	+
028-14-133	55	M	+	+	+	+	+	+	12	+
028-21-101	53	M	-	+	+	+	+	-	36	-
028-25-101	67	M	+	+	-	+	-	-	-	-
028-26-004	51	M	+	+	-	+	-	+	-	-
028-26-010	34	F	+	+	-	+	-	-	-	-
028-26-011	72	M	+	+	+	+	+	-	-	-
028-27-002	72	M	-	+	+	+	+	-	-	-
028-28-004	67	M	-	-	+	+	+	-	-	-
028-33-103	45	M	+	+	-	+	-	-	33	-
028-34-103	66	M	+	+	+	+	+	+	28	+
028-37-001	45	M	-	+	+	+	+	-	30	-
028-37-003	59	M	+	+	-	+	-	+	-	-
028-42-101	61	M	+	+	+	+	+	-	15-18	+
028-43-003	55	M	+	+	+	+	+	+	30	+
028-43-005	72	M	+	+	+	+	+	+	20	+
028-44-103	47	M	+	+	-	+	-	+	-	-
028-44-104	79	M	+	+	-	+	-	-	-	-
028-44-105	71	F	+	+	+	+	-	+	-	-
028-72-103	73	M	+	+	+	+	+	+	35	+
028-87-101	79	F	-	-	+	+	+	-	-	-

TABLE 76

Proarrhythmic Events
Characterization of New or Worsened Ventricular Tachycarhythmias

Criteria	Patient ID	No. Patients Satisfying Primary Criterion
Occurrence of non-sustained VT[a] with no previous history.		0
Occurrence of sustained VT with no recent[b] history of same.	028-26-010 028-27-002 028-37-001	3
Occurrence of VT with a more "malignant" morphology or higher rate than recently observed.	028-13-001 028-26-011 028-44-105 028-87-101	4
Asymptomatic VT which becomes symptomatic	028-44-103 028-44-104	2
VT progresses to VF[a] where this has not occurred recently.	028-26-004 028-28-004	2
Cardioversion is required where it has not been required recently.	028-21-101	1
Resuscitation is more difficult (or impossible to accomplish) than previous resuscitations.	028-12-101[c] 028-14-132[c] 028-14-133[c] 028-33-103 028-34-103[c] 028-37-003 028-42-101[c] 028-43-003[c] 028-43-005[c] 028-72-103[c]	10 Total 22

[a] VT = ventricular tachycardia.
VF = ventricular fibrillation.
[b] The definition of "recent" depends on the investigator's determination. "Recent" may be as short a period as a few weeks if there appeared to be a stable period prior to flecainide treatment.
[c] Patient died.

TABLE 77

Congestive Heart Failure - Summary of Patients who Developed New Or Worsened CHF During Flecainide Therapy

Patient I.D.	RHEF (%)	Age	Sex	History CHF	Cardiomegaly	On dig at baseline	Symptoms/Findings at baseline	Coronary artery disease	Old MI	Valvular Heart Disease	Hypertensive Heart Disease	Exposure to Flecainide at time of CHF	Dose at time of CHF	Outcome (d/c = flecainide discontinued)	In Riker's opinion was this a patient with flecainide-related CHF?
028-02-102		51	M	-	-	-	-	+	+	-	-	.46 Days	200 BID	ongoing, dose ↓ to 150 BID	Yes
-103		69	M	-	-	+	-	+	+	-	-	13 Days	200 BID	d/c, restart 100 BID	No
-07-101		76	M	+	+	+	+	+	+	+	+	3 Days	100 BID	died (CHF related death)	No
-107		58	M	+	+	+	+	-	-	-	-	14 Days	150 BID	d/c	Yes
-08-112		62	M	+	+	-	+	+	+	-	+	1 Day	200 BID	ongoing, dose ↓ to 100 BID	Yes
-11-104		61	M	+	-	+	+	+	+	-	-	23 Days	100 TID	pt. trans. to another flec. study, dose ↓ to 100 BID	Yes
-14-101		53	M	-	-	-	-	+	-	-	-	180 Days	150 BID	ongoing	No
-115		35	F	+	-	-	-	-	-	+	-	36 Days	100 BID	ongoing	No
-131		44	M	+	+	+	+	-	-	-	-	10 Days	200 BID	died (CHF related death)	Yes
-133		55	M	+	+	+	+	+	+	+	-	2 Days	200 BID	died (arrhythmic death)	Yes
-19-101		75	F	+	-	+	+	+	+	-	-	6 Days	200 BID	d/c	Yes
-26-002		72	M	+	-	+	+	+	+	-	-	37 Days	150 QAM	ongoing ↓ 100 BID	Yes
-003		47	M	+	+	+	+	-	-	-	-	75 Days	300 BID	ongoing, dose ↓ 200 BID	Yes
-27-011		74	M	+	-	-	+	+	+	-	-	75 Days	150 BID	continued fo 6 more weeks then d/c for other reasons	Yes
-28-002		76	F	+	+	+	+	+	+	-	-	65 Days	100 QAM	continued for 1 more month then d/c for other reasons	No
-004		67	M	+	+	+	+	-	-	-	-	3 Days	100 TID	d/c	No
-007		59	M	+	-	+	-	+	+	-	-	70 Days	200 QAM	ongoing	No
-012		61	M	-	+	-	-	-	-	-	+	71 Days	200 QAM	ongoing	No
-[illegible]-101		55	M	+	+	+	+	-	-	-	-	10 Days	150 QAM	died (CHF related death)	Yes
-102		56	M	+	+	+	+	+	+	-	-	24 Days	200 BID	continued for 4 more months, then d/c for other reasons	Yes
-008		84	M	+	+	+	-	+	+	-	-	1 Years	100 BID	ongoing	No
-37-003	30	59	M	-	-	-	-	+	+	-	-	9 Days	200 BID	d/c	No
-51-102		64	M	+	+	+	-	+	+	-	+	12 Days	200 BID	d/c	Yes
-103		69	M	-	-	-	-	-	-	-	+	80 Days	200 BID	ongoing	Yes
-60-101	26	75	M	+	+	+	+	-	-	-	-	101 Days	100 BID	ongoing	No
-63-101		57	M	+	+	+	+	+	+	-	+	33 Days	250 BID	died (acute MI)	No
-103	26	63	M	+	-	+	+	+	+	-	+	95 Days	200 BID	died (CHF related death)	Yes
-65-101		60	F	+	+	-	+	+	+	-	+	13 Days	200 BID	ongoing	No
-68-102	11[a]	63	M	+	+	-	+	+	+	-	-	2 Days	200 BID	d/c	Yes
-78-101		64	M	+	+	-	-	+	+	+	-	10 Days	200 BID	ongoing	Yes
-87-101		29	F	+	+	+	+	-	-	+	-	1 Day	200 BID	d/c	Yes
-98-10[illegible]		84	M	+	-	+	+	+	-	-	-	30 Days	100 BID	dose ↓, then pt. d/c due to intercurrent disease	Yes

[a] Baseline value of 44% spuriously high because patient's CHF status was worse at this time than several months earlier when RHEF was 24%.

TABLE 78

Laboratory Abnormalities

Patients with Clinically Significant Abnormalities in Liver Function Tests
During Flecainide Therapy

Patient Identification	Time of Sample	Total Bilirubin	Liver Enzymes SGOT	SGPT	LDH	Alk Phos	Comment
028-08-111	Baseline	0.40	40	not done	409(c)	144(a)	Elevated SGOT and LDH due to limited cardiac output. (Flecainide level 3082 ng/ml) Pt. discontinued after month 2 visit. No further information
	Month 1	1.90(a)	840(c)	not done	1680(c)	112	
	Month 2	not done	not done	not done	not done	298(a)	
028-11-101	Baseline	1.0	11.0	-	-	76	
	Post	0.60	15.0	31(c)	71	29	
028-26-007	Baseline	0.40	211(c)	384(c)	224(c)	198(c)	Presence of hepatitis, unknown etiology
	3 days (d/c)	0.60	110(c)	not done	228(c)	228(c)	
028-26-009	Baseline	-	34.0	98(c)	117	123(c)	
	D/C	-	34.0	80(c)	152	-	
028-27-011	Baseline	0.80	34	49(a)	192	81	Data beyond the time of this summary shows that values were also normal for M4
	M.5	0.50	20	19	173	76	
	M1	0.60	29	70(c)	172	77	
	M3	All values normal					
028-28-009	Baseline	0.20	31	38(a)	163	135	Cause unknown
	Month 0.5	0.20	152(c)	not done	169	161(c)	
	Month 2	0.20	28	not done	198	150(c) (Repeat 109)	
	Month 9	0.30	18	not done	198	105	
028-28-015	Baseline	0.40	70(c)	54(c)	252(c)	133(c)	According to investigator marginal elevation probably due to previous mexiletine therapy
	11 days	0.30	57(c)	56(c)	228(c)	128(c)	
028-37-003	Baseline	0.10	11(a)	22	198	82	SGOT, SGPT, LDH abnormalities secondary to cardiac arrest
	9 days	1.40	208(c)	194(c)	859(c)	76	
028-44-103	Baseline	0.10	16	16	319	73	SGPT and LDH abnormalities secondary to cardiac arrest, CPR and multiple defibrillation
	5 days(d/c)	0.50	27	164(c)	2891(c)	63	

TABLE 78 (Concluded)

Laboratory Abnormalities

Patients with Clinically Significant Abnormalities in Liver Function Tests
During Flecainide Therapy

Patient Identification	Time of Sample	Total Bilirubin	Liver Enzymes SGOT	SGPT	LDH	Alk Phos	Comment
028-59-103	Baseline	0.9	34	-	161(a)	60	M2 and M3 represent follow-up info.
	M.5	0.3	64(c)	-	184(c)	64	
	M1	0.5	52(c)	-	180(c)	75(b)	
	(M2)	0.4	38(c)	-	162(c)	83	
	(M3)	0.3	31	-	130	69	
028-59-104	Baseline	6.60(c)	50(c)	not done	169(c)	114(a)	Presence of compazine
	2 day(d/c)	not done	not done	not done	184(c)	89(c)	induced hepatitis
028-68-102	Baseline	.40	13	10	166	109(a)	Pt. on flecainide for only two
	Post	not done	119(c)	257(c)	not done	not done	days; flecainide had been discontinued for 4 days and patient on amiodarone for two days at time of post laboratory analysis

(a) Abnormal, not clinically significant
(c) Abnormal, clinically significant

TABLE 79

Holter Analysis
Frequency Distribution of
Percent Suppression of Baseline PVCs

Visit	No. Pts	Median Percent Suppression	No. of Patients (and Percent) in Suppression Categories		
			>50%	>80%	>95%
Week 1	18	94.8%	14 (78%)	13 (72%)	9 (50%)
Month 1	5	87.6%	4 (80%)	4 (80%)	2 (40%)
Month 3	7	97.5%	5 (71%)	5 (71%)	4 (57%)
Month 6	1	85.6%	1 (100%)	1 (100%)	0 (0%)

Percent Suppression of Paired Beats

Visit	No. Pts	Median Percent Suppression	No. of Patients (and Percent) in Suppression Categories			
			>50%	>80%	>95%	100%
Week 1	18	99.0%	14 (78%)	13 (72%)	12 (67%)	7 (39%)
Month 1	5	96.3%	4 (80%)	4 (80%)	3 (60%)	0 (0%)
Month 3	7	99.3%	7 (100%)	7 (100%)	5 (71%)	3 (43%)
Month 6	1	100%	1 (100%)	1 (100%)	1 (100%)	1 (100%)

Percent Suppression of VT Beats

Visit	No. Pts	Median Percent Suppression	No. of Patients (and Percent) in Suppression Categories			
			>50%	>80%	>95%	100%
Week 1	17	100%	15 (88%)	15 (88%)	13 (76%)	10 (59%)
Month 1	5	100%	4 (80%)	4 (80%)	4 (80%)	3 (60%)
Month 3	7	100%	5 (71%)	5 (71%)	4 (57%)	4 (57%)
Month 6	1	100%	(100%)	1 (100%)	1 (100%)	1 (100%)

TABLE 79

Holter Analysis
Frequency Distribution of
Percent Suppression of Baseline PVCs

Visit	No. Pts	Median Percent Suppression	No. of Patients (and Percent) in Suppression Categories		
			>50%	>80%	>95%
Week 1	18	94.8%	14 (78%)	13 (72%)	9 (50%)
Month 1	5	87.6%	4 (80%)	4 (80%)	2 (40%)
Month 3	7	97.5%	5 (71%)	5 (71%)	4 (57%)
Month 6	1	85.6%	1 (100%)	1 (100%)	0 (0%)

Percent Suppression of Paired Beats

Visit	No. Pts	Median Percent Suppression	No. of Patients (and Percent) in Suppression Categories			
			>50%	>80%	>95%	100%
Week 1	18	99.0%	14 (78%)	13 (72%)	12 (67%)	7 (39%)
Month 1	5	96.3%	4 (80%)	4 (80%)	3 (60%)	0 (0%)
Month 3	7	99.3%	7 (100%)	7 (100%)	5 (71%)	3 (43%)
Month 6	1	100%	1 (100%)	1 (100%)	1 (100%)	1 (100%)

Percent Suppression of VT Beats

Visit	No. Pts	Median Percent Suppression	No. of Patients (and Percent) in Suppression Categories			
			>50%	>80%	>95%	100%
Week 1	17	100%	15 (88%)	15 (88%)	13 (76%)	10 (59%)
Month 1	5	100%	4 (80%)	4 (80%)	4 (80%)	3 (60%)
Month 3	7	100%	5 (71%)	5 (71%)	4 (57%)	4 (57%)
Month 6	1	100%	1 (100%)	1 (100%)	1 (100%)	1 (100%)

Table 80

Patient Discontinuations

Center	Pt No.	Reason	No. Days on Flecainide
02	203	Personal	95
	204	Death	9
	205	Death	25
03	1	Adverse Experiences	7
	3	Death	12
05	2	Nonresponder	1
06	5	Nonresponder	6
	7	Death	60
08	1	Death	8
	5	Death	12
10[a]	1	Adverse Experience	4
	2	Adverse Experience	2
	3	Nonresponder	4
	4	Adverse Experience	4
	5	Nonresponder	4
	6	Adverse Experience	4
	7	Adverse Experience	4
	8	Adverse Experience/Nonresponder	4
	9	Nonresponder	6
11	2	Adverse Experience/Nonresponder	43
17	1	Nonresponder	24
28	1	Nonresponder	9

[a]At center 10 (Podrid), flecainide as well as other antiarrhythmics were screened prior to selecting a drug for chronic therapy.

Table 81

Adverse Experiences:
Number of Patients Reporting at Each Visit

WHO Preferred Term	Week 1	Month 1	Month 3	Month 6	No. of Patients
Cardiac Failure	2	1	2	1	6
Cholelithiasis	0	1	0	0	1
Coordination Abnormal	0	0	1	0	1
Dizziness	2	0	0	0	2
Dyspnea	0	0	1	0	1
Edema	0	0	1	0	1
Fatigue	0	2	4	1	4
Headache	1	1	0	0	2
Pruritus	0	1	0	0	1
Somnolence	0	1	0	0	1
Vision Abnormal	2	6	4	0	9
Vomiting	0	0	1	0	1
Total	7	13	14	2	-
Number of Patients Reporting at Least One Adverse Experience	6	12	8	2	19
Number of Patients At Risk	30	22	17	7	39
Percent of Patients Reporting at Least One Adverse Experience	20%	55%	47%	29%	51%

Table 82

ECG Intervals: Mean Increase From Baseline ± Standard Deviation (and Maximum)

	Baseline (Seconds)	Mean Increase From Baseline (seconds) ± SD			
		Week 1	Month 1	Month 3	Month 6
No. Pts	39	14	20	16	8
PR	0.186 ± 0.028	0.034* ± 0.038 (.100)	0.028* ± 0.032 (.100)	0.040* ± 0.037 (.100)	0.037* ± 0.018 (.060)
QRS	0.108 ± 0.023	0.028* ± 0.028 (.089)	0.018* ± 0.028 (.083)	0.028* ± 0.038 (.100)	0.019 ± 0.034 (.060)
QT	0.387 ± 0.053	0.027* ± 0.039 (.080)	0.029* ± 0.056 (.120)	0.029* ± 0.050 (.130)	0.023 ± 0.082 (.150)
JT	0.278 ± 0.055	-0.001 ± 0.031 (.050)	0.013 ± 0.064 (.120)	0.004 ± 0.057 (.135)	0.004 ± 0.101 (.150)

* = Statistically significant ($P \leq 0.05$) increase from baseline.

TABLE 83

PRESTUDY Study No. Center No. Patient No.	CHF HISTORY: History of CHF	CHF Classification	Symptoms, Findings on Entry (Yes, No)	Prev. Hospitalization For CHF (Yes, No)	Meds for CHF At Entry (Yes, No)	CT Ratio	Ejection Fraction	PRESTUDY LABS: Abnormal Laboratory Values	COMMENTS
Morganroth 028-12 101	Y	II	Y		Y		2.0%	↑SGOT ↑LDH*	*due to previous amiodarone therapy
Reid 028-14 112	Y	III+	Y		Y		30% (1978)	↑BUN↑creat.* ↑ALKP	*chronic mild renal insufficiency.
028-14 132	-	-	Y**	-	Y		13%	↑Creat. slightly ↑BUN	*EF 13% but no clinical failure **SOB only
028-14 133	Y	II	Y		Y	0.66	12% (1977)	↑ALKP, ↑BILI ↓albumin* ↓ Hct ↓Hb**	*2° to hepatic congestion ** anemia
Greene 028-34 103	Y	II	Y		Y		28%	-	
Benditt 028-42 101	Y	III	Y		-*		15-18%	↑WBC	*CHF meds discontinued due to hypotension.
Osborn 028-43 003	Y	II	Y**		Y*		27% (1978)	-	** SOB only deterioration in renal function prior to terminal event
028-43 005	Y	II	-	-	Y		20-30%	-	
Somberg 028-72 103	Y	II	Y**	Y	Y		35%	↑BUN, ↑creat.* ↑bilirubin ↑total protein	*Poss. renal dysfunction, age related ** rales, edema only
Moosley 031-03 009	-	-	-	-	-		-	-	
Hodges 033-02 007	Y	I	Y	Y	Y	0.59	-	↑bilirubin	
Reid 033-14 006	Y	II	Y		Y	0.53	16%	↑SGPT, ALKP	
Platt 033-17 005	Y	I	Y		Y	0.42	-	-	
Hodges 05 02 204	Y	III	Y	Y	Y	0.65	46%* (20-30%)	↑BUN, ↑creat. ↑LDH ↑Protein** WBC*** (urinalysis) +ANA↑K+	*46% is spuriously high because of mitral regurgitation, more likely EF is 20-30% **Renal insufficiency. *** chronic indw. Foley cath.
057-02 205	Y	III	Y		Y		2[illegible]%	+ANA*	*2° to procainamide
Singh 057-02 003	Y	III	Y	Y	Y	-	28%	Not done	

CODE
Y = yes
. = no
□ = not available

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TABLE 84

DATA OBTAINED WHILE PATIENTS ON FLECAINIDE

Study No. Center No. Patient No.	Length of Time on Flecainide at Death	Start Date (BID) Dose	Date at Death (BID) Dose at Death	Efficacy	Comments	Adverse Experiences	Non Terminal Arrests	Lab Abnormals Changes from Baseline	Concomitant Antiarrhythmic Therapy
028-12 101	6 days.	200 6-6-82	300 6-12-82	-	VT inducible after 4 days therapy	-	-	-	-
028-14 112	4 days	200 6-1-82	d/c at 100 mg b/d 6-6-82		bradycardia developed			creat↑(1.3-2.0)	Dilantin
028-14 132	3 days	200 10-22-82	200 10-25-82		VT prior to terminal event				
028-14 133	3 days	200 10-31-82	200 11-02-82			CHF exacerbation 2 hrs. prior to death		Bil.↑Serum alb.↓2° to hepatic cong.	
028-34 103	11 days	100 10-19-82	200 10-30-82	-	same persistent VT			-	
028-42 101	3 days	200 9-22-82	250 9-26-82	-	persistant VT	dizziness, c arp squeezing chest pain on day of death			
028-43 003	4 days	200 6-26-82	200 6-30-82	-	good init. supp., VT recurred after 2 days, pt. died 36 hr after last dose		?		lidocaine procainamide
028-43 005	4 days	200 7-10-82	300 7-14-82 one dose	-	dose increased due to lack of ther. effect		-		procainamide
028-72 103	5 days	100 TID 11-4-82	100 BID 11-9-82	+	excellent supp. by EPS, Holter	nausea, vomiting prior to death	-	-	-
031-03 009	>2 yr.	200 5-12-80	200 6-1-82	+	99% PVC supp. no VT	nausea, nervousness, cleared by 4 mo. therapy		creat↑LDH↑ HBC↑Cl↑glucose↑ alk. phos.↑ variable diff.	-
033-02 007	1 mo.	200 4-16-81	100 5-17-81	+	98% PVC supp.	dizziness, weakness blurred vision CHF (cleared with ↓ dose)	-	bili1.7	-
033-14 006	1 mo.	200 10-5-81	150 1-11-82	+/-	95% PVC supp., no VT initially, failed EP shortly prior to death	blurred vision lightheadedness		-	Aprinidine started 2 days prior to death
033-17 005	6 days	200 8-5-81	200 8-9-81	-	same or worse VT	-	-	not done	
057-02 204	8 days	100 10-1-82	200 10-11-82	-	Inc. PVCs from lidocaine baseline	-	- -	- -	
057-02 205	24 days	100 10-13-82	250 QD 11-7-82	+/-	No VT on Holter 4 days before death	blurred vision			-
057-03 003	13 days	100 9-1-82	200 9-13-82	+	93% PVC supp. on 9/9	-	-	Alk Phos. 95 cl 94 Glucose 291 No baseline lab	

TABLE 85

Chronic Oral Flecainide Administration

Plasma Level Data

Study Center	Pt. No.	Start Date Death Rate (Time)	Date of Sample (Time)	Post-Dose (hrs)	Dose (mg bid)	Flecainide Level ng/ml	Free Mete-Metab. Level (ng/ml)	Comments
028-12	101	6-6-82 6-12-82	not drawn		300			
028-14	112	6-1-82 6-6-82	not drawn		200			
028-14	132	10-22-82 10-25-82	not drawn		200			
028-14	133	10-31-82 11-02-82	not drawn		200			
028-34	103	10-19-82 10-30-82 (14:40)	10-30-82 (13:45)	4.5	200	471	13	
028-42	101	9-22-82 9-24-82	not drawn		250			
028-43	003	6-26-82 6-30-82 (13:30)	6-28-82 (08:49)		200	1296		
028-43	C05	7-10-82 7-14-82	not drawn		200 (last dose)300)			
028-72	[illegible]	11-4-82 11-9-82 (N.A.)	11-04-82 (11:50) 11-04-82 (12:15) 11-04-82 (15:30) 11-05-82 (10:00) 11-09-82 (13:30)	 6	100 tid 100 100 100 100 tid	133 (1 mg/kg dose 61 iv at 11:00 110 on 11/4) 70 ~2200		Dose up to 100 tid on 11-5 and down to 100 bid on 11-9. Final sample was near time of death.
031-03	009	5-12-80 6-1-82 (12:00)	5-18-82 (10:10) 6-01-82 (~11:30) 6-01-82 (13:30?)		200 200 200	1200 (883)* 3500 (1914)*	 <10	Levels obtained at site. 3500 obtained during resuscitation effort, pt. acidotic. *obtained by Riker.
033-02	007	4-16-81 5-17-81 (11:00)	4-21-81 (17:40) 4-30-81 (10:34)	 12	200 100	1390 853	 <10	No sample drawn on date of death.
033-14	006	10-5-81 1-11-82 (12:20)	10-12-81 (10:03) 1-08-82 (15:39)		250 250	1468 2594	 28	
033-17	005	8-5-81 8-9-81	not drawn					
057-02	204	10-2-82 10-11-82 (06.00)	10-07-82 (07:35) 10-11-82 (05:00)	9.5 21*	150 200	595 2050	 ~28	*21 hr. postdose confirmed by study nurse.
057-02	205	10-13-82 (20:00) 11-7-82	10-21-82 (08:00) 10-28-82 (15:00) 11-03-82 (11:20) 11-07-82 (20:15?)	7 15 	200 150 150 150 AM 100 PM	1235 1244 1303 2401	 <10	** Sample drawn within 1-2 minutes of death, somewhat hemolyzed.
057-03	003	9-11-82 9-13-82	not drawn		200			

TABLE 86

Study No. Center No. Patient No.	ARRHYTHMIA CONDUCTION BASELINE: PVCs unifocal	PVCs multifocal	V-Tach	Sustained V-Tach	V-Fibrillation	B B Block	Atrial Flutter/Fib	2° AV Block	Sinus Node Dys.	HR	PR	QRS	QT	ARRHYTHMIA CONDUCTION WHILE ON FLECAINIDE: PVCs Unifocal	PVCs Multifocal	V-Tach	Sustained V-Tach	V-Fibrillation	B B Block	Atrial Flutter/Fib	2° AV Block	Sinus Node Dys.	LAST ECG PRIOR TO ARREST: HR	PR	QRS	QT	% QRS Widening	Comments
028-12 101	Y	Y	Y					-		75	.15	.10	.41			Y							75	.16	.13	.49	30%	ECG obtained earlier on day of death
028-14 112			Y	Y eps	Y			-	-	54	.18	.10	.52		Y	Y			Y	-	-			.12	.49	20%	terminal ECG
028-14 132		Y	Y	-	Y*	-	-	-	-	79	.18	.11	.42			Y							76	.28	.14	.42	27%	*hx Torsades de Pointes
028-14 133		Y	Y	?	-	-	-	-	-	60	.22	.12	.40										58	.30	.12	.40	0%	
028-34 103		Y	Y	-	Y	-	-	-	-	75	.16	.10	.40			Y	Y						140-180		.22 QRS .10	.40	<11%	VT worse on flecainide poss. proarrhythmic effect
028-42 101	Y		Y	Y		-	-	-	-		.18	.10	.40		Y	Y								.20	.12	.40	20%	terminal tachyarrhythmia faster, morphology the same
028-43 003		Y	Y	Y	Y	Y	-	-	-	75	.22	.14	.36			Y							very wide QRS 90	.24	.20	.44	43%	new V-tach on flec.
028-43 005			Y	Y			-	-		55	.16	.08	.36						Y	Y			70	.24	.18	.44	125%	No RBBB at baseline initial RBBB attributed to catheterization.
028-72 103			Y EPS	Y				-		77	.23	.13	.44			-							70	.36	.17	.44	31%	QRS dropped to .16 on day of death
031-03 009	Y		Y					-		73 from 030 study	.21	.08	.39	Y	Y	-							78	.21	.11	.38	27%	
033-02 007	Y	-	-	-	-	-	-	-		78	.18	.12	.35	Y									64	.24	.14	.42	17%	
033-14 006	Y	Y	Y				Y	-			.16	.08	.32	Y	Y	?							86	.24	.12	.44	50%	
033-17 005	Y	Y	*					-		70	.19	.09	.51			Y				-			ECG in CCU	.24	.09	.36	0%	*one run of 3 beats (rate 110) on baseline Holter
057-02 204	Y	Y	Y	-	-	-	Y	-	-	96	-	.12	.33	Y	Y	Y			Y	Y			70	-	.13	.38	8%	New VT on flec. pt. in and out of RBBB
057-03 205	Y	Y	Y		-		-	-		81	.19	.11	.34	Y	Y	Y				Y			70	.21	.147	.41	29%	Pt. cardioverted on flecainide to wide QRS
057-03 003		Y	Y ep.		Y	-	-	-	-	60	.16	.10	.44											.23	.147	.976		

TABLE 87A

Ventricular Tachycardia Induction Studies

		Control Study				
R-818-053-01	Pt No	Induced Rhythm (No nondriven beats)	Cycle Length (mSec)	Morphology	Mode Initiation	Termination
	1	a. VT_s	290	RBBB	$S_1S_2S_3$	RVP
		b. VT_s	200	--	$S_1S_2S_3$	Cardiovert
	2	VT_s	360	LBBB	$S_1S_2S_3$	RVP
R-818-053-02	1	a. VT_s	430	RAD/RBBB	A-pace	Lidocaine
		b. VT_{ns} (10)	325	LAD/RBBB	$S_1S_2S_3S_4$	RVP
	2	VT_{ns} (14)	210	Polymorphous	$S_1S_2S_3S_4$	Spont
	3	VT_{ns} (14)	320	LAD/RBBB	$S_1S_2S_3$	Spont
	4	VT_s	325	LAD/RBBB	$S_1S_2S_3S_4$	Cardiovert
	5	VT_{ns}	220	Polymorphous	$S_1S_2S_3$	Spont
	6	VT_s	370	LAD/RBBB	S_1S_2	RVP
	7	VT_{ns} (13)	270	Polymorphous	$S_1S_2S_3$	Spont
	8	VT_{ns} (12)	245	LAD/RBBB	$S_1S_2S_3$	Spont
	9	VT_{ns} (20)	200	Polymorphous	S_1S_2	Spont
	10	a. VT_{ns} (13)	395	RAD/LBBB	V-burst	Spont
		b. VT_s	340	RAD/LBBB	V-burst; Isuprel	RVP
	11	VT_s	430	NL-LAD/LBBB	$S_1S_2S_3$	RVP
	12	VT_{ns} (6)	260	Polymorphous	$S_1S_2S_3S_4$	Spont
	13	VT_{ns} (6)	290	Polymorphous	$S_1S_2S_3$	Spont
	14	VT_{ns} (17)	280	RAD/RBBB	$S_1S_2S_3$	Spont
	15	VT_s	500	RAD/LBBB	S_1S_2	Spont

Abbreviations:
VT_s, VT_{ns} - ventricular tachycardia sustained, nonsustained
VR_s, VR_{ns} - ventricular rhythm sustained, nonsustained
V-burst - ventricular burst pacing (>300 msec)
A-atrial
RVP - rapid ventricular pacing
Spont - spontaneous
RBBB, LBBB - right, left bundle branch block-type morphology (lead V_1)
RAD,LAD - right, left axis deviation
NL - normal

TABLE 87B

Ventricular Tachycardia Induction Studies

R-818-053-01	Pt No	Plasma Flec ng/ml	Induced Rhythm (No nondriven beats)	Cycle Length (mSec)	Morphology	Mode Initiation	Mode Termination	Therapeutic Assessment
			Flecainide Study					
	1	1038	VT_s	360	LAD/RBBB	$S_1S_2S_3$	RVP	P
	COMMENT:		Atrial tachycardia and slow atrial flutter induced in HRA pacing at cycle length of 300 msec - terminated by overdrive pacing at 260 msec.					
	2	654	VT_{ns}	380	--	A-pace	Spont.	P
	COMMENT:		Sustained atrial tachycardia at 300 to 320 msec. cycle length - could not be paced out with RA overdrive - terminated spontaneously after 25 minutes.					
R-818-053-02	1	654	VT_s	375	LAD/RBBB	$S_1S_2S_3S_4$	Spont RVP	F
	2	758	4	310	Polymorphous	$S_1S_2S_3S_4$	—	S
	3	695	0	—	Polymorphous	$S_1S_2S_3$	—	S
	4	680	VR_s	610	LAD/RBBB	$S_1S_2S_3$	Spont RVP	P
	5	1081	4	400	RAD/RBBB	$S_1S_2S_3$	Spont	S
	6	678	3	440	LAD/RBBB	$S_1S_2S_3$	—	S
	7	1152	a. VT_{ns} b. VT_s	500 450	LAD/RBBB NL/RBBB	$S_1S_2S_3$ $S_1S_2S_3$	Spont RVP	P
	8*	755	VT_{ns} occurred spontaneously and patient discontinued study.					(F)
	9	929	3	360	Polymorphous	$S_1S_2S_3$	—	S
	10	377	2	—	—	$S_1S_2S_3S_4$ V-burst	—	S
	11	482	2	—	—	$S_1S_2S_3S_4$	—	S
	12	872	3	340	Polymorphous	$S_1S_2S_3S_4$	—	S
	13	751	VT_{ns} (10)	400	LAD/RBBB	$S_1S_2S_3$	Spont	F
	14	1049	0	—	—	$S_1S_2S_3S_4$	Spont	S
	15	660	VT_s	550	LAD/LBBB	Catheter (mechanical)	Lidocaine, RVP	F

*Patient No. 8 did not undergo repeat PES.

Abbreviations:
VT_s, VT_{ns} - ventricular tachycardia sustained, nonsustained
VR_s, VR_{ns} - ventricular rhythm sustained, nonsustained
V-burst - ventricular burst pacing (>300 msec)
A-atrial
RVP - rapid ventricular pacing
Spont - spontaneous
RBBB, LBBB - right, left bundle branch block-type morphology (lead V_1)
RAD,LAD - right, left axis deviation
NL - normal
S - successful
P - partially successful
F - failure

Table 89

R-818-031
Distribution of Number of Visits at Which
Patients Reported the Most Common Adverse Experiences

	No. Pts Reporting	No. Visits Reported							
		1	2	3	4	5	6	7	8
Dizziness	10	8	1	1	0	0	0	0	0
Visual Disturbance	11	3	2	1	0	0	1	2	2
Headache	7	2	3	2	0	0	0	0	0
Nausea	6	4	2	0	0	0	0	0	0
Chest Pain	5	2	2	0	1	0	0	0	0
Fatigue	3	3	0	0	0	0	0	0	0
Nervousness	4	3	1	0	0	0	0	0	0
Palpitation	3	2	1	0	0	0	0	0	0
Hypoaesthesia	3	0	3	0	0	0	0	0	0
Abdominal Pain	3	3	0	0	0	0	0	0	0

R-818-033
Distribution of Number of Visits at Which
Patients Reported the Most Common Adverse Experiences

	No. Pts Reporting	No. Visits Reported			
		1	2	3	4
Dizziness	49	36	10	3	0
Visual Disturbance	63	45	14	4	0
Headache	11	6	2	1	2
Nausea	15	14	1	0	0
Asthenia	13	13	0	0	0
Fatigue	11	10	0	1	0

R-818-035[a]
Distribution of Number of Visits at Which
Patients Reported the Most Common Adverse Experiences

	No. Pts Reporting	No. Visits Reported											
		1	2	3	4	5	6	7	8	9	10	11	12	13
Dizziness	31	13	5	2	1	1	1	1	1	0	0	2	0	1
Visual Disturbance	10	3	3	1	0	1	0	0	1	0	0	0	1	0
Headache	11	6	4	0	0	0	0	0	0	0	0	0	0	1
Nausea	6	6	0	0	0	0	0	0	0	0	0	0	0	0
Fatigue	3	2	1	0	0	0	0	0	0	0	0	0	0	0
Palpitations	3	3	0	0	0	0	0	0	0	0	0	0	0	0

[a]Also known as R-818-EN-03.

TABLE 88

PRESTUDY AND POSTSTUDY ECG INTERVALS (SECONDS)
FOR EACH PATIENT

STUDY CENTER	PATIENT NO.	PR (sec)		QRS (sec)		QT (sec)	
		PRE	POST	PRE	POST	PRE	POST
01	1	.21	.24	.10	.10	.44	.41
	2	.14	.16	.10	.12	.38	.40
02	1	.28	.28	.12	.09	.36	.38
	2	NA	NA	.08	.09	.36	.36
	3	.30	.40	.12	.14	.40	.40
	4	.13	.21	.09	.10	.34	.40
	5	.17	.20	.09	.08	.45	.42
	6	.20	.24	.10	.12	.46	.42
	7	.26	.24	.12	.12	.44	.42
	8	.19	.20	.13	.14	.36	.36
	9	.16	.16	.06	.08	.38	.40
	10	.13	.16	.08	.08	.35	.38
	11	.25	.26	.10	.12	.42	.39
	12	.21	.24	.12	.12	.43	.43
	13	.18	NA	.11	NA	.41	NA
	14	NA	NA	.18	NA	.43	NA
	15	.20	.20	.10	.11	.42	.46

NA = NOT AVAILABLE

Table 89

R-818-031
Distribution of Number of Visits at Which
Patients Reported the Most Common Adverse Experiences

	No. Pts Reporting	No. Visits Reported							
		1	2	3	4	5	6	7	8
Dizziness	10	8	1	1	0	0	0	0	0
Visual Disturbance	11	3	2	1	0	0	1	2	2
Headache	7	2	3	2	0	0	0	0	0
Nausea	6	4	2	0	0	0	0	0	0
Chest Pain	5	2	2	0	1	0	0	0	0
Fatigue	3	3	0	0	0	0	0	0	0
Nervousness	4	3	1	0	0	0	0	0	0
Palpitation	3	2	1	0	0	0	0	0	0
Hypoaesthesia	3	0	3	0	0	0	0	0	0
Abdominal Pain	3	3	0	0	0	0	0	0	0

R-818-033
Distribution of Number of Visits at Which
Patients Reported the Most Common Adverse Experiences

	No. Pts Reporting	No. Visits Reported			
		1	2	3	4
Dizziness	4	36	10	3	0
Visual Disturbance	63	45	14	4	0
Headache	11	6	2	1	2
Nausea	15	14	1	0	0
Asthenia	13	13	0	0	0
Fatigue	11	10	0	1	0

R-818-035[a]
Distribution of Number of Visits at Which
Patients Reported the Most Common Adverse Experiences

	No. Pts Reporting	No. Visits Reported												
		1	2	3	4	5	6	7	8	9	10	11	12	13
Dizziness	31	13	8	2	1	1	1	1	1	0	0	2	0	1
Visual Disturbance	10	3	3	1	0	1	0	0	1	0	0	0	1	0
Headache	11	6	4	0	0	0	0	0	0	0	0	0	0	1
Nausea	6	6	0	0	0	0	0	0	0	0	0	0	0	0
Fatigue	3	2	1	0	0	0	0	0	0	0	0	0	0	0
Palpitations	3	3	0	0	0	0	0	0	0	0	0	0	0	0

[a]Also known as R-818-EN-03.

TABLE 90: Summary of Deaths

Study No.	Patient No.	Active Treatment	Dose at Time of Death	Cause of Death
R-818-032-02	28	Quinidine	300 mg qid	Acute occlusion of left anteric descending coronary artery
R-818-032-04	1	Quinidine	300 mg qid	Acute inferior myocardial infarction
* R-818-032-06	4	Flecainide	Placebo qid	Complex arrhythmias, aberrant conduction, evidence of acute ischemia
R-818-032-07	15	Quinidine	300 mg qid	Fresh thrombus in the right coronary artery
* R-818-033-02	7	Flecainide	100 mg bid	Cardiac arrest (intractable ventricular fibrillation)
@ R-818-033-06	5	Flecainide	200 mg bid	Ventricular fibrillation
R-818-033-06	7	Flecainide	200 mg bid	Presumed cardiac arrest or arrhythmia possibly secondary to acute infarction
* R-818-033-13	8	Flecainide	200 mg bid	Presumed acute myocardial infarction
* R-818-033-17	5	Flecainide	200 mg bid	Cardiac arrest secondary to ventricular tachycardia
* R-818-033-17	16	Flecainide	200 mg bid	Acute myocardial infarction
* R-818-035-01	6	Flecainide	200 mg bid	Possible acute myocardial infarction with cardiac arrest
* R-818-035-01	16	Flecainide	200 mg bid	Ventricular fibrillation
* R-818-035-01	24	Flecainide	200 mg bid	Presumptive acute myocardial infarction
* R-818-035-02	105	Flecainide	200 mg bid	Probable ventricular fibrillation
* R-818-035-03	203	Flecainide	100 mg qid	Ventricular fibrillation
R-818-060	009	Flecainide	100 mg bid	Ventricular fibrillation

* Sudden death @ CHF

Table 91

Ophthalmology Examinations

Examination	Study No. 030/031 Center 01	030/031 02	030/031 03	032/033 All	035[a] All
Nearpoint of Accommodation	X	X	X		
Intraocular Tension	X	X	X		
Slit Lamp	X	X	X	X	X
Fundoscopy	X	X	X	X	X
Farnsworth D-15 Hue Test	X	X			
Am. Optical Hardy Rand Rittler Pseudo-isochromatic Plates	X		X		X
Central Color Visual Field Examination	X	X	X		
Electro-oculogram					X
Electroretinogram					X[b]
Visual Acuity	X	X	X		
Static Perimetry					X
Examinations at					
Baseline	X	X	X	X	X
6 months	X	X	X	X	
12 months	X	X	X	X	X

[a]Also known as R-818-EN-03.

[b]Conducted in selected patients if electro-oculogram (EOG) was abnormal.

TABLE 92

Discontinued Patients - ECG Changes

Study	Center	Pt No.	Flecainide Dose (mg bid)	Duration	Reasons	Interval Changes (seconds)
032	04	005	200	10 days	1° AV block, worsened, blurred vision, dizziness	PR: 0.24 to 0.32
		015	200	7 days	1° AV block, Bradycardia	PR: 0.18 to 0.23
		020	200	7 days	1° AV block, dizziness	PR: 0.16 to 0.28
	11	002	200	8 days	Widening of PR and QRS	PR: 0.21 to 0.26 QRS: 0.08 to 0.12
		007	200		Widened QRS nonqualifying patient	QRS: 0.10 to 0.16
	17	021	200		Widened PR nonqualifying patient	PR: 0.17 to 0.22
033	01	002	200	3 months	Sick sinus syndrome, 1° AV block	PR: 0.28 to atrial fibrillation
	03	003	200	6 days	1° AV block, complete RBBB with marked right axis deviation	PR: 0.18 to 0.22 QRS: 0.09 to 0.14
		008	200	6 days	1° AV block LBBB, severe dizziness	PR: 0.16 to 0.24
	04	009	150	3 days	NSR with sinus pauses, junctional escape beats, 1° AV block, PACs	PR: 0.16 to 0.22
	12	024	300	31 days	Lack of therapeutic response, 2° AV block (Wenckeback), blurred vision, light headedness, constipation	PR: 0.20 to 0.26

Table 93
Summary of Patients Who Developed CHF While on Flecainide Therapy

Patient ID.	Age	Sex	History of CHF	Cardiomegaly	On Dig/Diuretics at Study Start	Symptoms at Study Start	Coronary Artery Disease	Old MI	Cardiomyopathy	Valvular Heart Disease	Hypertensive Heart Disease	Exposure to Flecainide at Time of CHF (Months)	Dose at Time of CHF (mg bid)	Flecainide Discontinued?	Flecainide Restarted (mg bid)	In Riker's Opinion, Was This a Patient with Flecainide-Related CHF?
035-02 (#101)	57	M	+	+	+	+	+	+	-	-	-	2	200	Yes	200	Yes
												11	100 tid	No	---	---
030/031-03 (#002)	43	F	+	-	Dc'd	+	-	-	+	-	-	3-4	100 tid	No	---	No
032/033-02 (#006)	62	M	-	-	-	-	+	+	-	-	-	1 1/2	200	Yes	No	Yes
032/033-02 (#007)	63	M	+	+	+	-	+	+	-	-	+	8 days	200	Yes	100	Yes
032/033-05 (#008)	72	F	+	+	+	+	-	-	-	+	-	1 day	200	Yes	No	No
032/033-06 (#013)	73	M	-	-	-	-	+	+	-	-	+	1 dose	100	Yes	No	No
032/033-07 (#003)	70	M	+	+	+	+	+	+	-	-	-	2 1/2	200	No	---	Yes
032/033-07 (#020)	65	M	-	+	-	-	+	+	-	-	+	7 days	200	Yes	No	Yes
032-10 (#003)	63	F	+	+	+	+	+	+	-	-	+	1 day	200	Yes	No	Yes
032/033-11 (#002)	48	M	+	+	+	+	-	-	+	-	+	9	100	Yes	100	No
032/033-11 (#008)	47	M	+	+	+	+	-	-	+	-	-	1 1/2	100	No	---	Yes
												6	100	Yes	50	---
032/033-12 (#012)	62	M	+	+	+	+	+	-	-	-	+	7	150	Yes	No	Yes
032/033-13 (#007)	67	M	-	+	-	+	+	+	-	-	-	3	200	No	---	No
032/033-13 (#015)	64	M	-	+	-	-	+	+	-	-	-	7 days	200	Yes	No	No
032/033-17 (#014)	77	M	-	+/-	-	+	+	+	-	+	+	15	300 QD	No	---	No
032/033-17 (#026)	72	F	+	+	+	+	+	-	+	+	-	5	50 tid	No	---	No

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TABLE 94

FLECAINIDE VS DISOPYRAMIDE[a]

Demographics: (Total Patient Population)

Feature	Flecainide		Disopyramide	
	N	%	N	%
No. of patients	362		100	
No. of men	248	(69)	74	(74)
No. of women	114	(31)	26	(26)
Average Age	57.3		53.6	
Age Range	21-88		19-75	
Cardiac Diagnosis:				
Coronary heart disease	181	(50)	54	(54)
Cardiomyopathy	34	(9)	8	(8)
Valvular heart disease	70	(19)	12	(12)
Congenital heart disease	Not available		4	(4)
No demonstrable heart disease	51	(14)	22	(22)
History of congestive heart failure	62	(17)	22	(22)

[a]Data from Podrid et al, NEJM 302:614-617, 1980.

TABLE 95

Summary Demographics for Flecainide Patients in CHF Evaluation (N = 246)

Feature	Total Group	Those with History of CHF	Those Without History of CHF
No. of Patients	246 (100%)	115 (47%)	131 (53%)
No. of Males	185	95	90
No. of Females	61		
Mean Age (years)	59.1	63.6	54.9
Age Range	23-96	29-96	23-80
Cardiac Diagnoses[a] (No. of patients)			
1. Coronary Artery Disease	154 (63%)	89 (77%)	65 (50%)
Old Myocardial Infarctions	153 (62%)	105 (91%)	48 (37%)
2. Cardiomyopathy	47 (19%)	34 (30%)	13 (10%)
3. Valvular Heart Disease	49 (20%)	20 (17%)	29 (22%)
4. Hypertensive Heart Disease	45 (18%)	21 (18%))	24 (18%)
5. Primary Rhythm Disorder	20 (8%)	1 (0.9%)	19 (15%)
6. History of CHF	115 (47%)	115 (47%)	0 (0%)

[a]Patients may have more than one diagnosis.

TABLE 96

Congestive Heart Failure - Summary of
Patients who Developed New Or Worsened CHF During Flecainide Therapy

Patient I.D.	RNEF (%)	Age	Sex	History CHF	Cardiomegaly	On dig at baseline	Symptoms/Findings at baseline	Coronary artery disease	Old MI	Valvular Heart Disease	Hypertensive Heart Disease	Exposure to Flecainide at time of CHF	Dose at time of CHF	Outcome (d/c = flecainide discontinued)	In Miller's opinion was this a patient with flecainide-related CHF?
028-02-102		51	M	-	-	-	-	+	+	-	-	46 Days	200 BID	ongoing, dose ↓ to 150 BID	No
-103		69	M	-	-	+	-	+	+	-	-	13 Days	200 BID	d/c, restart 100 BID	No
-07-101		76	M	+	+	+	+	+	+	+	+	3 Days	100 BID	died (CHF related death)	Yes
-107		58	M	+	+	+	+	-	-	-	-	14 Days	150 BID	d/c	Yes
-08-112		62	M	+	+	-	+	+	+	-	+	1 Day	200 BID	ongoing, dose ↓ to 100 BID	Yes
-11-104		61	M	+	-	+	+	+	+	-	-	23 Days	100 TID	pt. trans. to another flec. study, dose ↓ to 100 BID	Yes
-14-101		53	M	-	-	-	-	+	-	-	-	180 Days	150 BID	ongoing	No
-115		35	F	+	-	-	-	-	-	+	-	36 Days	100 BID	ongoing	No
-131		44	M	+	+	+	+	-	-	-	-	10 Days	200 BID	died (CHF related death)	Yes
-133		55	M	+	+	+	+	+	+	+	-	2 Days	200 BID	died (arrhythmic death)	Yes
-19-101		75	F	+	-	+	+	+	+	-	-	6 Days	200 BID	d/c	Yes
-26-002		72	M	+	-	+	+	+	+	-	-	37 Days	150 Q8H	ongoing ↑ 100 BID	Yes
-003		47	M	+	+	+	+	-	-	-	-	75 Days	300 BID	ongoing, dose ↑ 200 BID	Yes
-27-011		74	M	+	-	-	+	+	+	-	-	75 Days	150 BID	continued fo 6 more weeks then d/c for other reasons	Yes
-28-002		76	F	+	+	+	+	+	+	-	-	65 Days	100 Q8H	continued for 1 more month then d/c for other reasons	No
-004		67	M	+	+	+	+	-	-	-	-	3 Days	100 TID	d/c	No
-007		59	M	+	-	+	-	+	+	-	-	70 Days	200- Q8H	ongoing	No
-012		61	M	-	+	-	-	-	-	-	+	71 Days	200 Q8H	ongoing	No
-34-101		55	M	+	+	+	+	-	-	-	-	10 Days	150 Q8H	died (CHF related death)	Yes
-102		56	M	+	+	+	+	+	+	-	-	24 Days	200 BID	continued for 4 more months, then d/c for other reasons	Yes
-008		84	M	+	+	+	-	+	+	-	-	1 Years	100 BID	ongoing	No
-37-003	30	59	M	-	-	-	-	+	+	-	-	9 Days	200 BID	d/c	No
-51-102		64	M	+	+	+	-	+	+	-	+	12 Days	200 BID	d/c	Yes
-103		69	M	-	-	-	-	-	-	-	+	80 Days	200 BID	ongoing	Yes
-60-101	26	75	M	+	+	+	+	-	-	-	-	101 Days	100 BID	ongoing	No
-63-101		57	M	+	+	+	+	+	+	-	+	33 Days	250 BID	died (acute MI)	No
-103	26	63	M	+	-	+	+	+	+	-	+	95 Days	200 BID	died (CHF related death)	Yes
-65-101		60	F	+	+	-	+	+	+	-	+	13 Days	200 BID	ongoing	No
-68-102	11%	63	M	+	+	-	+	+	+	-	-	2 Days	200 BID	d/c	Yes
-78-101		64	M	+	+	-	-	+	+	+	-	10 Days	200 BID	ongoing	Yes
-87-101		29	F	+	+	+	+	-	-	+	-	1 Day	200 BID	d/c	Yes
-88-101		84	M	+	-	+	+	+	-	-	-	30 Days	100 BID	dose ↓, then pt. d/c due to intercurrent disease	Yes
057-02-201	25	79	M	+	+	+	+	+	+	-	+	180 Days	100 BID	ongoing	Yes
-06-003	31	62	M	+	+	-	+	+	+	-	+	14 Days	150 BID	ongoing	No
-06-006	33	48	M	+	+	+	-	-	+	-	-	60 Days	300 BID	ongoing, changed schedule to 200 TID	Yes
-06-007	44[a]	72	M	+	+	+	+	+	+	-	+	30 Days	150 TID	died (cardiac arrest)	Yes
-10-007	20,	71	M	+	+	+	+	-	-	-	-	2 Days	300 BID	d/c	Yes
-11-003	Mo	64	F	+	+	-	+	-	-	+	-	1 Day	150 BID	ongoing, dose to 100 BID	No

[a] Baseline value of 44% spuriously high because patient's CHF status was worse at this time than several months earlier when RNEF was 24%.

TABLE 97

Patient Deaths

Study/Ptno	AGE	SEX	ASHD	OLD MI	HISTORY OF CHF	VT	CHF AND VT	DOCUMENTED PRIOR ARREST	LEFT VENTRICULAR EJECTION FRACTION (%)	CONCOMITANT MEDICATIONS	FLECAINIDE TOTAL DAILY DOSE (MG)	WEIGHT (KG)	PLASMA FLECAINIDE LEVELS (NG/ML)	DATE OF DEATH
028-12-101	44	M	+	+	+	+	+	+	17	Digoxin, Lasix, Coumadin, prednisone	600	64.4	6/10/82 553 ng/ml	6/12/82
028-14-112	75	M	+	+	+	+	+	+	30	Prazosin, Lasix, Isordil	200	64.4	none	6/06/82
028-14-132	61	M	+	+	+	+	+	+	25	Digoxin, Lasix, Minipress	400	89.4	none	10/22/82
028-14-133	55	M	+	+	+	+	+	+	12	Digoxin, Lasix, Isordil, hydralazine Coumadin	400	62.6	none	11/02/82
028-34-103	66	M	+	+	+	+	+	+	28	Digoxin, Lasix	400	69.4	10/30/82 471 ng/ml (4-1/2 hrs postdose)	10/30/82
028-42-101	61	M	+	+	+	+	+	-	15-18	Prednisone, Albuterol inhaler	500	67.1	none	9/24/82
028-43-003	55	M	+	+	+	+	+	+	30	Digoxin, Lasix, Isordil, allopurinol	400	90.7	6/28/82 1296 ng/ml	6/30/82
028-43-005	72	M	+	+	+	+	+	+	20	Digoxin, Lasix, Isordil	400*	81.7	none	7/14/82
028-72-103	73	M	+	+	+	+	+	+	35	Digoxin, Lasix	200	61.2	11/9/82 2238 ng/ml	11/09/82
033-14-006	22	M	-	-	+	+	+	+	16	Lasix, isosorbide, Coumadin, aprindine	300	79.8	10/12/81 1468 ng/ml 1/8/82 2594 ng/ml	1/11/82
057-02-204	80	M	+	+	+	+	+	-	46	Lanoxin, Lasix, nifedipine	400	84.8	10/7/82 595 ng/ml 10/11/82 2050 ng/ml	10/11/82
057-02-205	55	F	+	+	+	+	+	-	24	Digoxin, Lasix, Aldactone, nifedipine prazosin	250	68.0	11/3/82 1303 ng/ml 11/7/82 2401 ng/ml	11/07/82
057-03-003	66	M	+	+	+	+	+	+	28	Digoxin, Lasix, Coumadin	400	71.2	9/3/82 418 ng/ml	9/13/82
057-06-007	72	M	+	+	+	+	+	+	24	Digoxin, isosorbide, HCTZ, mexiletine	200	71.7	11/2/82 566 ng/ml	11/29/82

* Dose of flecainide had been increased from 200 BID to 300 BID, patient received one 300 mg dose.

TABLE 98

ECG INTERVALS (proarrhythmics)

STUDY/PTNO	P-R PRE	P-R DRUG	PR Δ	PR %Δ	QRS PRE	QRS DRUG	QRS Δ	QRS %Δ	QTc PRE	QTc DRUG	QTc Δ	QTc %Δ	QT PRE	QT DRUG	QT Δ	QT %Δ	JT PRE	JT DRUG	JT Δ	JT %Δ	JTc PRE	JTc DRUG	JTc Δ	JTc %Δ
CATEGORY I																								
028-25-101	.16	.24	.08	50	.10	.10	0	0	.40	.42	.02	5	.40	.40	0	0	.30	.30	0	0	.30	.31	.01	5
030-02-001	.17	.20	.03	18	.08	.10	.02	25	.38	.45	.07	18	.29	.36	.07	24	.21	.26	.05	24	.27	.33	.06	22
032-05-009	.15	.22	.07	47	.08	.12	.04	50	.40	.39	(-).01	(-)3	.45	.42	(-).03	(-)7	.37	.30	(-).07	(-)19	.32	.28	(-).40	(-)14
032-17-021	.19	.22	.03	16	.08	.09	.01	13	.40	.41	.01	3	.38	.36	(-).02	(-)5	.30	.27	(-).03	(-)10	.32	.31	(-).01	(-) 4
033-05-016	.16	.18	.02	13	.08	.08	0	0	.39	.38	(-).01	(-)3	.40	.39	(-).01	(-)3	.32	.31	(-).01	(-) 3	.31	.30	(-).01	(-) 3
033-17-025	.28	.20	(-).08	(-)29	.10	.09	(-).01	(-)10	.50	.57	.07	14	.46	.52	.06	13	.36	.43	.07	19	.39	.48	.09	22
CATEGORY II																								
028-14-112-D	.18	.18	0	0	.10	.14	.04	40	.50	.46	(-).04	(-) 8	.52	.44	(-).08	(-)15	.42	.30	(-).12	(-)29	.40	.33	(-).07	(-)18
033-04-009	.16	.22	.06	27	.08	.08	0	0	.39	.40	.01	3	.40	.42	.02	5	.32	.32	0	0	.31	.32	.01	2
033-07-008	.18	.28	.10	5	.16	.20	.04	25	.48	.43	(-).05	(-)10	.42	.40	(-).02	(-)5	.26	.20	(-).06	(-)23	.30	.21	(-).09	(-)29
033-16-005	.14	.16	.02	14	.08	.08	.0	0	.47	.46	(-).01	(-) 2	.36	.40	.04	11	.28	.32	.04	14	.37	.37	.00	0
057-02-205-D	.19	.21	.02	11	.11	.14	.03	27	.39	.44	.05	13	.34	.41	.07	21	.23	.27	.04	17	.27	.29	.02	9
CATEGORY III																								
028-12-101-D	.15	.16	.01	7	.10	.13	.03	30	.46	.54	.08	17	.42	.49	.07	17	.32	.36	.04	13	.36	.40	.04	12
028-13-001	.19	.26	.07	37	.10	.13	.03	30	.45	.44	(-).01	(-) 2	.38	.43	.05	13	.28	.30	.02	7	.33	.31	(-).02	(-) 6
028-14-132-D	.18	.28	.10	56	.11	.14	.03	27	.48	.47	(-).01	(-) 2	.42	.42	0	0	.31	.28	(-).03	(-)10	.36	.32	(-).04	(-)11
028-14-133-D	.22	.26	.04	18	.12	.12	0	0	.40	.48	.08	20	.40	.40	0	0	.28	.28	0	0	.28	.34	.06	20
028-21-101	.16	.19	.03	19	.08	.12	.04	50	.47	.47	0	0	.44	.45	.01	2	.36	.33	(-).03	(-) 8	.38	.34	(-).04	(-)10
028-26-010	.16	.18	.02	13	.08	.08	0	0	.36	.37	.01	3	.42	.52	.10	24	.34	.44	.10	29	.38	.46	.08	23
028-26-011	.18	x	x	x	.12	.14	.02	17	.48	.48	0	0	.44	.38	(-).06	(-)14	.32	.24	(-).08	(-)25	.35	.31	(-).04	(-)12
028-27-002	.30	.40	.10	33	.12	.14	.02	17	.45	.39	(-).06	(-)13	.40	.40	0	0	.28	.26	(-).02	(-) 7	.31	.25	(-).06	(-)20
028-33-103	.18	.24	.06	33	.08	.12	.04	50	.43	.45	.02	5	.44	.46	.02	5	.36	.34	(-).02	(-) 6	.36	.35	(-).01	(-) 1
028-34-103-D	.16	.22	.06	38	.10	.10	0	0	.45	.52	.07	16	.40	.50	.10	25	.30	.40	.10	33	.34	.42	.08	24
028-43-003-D	.22	.24	.02	9	.14	.20	.06	43	.40	.52	.12	30	.36	.44	.08	22	.22	.24	.02	9	.25	.29	.04	20
028-43-005-D	.16	.20	.04	25	.08	.16	.08	100	.35	.47	.12	34	.36	.44	.08	22	.28	.26	(-).02	(-) 7	.27	.28	.01	5
028-44-104	.18	.22	.04	22	.08	.10	.02	25	.47	.49	.02	4	.44	.46	.02	5	.36	.36	0	0	.38	.39	.01	1
028-44-105	.24	.19	(-).05	(-)21	.08	.08	0	0	.45	.40	(-).05	(-)11	.38	.36	(-).02	(-)5	.30	.28	(-).02	(-) 7	.35	.31	(-).04	(-)13
028-72-103-D	.23	.36	.13	57	.13	.17	.04	31	.49	.47	(-).02	(-) 4	.44	.44	0	0	.31	.27	(-).04	(-)13	.35	.29	(-).06	(-)17
028-87-101	.18	.18	0	0	.12	.12	0	0	.48	.46	(-).02	(-) 4	.39	.40	.01	3	.27	.28	.01	4	.33	.32	(-).01	(-) 2
028-WD-101	x	.24	x	x	.12	.12	0	0	.43	.44	.01	2	.40	.46	.06	15	.28	.34	.06	21	.30	.32	.02	7
032-08-006	.16	.22	.06	38	.08	.18	.10	125	.49	.56	.07	14	.44	.48	.04	9	.36	.30	(-).06	(-)17	.40	.34	(-).06	(-)16
032-17-017	.19	.23	.04	21	.09	.13	.04	44	.35	.45	.10	29	.36	.44	.08	22	.27	.31	.04	15	.26	.32	.06	22
033-13-015	.14	.20	.06	43	.13	.14	.01	8	.48	.47	(-).01	(-) 2	.42	.40	(-).02	(-)5	.29	.26	(-).03	(-)10	.33	.31	(-).02	(-) 6
033-14-006-D	.18	.20	.02	11	.14	.12	(-).02	(-)14	.41	.65	.24	59	.44	.52	.08	18	.30	.40	.10	33	.35	.50	.15	43
033-17-012	.18	.24	.06	33	.09	.12	.03	33	.42	.59	.17	40	.42	.54	.12	29	.33	.42	.09	27	.32	.47	.15	48
053-02-002	x	x	x	x	.08	.10	.02	25	.41	.42	.01	2	.36	.36	0	0	.28	.26	(-).02	(-) 7	.32	.30	(-).02	(-) 5
057-02-204-D	x	x	x	x	.12	.13	.01	8	.42	.40	(-).02	(-) 5	.33	.38	.05	15	.21	.25	.04	19	.27	.27	0	0
057-06-007-D	.24	.24	0	0	.12	.16	.04	33	.48	.48	0	0	.48	.52	.04	8	.36	.36	0	0	.40	.36	(-).04	(-)10

D = DECEASED

Proarrhythmic Events Associated With Flecainide Therapy

Table 99A

Mean Absolute Increase from Baseline ± 1 Standard Error (Seconds)

ECG Interval	Patients with PA[a] Events (n=36)	PA Deaths (n=12)	PA Non-Deaths (n=24)	PA Patients Categories I & II (n=11)	PA Patients Category III (n=25)	Chronic Patients on Flecainide 031-Month 12 (n=23)	Chronic Patients on Flecainide 033-Month 6 (n=95)
PR	0.040 ± 0.008	0.044 ± 0.013	0.038 ± 0.009	0.030 ± 0.014	0.045 ± 0.009	0.042 ± 0.006	0.032 ± 0.002
QRS	0.023 ± 0.004	0.030 ± 0.009	0.020 ± 0.005	0.015 ± 0.006	0.026 ± 0.006	0.025 ± 0.003	0.015 ± 0.002
QTc	0.029 ± 0.011	0.056 ± 0.023	0.015 ± 0.010	0.010 ± 0.012	0.037 ± 0.014	0.020 ± 0.010	0.023 ± 0.005
JTc	0.006 ± 0.010	0.018 ± 0.019	0.000 ± 0.011	-0.003 ± 0.015	0.010 ± 0.012	-0.004 ± 0.009	0.005 ± 0.008

Table 99B

Mean Percent Increase from Baseline ± 1 Standard Error (Seconds)

ECG Interval	Patients with PA Events (n=36)	PA Deaths (n=12)	PA Non-Deaths (n=24)	PA Patients Categories I & II (n=11)	PA Patients Category III (n=23)	Chronic Patients on Flecainide 031-Month 12 (n=23)	Chronic Patients on Flecainide 033-Month 6 (n=95)
PR	23 ± 4	23 ± 7	23 ± 5	20 ± 7	25 ± 4	26 ± 4	20 ± 2
QRS	24 ± 5	29 ± 10	22 ± 6	15 ± 6	28 ± 7	32 ± 5	18 ± 2
QTc	7 ± 3	14 ± 6	4 ± 2	3 ± 3	9 ± 4	5 ± 3	6 ± 1
JTc	0.0 ± 0.03	0.1 ± 0.05	0.0 ± 0.03	0.0 ± 0.05	0.0 ± 0.04	-0.4 ± 3	3 ± 2

[a]PA = Proarrhythmic.

Proarrhythmic Events Associated With Flecainide Therapy

Table 99C

Patients Who Developed Large (≥ 50%) ECG Interval Changes During Flecainide Therapy

	Increased PR	Increased QRS	Increased QTc
Patients who experienced proarrhythmic events (n=32-36)	3/32[a] (9%)	5/36 (14%)	1/36 (3%)
Patients who died during proarrhythmic events (n=11-12)	2/11[b] (18%)	1/12 (8%)	1/12 (8%)
Patients in R-818-032 study who did not experience proarrhythmic events (n=123-125)	14/123[c] (11%)	29/125 (23%)	8/125 (6%)

[a] Four of the 36 patients demonstrated atrial fibrillation (no PR interval).
[b] One of the 12 patients demonstrated atrial fibrillation.
[c] Two of the 125 patients demonstrated atrial fibrillation.

Use of Programmed Electrical Stimulation (PES) to Provoke Proarrhythmic Events

In three patients, a proarrhythmic event was observed during PES. One patient (No. 101, R-818-028-21) developed hypotensive VT requiring repeated cardioversion. One patient (No. 103, R-818-028-33) developed a "strange malignant" (new morphology) VT requiring cardioversion. One patient (No. 003, R-818-028-37) developed sustained VT which degenerated into VF followed by a difficult but successful resuscitation.

Table . 100

Literature Reports of Incidence (%) of Proarrhythmic (PA) Events for Various Antiarrhythmic Drugs

Drug	Percent of Tests[a] (No. PA tests)	Percent of Patients[a] (No. PA Patients)					
	Velebit et al[1]	Poser et al[2]	Chesnie et al[3]	Westveer et al[4]	Winkle et al[5]	Nathan et al[6]	Merck/ Astra[7]
Aprindine	11 (9)	19 (5)					
Disopyramide	5.9(6)	5 (1)					
Encainide		43 (6)			11;2.2[b]		
Flecainide						4.6 (7)	
Lorcainide		29 (5)	7.9 (6)				
Metoprolol	7.1 (3)						
Mexiletine	7.6 (11)	18 (7)		15 (5)			
Pindolol	16 (7)						
Procainamide	9.1 (5)	21 (4)					
Quinidine	15 (20)	16 (4)					
Tocainide	16 (12)	5 (1)					2.8;10.8[c]

[a]Criteria used:
Reference:
(1) Four-Fold increase in frequency of premature ventricular complexes; or ten-fold increase in repetitive forms; or the first emergence of sustained VT coincident with time course of action of drug, on Holter monitoring or exercise testing. 155 patients were tested with multiple drugs.
(2) PES testing, induction of sustained VT or VF for the first time; or, fewer extrastimuli required to provoke arrhythmia. 63 patients were tested with multiple drugs.
(3) Monitoring; exercise testing; or EP testing. (No criteria indicated)
(4) Serial ambulatory recordings. Increased VT rate, or occurrence of VF. (No other quantitative details)
(5) Worsening of tachyarrhythmias requiring cardioversion, resuscitation, or leading to death.
(6) Appearance of new or worsened arrhythmias of any type.
(7) Criteria not defined.

[b]Eleven percent of 90 patients with a prior diagnosis of recurrent sustained VT and/or VF; 2.2% of 47 patients with a diagnosis of chronic complex ventricular ectopic activity.

[c]Incidence for inpatient compassionate-use was 2.8%; the incidence for long-term treatment was 10.8%.

SUMMARY OF PATIENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

Table 101

Group III: Patients Who Died of Congestive Heart Failure and Low Output States

NDA 18-830

Study No. Patient No. R-818-	Age	Sex	Anatomic Diagnosis	History of Resus-citation	History of CHF	Arrhythmia	Last Daily Dose of Flecainide (mg/day)	Duration of Therapy	Cause of Death	Invest Opinion: Death Related to Flecainide?
028-07-101	76	M	ASHD, Previous MI Aortic insufficiency Mitral insufficiency	No	Yes	VT	200	3 days	Myocardial ischemia, terminal VT and CHF	Probably not
028-14-131	44	M	Cardiomyopathy	Yes	Yes	VT	400	10 days	↓ Cardiac output due to cardiomyopathy	Probably
028-34-101	55	M	Cardiomyopathy	Yes	Yes	VT/VF	300	17 days	Pump failure resulting in VT/VF	Possibly
028-60-101	75	M	Cardiomyopathy	No	Yes	VT	200	7 mos	Progressive heart failure	No
028-63-103	64	M	ASHD Previous MI x 2	Yes	Yes	VT	500	3-1/2 mos	Severe CHF, refractory to conventional therapy leading to cardiac dysrhythmias	Probably not
033-17-026	71	F	ASHD, Previous MI	No	Yes	Chronic PVCs	150	9 mos	CHF	No
037-05-008	[illegible]	M	ASHD, Recent MI	No	No	Post-MI, PVCs	400	10 days	Low output state-shock (2° to pulmonary emboli)	No
057-08-001	70	M	ASHD, Previous MI Cardiomyopathy	Yes	Yes	VT	200	7 days	Hypotension 2° to prazosin	No

SUMMARY OF PATIENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

Table 102A

Patients Who Developed Arrhythmias In-Hospital Leading to Death

R-818 Study No.- Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion Death Related to Flecainide?
⊖*028-12-101	44	M	+	+	+	VT	+	+	600	6 days	VT	No
⊖*028-14-112	75	M	+	+		VT	+	+	200	5 days	Cardiac arrest	No
028-14-114	76	F	+	+	+	VT	+	+	250	6 mos	VT/VF as a result of ischemic heart disease and E-M disassociation	No
028-14-123	61	M	+	+		VT	+	+	500	5 days	VT	No
⊖*028-14-132	63	M	+	+	+	VT	+	No CHF EF 13%	400	3 days	Cardiac arrest as consequence of VT	Probably
⊖*028-14-133	55	M	+	+	+	VT/VF	+	+	400	2 days	VT/VF	Probably
⊖*028-34-103	66	M	+	+		VT/VF	+	+	400	11 days	Incessant VT	Probably
*028-42-101	61	M	+	+	+	VT		+	500	2 days	Acute coronary insufficiency with subsequent exacer-bation of ventric-ular dysrhythmias	Probably not
⊖*028-43-003	55	M	+	+		VT/VF	+	+	400	5 days	Ref.V-arrhythmia, low cardiac out-put → acidosis	Possible
⊖*028-43-005	71	M	+	+		VT	+	+	600	4 days	Refractory VT	Unknown
⊖*028-72-103	73	M	+	+		VT	+	+	300	5 days	Cardiac arrest	Possible

* Patients discussed at Investigator's Meeting, December 10, 1982.
⊖ Deaths related to proarrhythmic events in survey, February, 1983.

SUMMARY OF PATIENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

Table 102A (Concluded)

Patients Who Developed Arrhythmias In-Hospital Leading to Death

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
033-06-005	74	M	+			PVCs		+	400 (off F 5 days)	30 days	Terminal VF	No
033-06-018	75	M	+			PVCs			400	8-1/2 mos	Cardiac arrest (VT/VF)	Probably not
⊕*033-14-006	22	M			+	VT/VF	+	+	300	3-1/2 mos	VT/VF asystole	No
⊕*057-02-204	80	M	+	+		PVCs		+	400	9 days	VT resulting in cardiogenic shock & death	Possible
*057-03-003	66	M	+		+	VT/VF	+	+	200	3 days	Incessant VT	Possible
*057-06-007	72	M	+	+		VT	+	+	200	2 mos	Recurrent VT	Probably not
057-08-005	54	M			+	VT	+	+	500	12 days	Intractable VF	Probably not
(035)-EN-03-203	39	M				VT		+	400	4 days	VF	Probably not
(035)-EN-03-016	53	M	+	+		VT		+	400	1 day	VF	Possible
(035)-EN-03-006	31	M				VT			400	8 mos	VT - asystole	Probably not

* Patients discussed at Investigator's Meeting, December 10, 1982
⊕* Deaths related to proarrhythmic events in survey February, 1983.

SUMMARY OF PATIENTS WHO DIED WHILE RECEIVING FLECAINIDE THERAPY

Table 102B

Patients Who Died Following Out-of-Hospital Sudden Death Experiences or Unobserved Deaths

NDA 18-830

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
028-02-104	76	M	+	+		VT/VF	+	+	200	13 1/2 mos	Probable cardiac arrest due to ischemic heart disease	Probabaly not
028-07-105	62	M	+	+		PVCs			300	7 mos	Possible CVA	Probably not
028-14-120	61	M	+		+	VT			200	2 mos	Probable cardiac arrest and sudden death	Probably not
028-55-001	71	M	+	+		VT	+		400	1 1/2 mos	Cardiac arrhythmia	Unknown
028-59-101	64	M	+	+		PVCs	+		400	4 days	V-fib	Possible
028-74-102	52	M	+			VT			350	5 mos	AMI, Cardiac arrest?	No
*031-03-009	63	M	+	+		VT			400	25 mos	VF	Possible
032-06-004	71	M	+	+		PVCs	+		600	14 days	Possible acute arrhythmia	Probably not
033-02-001	66	M				PVCs			400	16 mos	Probable arrhyth-mia either with or without MI	Probably not
*033-02-007	63	M	+	+		PVCs	+		200	21 days	Either VT or V-asystole	Possible
033-06-007	76	M	+	+		PVCs	+		400	6 mos	Cardiac arrest & arrhythmia. ? 2° to AMI	No

* Patients discussed at Investigator's Meeting, December 10, 1982.

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SUMMARY OF PATIENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

Table 102B

Patients Who Died Following Out-of-Hospital Sudden Death Experiences
or Unobserved Deaths

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion Death Related to Flecainide?
033-11-002	49	M	+		+	VT		+	200	15 1/2 mos	Cardiac arrhyth-mia probable VF	No
033-13-008	71	M	+			VF			400	2 mos	Sudden death ? MI ? arrhythmia	No
033-14-14	61	M	+	+		VT			400	10 mos	Probable MI, cardiac arrest	Probably not
*033-17-005	50	M	+	+		PVCs		+	400	4 days	VF with severe ASHD, severe CHF	Probably not
057-01-101	51	M	+	+		VT	+		400	2 1/2 mos	VT/VF sudden death	Possible
⊛*057-02-205	55	F	+	+		VT		+	250	24 days	Arrhythmia ?type ? cause	Possible
057-02-206	75	M			+	VT/VF	+	+	200	7 mos	Sudden death, either AMI or arrhythmia	Unknown
057-07-101	71	M	+	+	+	VT/VF	+	+	300	70 days	Arrhythmia-either primary or secon-dary to ischemic event	Probably not
057-07-103	67	M	+	+	+	VT		+	200	13 days	Ischemia causing pulmonary edema (inferred)	Proabably not

* Patients discussed at Investigator's Meeting, December 10, 1982.
⊛ Deaths related to proarrhythmic events in survey February, 1983.

NDA 19-830

SUMMARY OF PATIENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

Table 102B (Concluded)

Patients Who Died Following Out-of-Hospital Sudden Death Experiences
or Unobserved Deaths

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
(035)-EN-03-209	55	M	+	+		PVCs			300	14 mos	Cardiac arrest	No
(035)-EN-03-105	66	M	+	+		PVCs			400	1 mo	Sudden death, Probable VF	No
(035)-EN-03-024	67	F	+	+		VT		+	400	6 days	Myocardial infarction	Probably not

Table 103

PLASMA FLECAINIDE LEVELS AND CARDIAC ADVERSE EXPERIENCES

Study-Patient No.	Greatest Tolerated C_p (ng/ml)	Smallest C_p with CAE (ng/ml)
030,031-02-2	891	
-4	1424	2053 (LBBB)
-5	1460	
-7	1381	1500 (Bradycardia)
-8	1074	
-9	710	
-10	1152	
-12	718	
-15	1433	
-16	1378	
032,033-02-1	609	
-2	364	296 (RBBB) 778 (Bifasc. block)
-3	659	
-4	390	
-5	1027	711 (RBBB)
-6	1140	811 (Bradycardia)[1]
-7	853	1390 (CHF)
-8	542	
-9	1147	
-10	715	
-12	947	
-13	326	
-14	862	
-18	533	
-19	918	
-20	1508	
-21	-	1109 (Bifasc. block, RBBB)
-22	1276	
-23	-	707 (Syncope, junctional bradyc.)
-25	1178	
-26	659	
-27	697	

[1]According to investigator "probably related to metoprolol" started that day.

Table 104

PLASMA FLECAINIDE LEVELS AND EFFICACY

Study-Patient No.	Estimates of plasma levels required for 70% PVC Suppression	80% PVC Suppression	90% PVC Suppression	Number of Holters with plasma levels
R818-030,031-02-2	278	372	531	9
-4	131	175	251	7
-5	590	789	1128	11
-7	257	344	492	10
-8	248	332	474	11
-9	167	224	320	11
-10	101	134	192	10
-12	415	555	794	5
-15	225	300	429	9
-16	58	78	112	10
R818-032,033-02-1	108	145	208	5
-2	181	241	345	6
-3	206	276	394	5
-4	104	139	199	1
-5	1158	1548	2214	4
-6	898	1201	1718	2
-7	301	402	576	2
-8	90	121	173	5
-9	99	132	189	4
-10	81	109	155	6
-12	110	147	211	4
-13	82	110	157	1
-14	206	276	394	5
-18	59	79	113	4
-19	316	422	604	6
-20	42	56	80	6
-21	[1]			1
-22	4631	6190	8856	6
-23	- - - - - - -NO HOLTER DATA- - - - -			
-25	63	84	120	5
-26	169	226	323	3
-27	596	797	1140	1

[1] Estimate of means no suppression on the Holter available for this patient.

Table 105

Maximum Dosage Level Administered to Patients
During the Dose Ranging Trials - 030-01,2,3

	100 mg bid	200 mg bid	250 mg bid	300 mg bid	100 mg q8h
30-01 (Anderson)	4[a]	5	2[c]	1	0
30-02 (Hodges)	2[b]	7	0	3	0
30-03 (Woosley)	1	5	4[c]	0	1[d]
Total	7	17	6	4	1

[a] Two of these patients discontinued due to adverse experiences.
[b] One patient discontinued due to an increase in PVCs, no Holter was available for analysis.
[c] These six patients went from 200 mg bid to 250 mg bid rather than 300 mg bid.
[d] This patient (#30-03-10) went from 100 mg bid to 200 mg bid before being put on the 100 mg q8h regimen. No Holter data is available for the 200 mg bid dosage regimen.

Table 106

Summary of Times After Last Dose and Estimated Plasma Flecainide Levels Associated With Initial Return to

Studies		<90%	<80%	<70%	<60%
	Median Time (hrs.)	22.5	24.5	25	26
	Range	8 - >35	10 - >35	13 - >35	13 - >35
30-01					
30-02	Mean Plasma				
Combined	Level (ng/ml)	450	423	415	400
	St. Deviation	232	219	216	213
	N	18	18	18	18
	Median Time (hrs.)	13	18	20.5	24
	Range	7 - 25	12 - 25	13 - >24	14 - >24
30-03					
	Mean Plasma				
	Level	622	537	482	468
	St. Deviation	333	278	242	254
	N	10	10	10	10

TABLE 107

Time to Peak Plasma Level and Peak Plasma Concentration of Flecainide Acetate Following Oral Administration of Single 100, 200 or 300 mg Doses to 12 Subjects

Subject No.	Time to Peak Level (hours) Dose (mg): 100	200	300	Peak Plasma Level (ng/ml) Dose (mg): 100	200	300
1	1.5	6	4	141	242	387
2	3	3	2	91	178	264
3	6	2	2	114	275	356
4	3	4	8	92	215	270
6	4	6	4	80	139	260
7	4	1	6	63	134	206
8	4	4	1.5	74	184	275
10	3	4	1	55	96	206
11	1.5	1.5	2	100	274	378
12	1.5	3	4	92	156	313
13	4	4	3	67	168	239
15	1.5	1	3	124	205	277
MEAN	3.1	3.3	3.4	91	189	286
±SD	1.4	1.7	2.0	26	56	61
N						

TABLE 108 R-818-061--01

Plasma Pharmacokinetic Data for Flecainide Acetate Following Oral Administration of Single 100, 200 or 300 mg Doses to 12 Subjects

Subject No.	Plasma Half-Life (hours)[a]			Plasma Clearance (ml/min/kg)[b]			Volume of Distribution (l/kg)[c]		
	Dose (mg): 100	200	300	Dose (mg): 100	200	300	Dose (mg): 100	200	300
1	12.4	10.5	12.4	11.07	11.16	10.19	11.9	10.2	10.9
2	16.2	20.1	19.7	9.61	8.22	8.83	13.5	14.3	15.1
3	11.0	11.0	12.6	12.42	9.98	8.14	11.8	9.5	8.9
4	8.2	8.5	10.1	15.71	13.66	11.51	11.2	10.9	10.1
6	11.3	10.2	10.0	14.60	14.76	13.26	14.3	13.0	11.5
7	9.2	12.4	11.2	21.56	19.15	15.82	17.1	20.6	15.4
8	9.9	8.5	9.1	14.11	15.57	14.18	12.1	11.5	11.2
10	9.7	11.8	12.3	21.94	20.45	17.88	18.4	20.9	19.0
11	6.3	8.4	9.2	19.46	13.21	13.12	10.7	9.6	10.5
12	13.9	13.2	15.9	12.89	13.03	10.35	15.5	14.9	14.3
13	4.9	6.9	7.3	34.28	22.73	20.85	14.6	13.6	13.2
15	7.7	9.1	10.2	16.64	15.03	14.92	11.1	11.8	12.9
MEAN	10.1	10.9	11.7	17.02	14.75	13.25	13.5	13.3	12.8
±SD	3.2	3.4	3.4	6.70	4.28	3.76	2.5	3.9	2.8

[a] The terminal or beta phase plasma half-life of unchanged flecainide.
[b] Plasma (total body) clearance is the dose divided by the AUC from zero to infinity.
[c] Apparent volume of distribution is the dose divided by the product of the plasma AUC and the elimination rate constant.

TABLE 109

Area Under the Plasma Level Versus Time Curve Following Oral Administration of Single 100, 200 or 300 mg Doses to 12 Subjects

Subject No.	Plasma AUC-zero to 24 hours (ng·hrs/ml) Dose (mg): 100	200 (Ratio)[a]	300 (Ratios)[b]	Plasma AUC-zero to infinity (ng·hrs/ml) Dose (mg): 100	200 (Ratio)[a]	300 (Ratios)[b]
1	1661	3441 (2.07)	5186 (3.12,1.51)	2228	4422 (1.98)	7259 (3.26,1.64)
2	1393	2822 (2.03)	3965 (2.85,1.41)	2237	5228 (2.34)	7308 (3.27,1.40)
3	1382	3363 (2.43)	6014 (4.35,1.79)	1798	4458 (2.48)	8212 (4.57,1.84)
4	1104	2501 (2.27)	4140 (3.75,1.66)	1305	3002 (2.30)	5343 (4.09,1.78)
6	1068	2168 (2.03)	3781 (3.54,1.74)	1427	2835 (1.99)	4725 (3.31,1.67)
7	851	1734 (2.04)	3105 (3.65,1.79)	1036	2333 (2.25)	4246 (4.10,1.83)
8	1205	2259 (1.87)	3634 (3.02,1.61)	1477	2676 (1.81)	4395 (2.98,1.64)
10	713	1366 (1.92)	2364 (3.32,1.73)	881	1891 (2.15)	3243 (3.68,1.71)
11	1125	3063 (2.72)	4455 (3.96,1.45)	1225	3609 (2.95)	5450 (4.45,1.51)
12	1219	2458 (2.02)	4177 (3.43,1.70)	1784	3531 (1.98)	6649 (3.73,1.88)
13	637[c]	1701 (2.67)	2748 (4.31,1.62)	637	1921 (3.02)	3149 (4.94,1.64)
15	1094	2310 (2.11)	3380 (3.09,1.46)	1262	2795 (2.21)	4281 (3.39,1.53)
MEAN	1146	2432 (2.18)	3912 (3.53,1.62)	1441	3225 2.29	5355 (3.81,1.67)
±SD	291	655 (0.28)	1011 (0.49,0.14)	497	1052 0.38	1660 (0.61,0.15)

[a] Ratio of 200/100 mg doses.
[b] Ratios of: 1) 300/100 mg doses; 2) 300/200 mg doses.
[c] Value for 24 hour time point estimated by extrapolation of least squares line from 12 to 24 hours.

TABLE 110

Efficacy Results

	All Patients	Patients With Sustained VT	Patients With Non-sustained VT	Patients With PVCs Only
Number of patients enrolled	96	49	45	2
Number of patients with no followup data	4	2	1	1
Number of patients included in efficacy analysis	92 (100%)	47 (100%)	44 (100%)	1 (100%)
Number of patients discharged from the hospital (therapeutic successes in the opinion of the investigator)	67 (73%)	27 (57%)	39 (89%)	1 (100%)
Number of patients ongoing as of data cutoff (mean duration of therapy, 55 days)	59 (64%)	26 (55%)	32 (73%)	1 (100%)
Number of patients who met one or more of the efficacy criteria established by Riker	42 (46%)	19 (40%)	23 (52%)	0 (0%)
Number of patients who met one or more of the efficacy criteria established by Riker who are ongoing as of data cutoff	36 (39%)[a]	16 (34%)	20 (45%)	0 (0%)

[a] An additional 14 (15%) patients, 13 of whom are ongoing, may have met the criteria established by Riker; but had insufficient data to evaluate.

TABLE 111

Riker Efficacy Criteria
for Those Patients Released From the Hospital

Center	Pt No.	Holter 100% Supp. VT	Holter 80% Supp. PVCs	PES Testing[a] No VT Induced
01	101	0	-	+
01	106	0	0	-
02	302	0	-	0
02	303	+	+	0
06	101	-	-	0
06	102	-	-	0
06	103	+	+	0
06	105	+	+	+ (stress)
06	106	0[b]	+[b]	-
06	107	0	+	-
06	108	0	0[c]	+
06	110	-	-	0
06	113	+	+	-
06	114	-	+	0
06	115	0	0	0
07	101	+	-	0
07	102	0	-	0
07	103	+	+	0
10	102	0	0	-
12	102	+	-	0
12	103	+	-	-
12	104	+	+	0
12	105	+	+	0
12	107	+	+	0
12	110	+	+	0
12	111	0	+	-
12	114	0	+	+
12	116	+	+	0
12	117	+	+	0
12	118	+	+	+
12	119	-	+	0
12	120	+	+	0
12	121	+	+	0
12	122	+	+	0
26	101	0	0	0
26	104	0	0	+ (stress)
26	105	+	+	0
26	106	+	+	+ (stress)
26	111	0	+	0
31	101	+[b]	+[b]	0
31	102	+[b]	+[b]	0
31	103	-	-	0
34	101	+	+	0
34	102	+	+	0
34	103	0	0	0
34	105	-	+	0
34	106	+[b]	0[b]	0
47	101	+[b]	+[b]	0
63	104	0	+	0
63	105	0	0	+
65	102	-	-	0
65	103	+	+	-
65	104	+	+	0
65	105	+	+	+
72	103	+	+	0
72	104	0	0	0
72	106	+	+	0
72	107	0	0	0
72	110	-	0	0
72	112	0	0	0
72	113	0	0	0
72	114	-	-	0
72	115	0	0	+
72	116	0	0	0
72	121	+[b]	+[b]	0
72	122	0	0	0
72	123	0	0	0

+ = Criterion met
- = Criterion not met
0 = Not done

[a] PES testing used except where otherwise indicated.
[b] Different dose at time of discharge; not used in analysis.
[c] One PVC on baseline Holter, one PVC on discharge Holter.

TABLE 112

Flecainide Dose Distribution and Efficacy in Patients With Holter Data at Baseline and Discharge From Hospital

A. PVC Suppression

Total Daily Dose (mg)	Median PVC Suppression	No. of Patients With ≥80% PVC Suppression
200	93.7%	12/15 (80%)
250	91.1%	1/1 (100%)
300	92.7%	16/24 (67%)
400	89.8%	4/6 (67%)
All Patients	91.4%	33/46 (72%)

B. VT Suppression

Total Daily Dose (mg)	No. of Patients With Complete Suppression of Baseline VT
200	10/12 (83%)
250	1/1 (100%)
300	15/22 (68%)
400	3/4 (75%)
All Patients	29/39 (74%)

TABLE 113

Patient Discontinuations (DC)

Center	Pt. No.	No. Days on Oral Flecainide	Total Daily Dose (mg) at DC	Reason for Discontinuation
-01	101	77	400	Death
	102	13	300	Inadequate response - worsened arrhythmia
	103	14	300	Inadequate response
	105	1	200	Inadequate response - worsened arrhythmia
-02	301	3	200	Inadequate response
-06	101	86	350	Adverse experience - palpitations, malaise, blurred vision, anorexia
	104	15	300	Worsened arrhythmia
-07	101	69	300	Death
	103	12	200	Death
-10	101	7	300	Inadequate response
-11	101	3	200	Worsened arrhythmia
-12	101	2	100 oral + 80 IV	Inadequate response
	103	44	300	Inadequate response
	104	98	200	Adverse experience - vertigo associated with blurred vision
	106	1	200	Personal reason - patient withdrew consent
	108	4	200	Inadequate response
	109	13	400	Inadequate response
	110	21	200	Death
	112	14	400	Signs of congestive heart failure
	113	5	200	Conduction disturbance - complete AV block
	115	2	200	Conduction disturbance - complete heart (AV) block
-26	102	8	300	Inadequate response - worsened arrhythmia
	107	16	400	Inadequate response - worsened arrhythmia

TABLE 113 (Concluded)

Patient Discontinuations (DC)

Center	Pt. No.	No. Days on Oral Flecainide	Total Daily Dose (mg) at DC	Reason for Discontinuation
-26	108	4	200	Inadequate response
	110	3	200	Inadequate response - other reason - wanted to increase dose before protocol would allow
	113	17	400	Inadequate response - worsened arrhythmia
-31	102	83	300	Death
	103	41	200	Patient felt weak, short of breath
-34	104	12	300	Inadequate response
-63	101	16	500	Inadequate response - worsened arrhythmia
-65	101	5	200	Inadequate response
-72	101	14	200	Inadequate response
	105	58	150	Personal reason - dischared to nursing home

TABLE 114

Followup Results for Patients With Baseline RNEFs ≤ 30%

Center	Pt.No.	RNEF Values Baseline	Week 1	Month 1	Month 3	Month 4
02	302	19%	11%	9%	11%	
02	303	22%	24%			
12	103	17%	19%			
12	107	29%	24%	31%	30%	34%
12	110	22%	25%			
12	112	18%	19%			
12	118	29%	30%			
12	119	15%	16%			
26	101	25%	41%[a]		34%	
26	105	20%	27%		21%	
34	106	23%	24%	17%		
63	104	20%	28%			
63	105	27%	22%	———	———	
Mean ± SD		22.0% ± 4.5	23.9% ± 7.3	19.0% ± 11.1	24.0% ± 10.2	

[a] Week 2 RNEF

Table 115

Plasma Flecainide Levels, Efficacy, and Cardiac Adverse Experiences For Those Patients Who Had Suppression of PVCs Based on Holter Monitoring
(R-818-057B)

Study-Patient No	Estimated Plasma Level (ng/ml) for 80% Suppression of PVCs	Greatest Tolerated C_p (ng/ml)	Smallest C_p with CAE (ng/ml)
057-02-302	997	785	
-303	242	520	
057-06-101	608	828	
-102	667	1051	
-103	234	737	
-105	194	369	
-106	399	706	
-107	321	709	
-113	387	1684	
-114	313	923	
057-12-102	631	655	
-103	626	631	
-104	372	1317	
-105	217	517	
-107	489	752	
-110	382	497	
-111	632	856	
-112	1546	324	620 (CHF)
-114	367	450	
-116	915	242	
-118	347	528	
-119	606	864	
-120	108	700	
-121	521	1022	
-122	209	531	

Table 115 (cont.)

Plasma Flecainide Levels, Efficacy, and Cardiac Adverse Experiences For Those Patients Who Had Suppression of PVCs Based on Holter Monitoring (R-818-057B)

Study-Patient No	Estimated Plasma Level (ng/ml) for 80% Suppression of PVCs	Greatest Tolerated C_p (ng/ml)	Smallest C_p with CAE (ng/ml)
057-26-104	2300	1311	
-105	272	837	
-106	303	851	
-107	1010	966	1112 (worsened arrhythmia)
-111	248	909	
-112	329	1422	
-113	459	434	676 (worsened arrhythmia)
057-31-101	95	216	
-102	189	354	
-103	1750	895	
057-34-101	279	492	
-102	124	667	656 (RBBB)
-105	243	522	
057-47-101	374	1076	
057-65-102	316	270	
-103	245	657	
-104	190	604	
-105	1149	636	
057-72-101	414	717	
-103	. 3	316	
-106	132	210	
-121	220	702	

Table 116

SERUM LEVELS OF BILIRUBIN AND SEVERAL ENZYMES

before, during (highest reported value) and after discontinuing Tambocor (lowest reported value)

Left column = pre-drug Middle column = max. on-drug Right column = post-drug

Case No.	Sex	Bilirubin mg %		SGOT			SGPT			γGT			Alk. Phosph.			LDH		LAP		
10	F			el		n	el		n	el		n	el		n	el	n			
22	M	1.0	1.9 n										200	300	n					
124	F		>5																	
150	M		3.77 n	2033		n	2720		n	60		n				820	n			
159	M		5.89							el			el	el						
161	M		14.3																	
162	M		13.2	822																
182	M			8	52	16	5	47	21											
183	M		22.1	15			52			133						196				
185	M	6	0.9	117			160			262			125			130		98		
192	F			12	78	10	22	126	21	77	628	239	170	830	289	70	115	51	77	54
200	M		2.3 ~n	40		~n	95		~n	291		~n	273		~n					
209	M	~8	~2	21	250		16	347		61	333	80	146	427						
211	F	8.7	4.8	620		160	710		326	52		62	418		267					
219	M		1.7							76										

NO DATA FOR CASES No.28 (F), 30 (M) and 202 (F)

Abbreviations: el = elevated, n = normal, ~n = nearly normal

BIO/DISSOLUTION

REVIEW

6.1

HFN-110

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

DATE : AUG 17 1984

TO : Raymond J. Lipicky, M. D.
Acting Director in Division of Cardio-Renal Drug Products
(HFN-110).

FROM : Jerome P. Skelly, Ph. D.
Acting Director in Division of Biopharmaceutics
(HFN-220)

SUBJECT: Biopharmaceutics Recommendation of Approval
Flecainide Acetate
100, 200mg tablets

Riker Laboratories, Inc.
NDA 18-830

BACKGROUND

Flecainide Acetate, an antiarrhythmic drug, chemically is 2,5 - bis - (2,2,2,-trifluoroethoxy) - N - (2-piperidylmethyl) benzamide acetate. It is a white crystalline substance with a pKa of 9.3. The solubility in water at 37 C is 48.4 mg/ml. The following studies were reviewed in the submission:

1. R-818-049-01 (relative bioavailability study)
2. R-818-018-01 (multiple dosing study)
3. R-818-061-01 (single dose dose-proportionality study)
4. Chronic dosing study (Data submitted on January 27, 1984)
5. R-818-050-03 (radioisotope study)
6. Disease State Study
7. R-818-045-01 (interaction study)

6.1

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4. Chronic dosing study (Data submitted on January 27, 1984)
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6. Disease State Study
7. R-818-045-01 (interaction study)

OVERALL COMMENTS

1. Pharmacokinetics

For single intravenous dose (0.65 to 1.70 mg/kg) to healthy volunteers, the pharmacokinetics can be deiscribed as follows:

T1/2 = 14 hours (6.9 - 19.1)
Cl = 7.6 ml/min/kg. (4.6 - 12.1)
Vd = 8.7 L/kg (5.0 - 13.4)
Cl_r = 2.4 ml/min/kg
Protein binding = 33% to 41%
Concentration independent over therapeutic levels.

2. Bioavailability / Bioequivalence:

For single oral dose study (0.65 to 3.57 mg/kg), the pharmacokinetic parameters did not deviate from those of intravenous study and the absolute bioavailability was more than 90%. In the bioequivalence study to compare tablet, capsule and oral solution, the time to peak for capsule was 5.1h±26% and those for tablet and solution were 2.8h±39% and 2.2h±37% respectively. In other words, the absorption rate constants for capsule was smaller than those for tablet or solution (0.59 hr^{-1}±49% for capsule; 1.13 hr^{-1}±35% for tablet, 1.83 hr^{-1}±55% for solution). Following administratin of capsule, the peak level (164±48 ng/ml) was significantly lower than either tablet (192±57 ng/ml) or solution (204±49 ng/ml). The availabilities for the three formulations were similar.

3. Dose Proportionality

a. Following multiple oral dosage regimens for 7 days (1.12 to 2.83 mg/kg b.i.d.), 15 out of 16 subjects were able to reach steady-state on day 3. The steady state blood levels for 12 of 16 subjects were predictable by a linear model form single dose data. Subject #15 had steady-state plasma levels lower than values predicted by linear model. Three subjects had higher levels.

b. Single dose dose proportionality study (P-818-061-01) indicated that flecainide followed linear kinetics.

c. Chronic dosing studies indicated that plasma drug levels did not increase with time. However, one out of 84 patients studied had a trend of decreasing plasma levels over 20 months on the drug. The normalized volume decreased stowly from 3.40 ng/ml-mg to 0.31 ng/ml-mg.

4. Metabolism

A substantial amount of the Carbon-14 labeled drug was excreted in the urine as unchanged drug. Cumulative drug excretion varied from 35 to 50% of the dose of unchanged drug administered. The rate of urinary excretion of unchanged flecainide is moderately slow. The urinary excretion of meta-O-dealkylated flecainide (free and conjugated) accounts for about 11 to 16% of the dose. This metabolite is extensively conjugated; the ratio of total conjugated metabolite to metabolite free, in urine ranges from 2.3 to 5.9. The second major metabolite is 5-hydroxy-N-[2-(6-oxopiperidylmethyl)]-2-(2',2',2'-trifluoroethoxy) - benzamide. In one patient study, flecainide under little biliary excretion. There was no information as to enterohepatic recycling.

5. Disease States

Patients with premature ventricular contractions, renal disease, or congestive heart failure have longer flecainide half lives and slower clearance than normal subjects. The volume of distribution remains about the same for both normals and patients.

6. Interactions

a. During multiple oral dosage of flecainide to healthy subjects stabilized on a maintenance dose of digoxin, a 13%±19% (% C.V.) increase in plasma digoxin levels occurred at six hours postdose.

b. During coadministration of flecainide and propranolol, plasma flecainide levels are about 20% higher and propranolol levels are about 30% higher in comparison to control values.

c. Flecainide is not displaced from human plasma proteins in vitro by therapeutic levels of any of ten drugs (digoxin, propranolol, quinidine, procainamide, disopyramide, diazepam, and furosemide) which may be administered concomitantly with flecainide.

d. Food And/or Aluminum Hydroxide antacid do not affect pharmacokinetic parameters

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d. Food And/or Aluminum Hydroxide antacid do not affect pharmacokinetic parameters

7. Concentration & Effect

a. The minimal effective (greater than 90% suppression) concentration range was 245 to 980 ng/ml. After the final dose of flecainide, the meantime of arrhythmia recurrence to greater than 10% of control frequency was 14.8±5 hours.

b. Concentration - related prolongations of P.R. QRS and Q-Tc intervals were observed in all 11 patients of a study. Prior to abolition of ventricular arrhythmia, there was a progressive prolongation in the coupling interval (R-R') of the predominant ectopic focus. The degree of coupling interval prolongation was linearly related (r=0.61) to the plasma flecainide concentration. The extent of antiarrhythmic effect of flecainide was linearly related to both the extent of QRS prolongation (r=0.68) and to the plasma concentration (r=0.70).

8. Strengths

The firm intended to market both 100 and 200mg tablets (both strengths are composition proportional), however, the firm only performed 100mg bioavailability study. Since this drug follows linear kinetics, 200mg strength bioavailability study may not be required. The capsule formulation was used in bioequivalence study as well as pivotal therapeutic study, and the final market tablet formulation was used in bioequivalence as well as long term safety study.

CONCLUSION

The studies of NDA 18-830 submitted on March 8, 1983 have been found acceptable by the Division of Biopharmaceutics in regard to bioavailability / bioequivalence requirements. The application has fulfilled every necessary element of bioavailability / bioequivalence requirements provided that the firm agrees dissolution specification to be minutes using USP method II at 50 rpm in 900 ml 0.075 N HCl.

Jerome P. Skelly
Division of Biopharmaceutics

FT initialed by H. Malinowski, Ph.D.

cc: NDA 18-830 orig., HFN-110, HFN-220(Skelly,Marlene), HFN-225(Huang), Chron, Drug, Review, and Division Files

JPS/kek:#2126x(7-31-84)

N18830

AUG 23 1988

NDA 18-830/S-008

Riker Laboratories, Inc.
Attention: Ms. Jeanne M. Fox
270-3A-01 3M Center
St. Paul, Minnesota 55144

Dear Ms. Fox:

Please refer to your February 10, 1988 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide acetate) Tablets.

We also acknowledge receipt of your amendment dated August 5, 1988.

The supplemental application, as amended, provides for a new 50 mg dosage strength of Tambocor. We note that you have agreed to decrease the dissolution time interval for this product from to as requested in our May 5, 1988 letter and again by Dr. Nhan Tran of the Division of Biopharmaceutics in a July 15, 1988 telephone call.

We have completed the review of this supplemental application and it is approved. Our letter of October 31, 1985 detailed the conditions relating to the approval of this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-100
HFD-232 (with labeling)
HFD-730
HFD-110/NRosenthal N.R. Rosenthal 8-11-88
HFD-110/VO'Hagan/8/9/88
sb/8/10/88;8/12/38/1214S
R/D: NRosenthal
RWolters/8/11/88
CResnick/8/11/88
SChun/8/12/88
NMorgenstern/8/11/88

APPROVAL

Tambocor Tablets

Package Insert

HFD-110

230 Rec'd. Aug 8, 1988

Revised 8/9/88

TAMBOCOR® (flecainide acetate) Tablets

AUG 23 1988

DESCRIPTION:

TAMBOCOR® (flecainide acetate) is an antiarrhythmic drug available in tablets of 50, 100, 150 or 200 mg for oral administration.

Flecainide acetate is benzamide,N-(2-piperidinylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)-,monoacetate. The structural formula is given below:

APPROVED

Flecainide acetate is a white crystalline substance with a pK$_a$ of 9.3 [illegible] at 37°C.

TAMBOCOR tablets also contain: croscarmellose sodium, hydrogenated vegetable oil, magnesium stearate, microcrystalline cellulose and starch.

CLINICAL PHARMACOLOGY:

TAMBOCOR has local anesthetic activity and belongs to the membrane stabilizing (Class I) group of antiarrhythmic agents; it has electrophysiologic effects characteristic of the IC class of antiarrhythmics.

Electrophysiology. In man, TAMBOCOR produces a dose-related decrease in intracardiac conduction in all parts of the heart with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods were observed only in the ventricle. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction (see Warnings).

TAMBOCOR causes a dose related and plasma-level related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful 30-40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 μg/ml may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 μg/ml. Plasma levels above 0.7 - 1.0 μg/ml are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally.

In animals and isolated myocardium, a negative ionotropic effect of flecainide has been demonstrated. Decreases in ejection fraction, consistent with a negative inotropic effect, have been observed after single administration of 200 to 250 mg of the drug in man; both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses (see Warnings).

Metabolism in Humans. Following oral administration, the absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range, 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life with steady-state levels approached in 3 to 5 days; once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one-fifth as potent) and the meta-O-dealkylated lactam of flecainide (non-active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found in urine; only 5% of an oral dose is excreted in feces. In patients, free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 μg/ml).

When urinary pH is very alkaline (8 or higher), as may occur in rare conditions (e.g., renal tubular acidosis, strict vegetarian diet), flecainide elimination from plasma is much slower.

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. (See Dosage and Administration.)

In patients with congestive heart failure (NYHA class III), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 14 hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar. (See Dosage and Administration.)

From age 20 to 80, plasma levels are only slightly higher with advancing age; flecainide elimination from plasma is somewhat slower in elderly subjects than in younger subjects. Patients up to age 80+ have been safely treated with usual dosages.

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 μg/ml. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs (see Precautions, Drug Interactions).

INDICATIONS AND USAGE:

TAMBOCOR is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

TAMBOCOR is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of TAMBOCOR, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, TAMBOCOR, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients, depending on the cardiac status and underlying cardiac disease (see Dosage and Administration).

The effects of TAMBOCOR in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including TAMBOCOR, has been shown to have a favorable effect on mortality or sudden death.

CONTRAINDICATIONS:

TAMBOCOR is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Proarrhythmic Effects.

TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia (e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences). In studies of TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias.

In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. Their frequency appears to be related to dose and to the underlying cardiac

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Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule (see Dosage and Administration).

Patients with less serious arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal.

The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).

Heart Failure.

TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of preexisting CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg bid (see Dosage and Administration) and patients should be monitored carefully. Close attention must be given to maintenance of cardiac function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics, others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/ml.

Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose-related increases in PR, QRS, and QT intervals.

PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one-third of patients may develop new first degree AV heart block (PR interval ≥0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study, 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur, and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythm a associated with TAMBOCOR-induced QT prolongation and bradycardia.

Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block, or right bundle branch block associated with a left hemiblock occur, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally, threshold changes are within the range of multiprogrammable pacemakers and, when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture.

Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

PRECAUTIONS:

Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin, a 13% ± 19% increase in plasma digoxin levels occurred at six hours postdose.

In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, plasma flecainide levels were increased about 20% and propranolol levels were increased about 30% compared to control values. In this formal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects. When the drugs were administered together, the effects were additive. The effects of concomitant administration of TAMBOCOR and

blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.

Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction. Limited data in patients receiving known enzyme inducers (phenytoin, phenobarbital, carbamazepine) indicate only a 30% increase in the rate of flecainide elimination. In healthy subjects receiving cimetidine (1 gm daily) for one week, plasma flecainide levels increased by about 30% and half-life increased by about 10%.

When amiodarone is added to flecainide therapy, plasma flecainide levels may increase two-fold or more in some patients, if flecainide dosage is not reduced. (See Dosage and Administration.)

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgment of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

Pregnancy. Pregnancy category C. Flecainide has been shown to have teratogenic effects (club paws, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day, respectively; however, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. Limited data suggest that flecainide is excreted in human milk. Because of the drug's potential for serious adverse effects in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.

Hepatic Impairment. Since flecainide elimination from plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma level monitoring is required to guide dosage (see Plasma Level Monitoring); dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days).

ADVERSE REACTIONS:

The most serious adverse effects reported for TAMBOCOR (described in detail in *Warnings* section) were new or exacerbated ventricular arrhythmias, which occurred in 7% of patients, and new or worsened congestive heart failure, which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest, about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/ml.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign post-marketing surveillance studies, there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure, and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects are based on a multicenter efficacy study, utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table 1

Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 429 Patients at Any Dose	Incidence by Dose During Upward Titration: 200 mg/Day (N=426)	300 mg/Day (N=293)	400 mg/Day (N=100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance†	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.7%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400-600 mg/day, the incidence of these adverse experiences was similar, except for dizziness (32%) and visual disturbances (28%).

The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies: *Body as a Whole* – malaise, fever; *Cardiovascular* – tachycardia, sinus pause or arrest; *Gastrointestinal* – vomiting, diarrhea, dyspepsia, anorexia; *Skin* – rash; *Visual* – diplopia; *Nervous System* – hypoesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus; *Psychiatric* – anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients: *Body as a Whole* – swollen lips, tongue and mouth, arthralgia, bronchospasm, myalgia; *Cardiovascular* – angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension; *Gastrointestinal* – flatulence; *Urinary System* – polyuria, urinary retention; *Hematologic* – leukopenia, thrombocytopenia; *Skin* – urticaria, exfoliative dermatitis, pruritus; *Visual* – eye pain or irritation, photophobia, nystagmus; *Nervous System* – twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor; *Psychiatric* – amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the T-wave, a reduction in myocardial rate and contractility, conduction disturbances, hypotension, and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: removal of unabsorbed drug from the gastrointestinal tract, administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol, mechanically assisted respiration, circulatory assists such as intra-aortic balloon pumping, and transvenous pacing in the event of conduction block. Because of the long plasma half-life of flecainide (12 to 27 hours in patients receiving usual doses), and the possibility of markedly non-linear elimination kinetics at very high doses, these supportive treatments may need to be continued for extended periods of time.

Hemodialysis is not an effective means of removing flecainide from the body. Since flecainide elimination is much slower when urine is very alkaline (pH 8 or higher), theoretically, acidification of urine to promote drug excretion may be beneficial in overdose cases with very alkaline urine. There is no evidence that acidification from normal urinary pH increases excretion.

DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels, in patients with normal renal and hepatic function, may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, **increases in dosage should be made no more frequently than once every four days** since during the first 2

Table 1
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Adverse Effect	Incidence in All 429 Patients at Any Dose	Incidence by Dose During Upward Titration		
		200 mg/Day (N = 426)	300 mg/Day (N = 231)	400 mg/Day (N = 100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance†	15.3%	5.4%	12.1%	18.0%
Dyspnea	10.3%	2.3%	7.4%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	9.0%	1.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	3.1%	3.0%
Palpitation	6.5%	3.3%	3.4%	2.0%
Chest Pain	5.4%	3.1%	3.0%	1.0%
Asthenia	4.9%	2.1%	2.6%	4.0%
Tremor	4.7%	3.4%	1.3%	2.0%
Constipation	4.4%	2.8%	1.7%	3.0%
Edema	4.0%	1.9%	1.3%	2.0%
Abdominal Pain	3.3%	1.9%	1.3%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, loss of consciousness, syncope.

†Visual disturbance includes reports of blurred vision, difficulty in focusing, pain in one eye, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400 mg/day, the incidence of these adverse experiences was similar except for dizziness (3.5%) and visual disturbances (3.5%).

The following additional adverse experiences, possibly related to TAMBOCOR therapy, have occurred in 1% to less than 3% of patients, have been reported in acute and chronic studies. *Body as a Whole* — sudden death, asthenia. *Cardiovascular* — tachycardia, sinus pause or arrest. *Gastrointestinal* — vomiting, diarrhea, dyspepsia, anorexia, taste perversion, dry mouth. *Special Senses* — diplopia. *Nervous System* — hypoesthesia, paresthesia, paresis, ataxia, vertigo, increased sweating, vertigo, syncope, somnolence, tinnitus. *Psychiatric* — anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients: *Body as a Whole* — swollen lips, tongue and mouth, allergic reactions, hypoglycemia. *Cardiovascular* — angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, congestive heart failure. *Gastrointestinal* — flatulence. *Urinary System* — polyuria, urinary retention, nocturia, impotence, decreased libido, urinary frequency. *Skin* — urticaria, exfoliative dermatitis, pruritus. *Visual* — eye pain, photophobia, conjunctivitis. *Nervous System* — twitching, weakness, change in taste, dry mouth, confusion, incoordination, dysarthria, speech disorder, slurred speech, *Psychiatric* — amnesia, confusion, decreased libido, depersonalization, confusion, verbal hostility, irritability.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the T wave, a reduction in myocardial rate and contractility, conduction disturbances, hypotension, and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: removal of unadsorbed drug from the gastrointestinal tract, administration of cardiotropic agents of cardiac stimulants such as dopamine, dobutamine or isoproterenol, mechanically assisted respiration, intra-aortic balloon pumping, and transvenous pacing in the event of complete block. Because of the long plasma half-life of flecainide (12 to 27 hours in patients receiving usual doses), and the possibility of markedly non-linear elimination kinetics at very high doses, these supportive treatments may need to be continued for extended periods of time.

Hemodialysis is not an effective means of removing flecainide from the body. Since flecainide elimination is much slower when urine is very alkaline (pH 8 or higher), theoretically acidification of urine to promote drug excretion may be beneficial in overdose cases with very alkaline urine. There is no evidence that acidification from normal urinary pH increases excretion.

DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels in patients with normal renal and hepatic function may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, **increases in dosage should be made no more frequently than once every four days**. Since during the first 2 to 3 days of therapy the optimal effect of a given dose may not be achieved.

For sustained ventricular tachycardia patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 150 mg every 12 hours (300 mg/day), and the maximum dose is 400 mg/day.

For patients with symptomatic nonsustained ventricular tachycardia or frequent premature ventricular complexes the recommended starting dose is also 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day and the plasma level is below 0.6 μg/ml, the dosage may be cautiously increased to a maximum of 600 mg/day.

Use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and congestive heart failure, particularly during the first few days of dosing (see Warnings). Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12 hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on coexisting disease. In such patients, the dose at the start dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction (see Warnings). The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg bid every four days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

In patients with severe renal impairment (creatinine clearance of 35 ml/min/1.73 square meters or less), the initial dosage should be 100 mg once daily (or 50 mg bid), when used in such patients. Frequent plasma level monitoring is required to guide dosage adjustments (see Plasma Level Monitoring). In patients with less severe renal disease, the initial dosage should be 100 mg every 12 hours; plasma level monitoring may also be useful in these patients during dosage adjustment. In both groups of patients, dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days), observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change.

Based on theoretical considerations, rather than experimental data, the following suggestion is made: when transferring patients from another antiarrhythmic drug to TAMBOCOR, allow at least two to four plasma half lives to elapse for the drug being discontinued before starting TAMBOCOR at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

When flecainide is given in the presence of amiodarone, reduce the usual flecainide dose by 50% and monitor the patient closely for adverse effects. Plasma level monitoring is strongly recommended to guide dosage with such combination therapy (see below).

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 μg/ml. The probability of adverse experiences, especially cardiac ones, increases with higher trough plasma levels, especially when these exceed 1.0 μg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Plasma level monitoring is required in patients with severe renal failure or severe hepatic disease, since elimination of flecainide from plasma may be markedly slowed. Monitoring of plasma levels is strongly recommended in patients on concomitant amiodarone therapy, and may also be helpful in patients with congestive heart failure and in patients with moderate renal disease.

HOW SUPPLIED:

All tablets are embossed with RIKER on one side and TR 50, TR 100, TR 150 or TR 200 on the other side.

Tambocor 50 mg per white, round tablet, is available in:
- Bottles of 100 — NDC #0089-0305-10.
- Boxes of 100 in unit dose blister strips — NDC #0089-0305-16.
- Bottles of 500 — NDC #0089-0305-50, and
- Bottles of 1000 — NDC #0089-0305-80.

Tambocor 100 mg per white, round, scored tablet, is available in:
- Bottles of 100 — NDC #0089-0307-10.
- Boxes of 100 in unit dose blister strips — NDC #0089-0307-16.
- Bottles of 500 — NDC #0089-0307-50, and
- Bottles of 1000 — NDC #0089-0307-80.

Tambocor 150 mg per white, oval, scored tablet, is available in:
- Bottles of 100 — NDC #0089-0314-10.
- Boxes of 100 in unit dose blister strips — NDC #0089-0314-16.
- Bottles of 500 — NDC #0089-0314-50, and
- Bottles of 1000 — NDC #0089-0314-80.

Tambocor 200 mg per white, round, scored tablet, is available in:
- Bottles of 100 — NDC #0089-0317-10.
- Bottles of 500 — NDC #0089-0317-50, and
- Bottles of 1000 — NDC #0089-0317-80.

Store at controlled room temperature 15°-30°C (59°-86°F) in a tight, light-resistant container.

CAUTION: Federal law prohibits dispensing without prescription.

3M Riker
3M Health Care Group
Northridge, CA 91324

3M

TR-7A JUNE 1988

NDA 18-830/S-002
S-003

Riker Laboratories, Inc.
Attention: Florence N. Wong, Pharm.D.
Building 270-3A-01, 3M Center
St. Paul, MN 55144-1000

Dear Dr. Wong:

Please refer to your September 17, 1986 and October 14, 1986 supplemental new drug applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide acetate) Tablets.

We also acknowledge receipt of your amendments dated December 30, 1986 and February 2, 1987.

The supplemental applications as amended provide for the following revisions in the package insert:

S-002

1. A revised paragraph dealing with guidelines for reduced dosage in patients with renal impairment - Dosage and Administration section.

2. A sample "Dear Doctor" letter alerting physicians to the new recommended dosage of flecainide acetate for patients with severe renal impairment.

S-003 added statements providing the following information:

1. Effect of alkaline urine on drug elimination rate - Metabolism section; and a statement that acidification of the urine may promote elimination - Overdosage section.

2. Removal of unabsorbed drug after an overdose - Overdosage section.

3. Effect of age on drug elimination rate - Metabolism section.

4. Excretion of drug in breast milk - Precautions section.

5. Effect of enzyme inducers on drug elimination rate - Drug Interactions, Precautions section.

6. Effect of concomitant use of cimetidine on drug elimination rate - Drug Interactions, Precautions section.

7. Effect of liver disease on drug elimination rate - Precautions section.

8. Interaction with amiodarone - Drug Interactions, Precautions section and Dosage and Administration section.

9. Plasma monitoring - Dosage and Administration section.

We have completed the review of these supplemental applications as amended and they are approved. Our letter of October 21, 1985 detailed the conditions relating to the approval of this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-713/GChi
HFN-80/DDIR
HFN-232 (with labeling)
HFN-110/GBuehler/2/20/87;2/27/87
sh/2/26/87;3/4/87/5071s
R/D: CResnick/3/3/87
NRosenthal/3/3/87
THassall for NAM/3/4/87
RWolters/3/3/87

APPROVAL

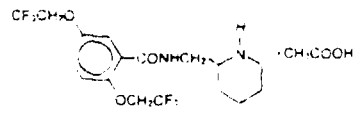
NDA-110
18-830 BO 02-687
Bueller
2/20/87

TAMBOCOR®
(flecainide acetate)
Tablets

DESCRIPTION:

TAMBOCOR® (flecainide acetate) is an antiarrhythmic available in tablets of 100 mg for oral administration.

Flecainide acetate is benzamide,N-(2-piperidinylmethyl)-2,5-bis (2,2,2-trifluoroethoxy)-, monoacetate. The structural formula is given below



Flecainide acetate is a white crystalline substance with a pK_a of 9.3. It has an aqueous solubility of 48.4 mg/ml at 37°C.

TAMBOCOR tablets also contain: hydrogenated vegetable oil, magnesium stearate, microcrystalline cellulose and starch.

CLINICAL PHARMACOLOGY:

TAMBOCOR has local anesthetic activity and belongs to the membrane stabilizing (Class I) group of antiarrhythmic agents; it has electrophysiologic effects characteristic of the IC class of antiarrhythmics.

Electrophysiology. In man, TAMBOCOR produces a dose-related decrease in intracardiac conduction in all parts of the heart with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods were observed only in the ventricle. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction (see Warnings).

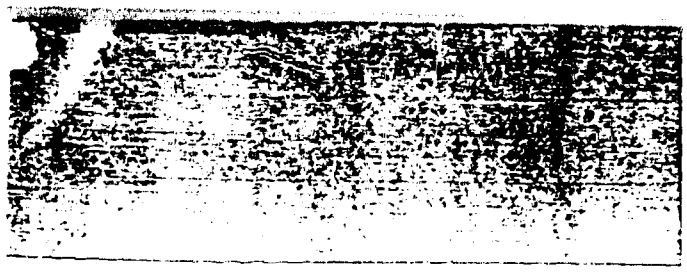
TAMBOCOR causes a dose-related and plasma-level related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful 30-40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 μg/ml may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 μg/ml. Plasma levels above 0.7 - 1.0 μg/ml are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally.

In animals and isolated myocardium, a negative inotropic effect of flecainide has been demonstrated. Decreases in ejection fraction consistent with a negative inotropic effect have been observed after single administration of 200 to 250 mg of the drug in man; both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses (see Warnings).

Metabolism in Humans. Following oral administration, the absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-



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The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life with steady-state levels approached in 2 to 5 days. Once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one-fifth as potent) and the meta-O-dealkylated lactam of flecainide (non-active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found in urine. Only 5% of an oral dose is excreted in feces. In patients, free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 μg/ml).

When urinary pH is very alkaline (8 or higher), as may occur in rare conditions (e.g., renal tubular acidosis, strict vegetarian diet), flecainide elimination from plasma is much slower.

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. (See Dosage and Administration.)

In patients with congestive heart failure (NYHA class III), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 14 hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar. (See Dosage and Administration.)

From age 20 to 80, plasma levels are only slightly higher with advancing age. Flecainide elimination from plasma is somewhat slower in elderly subjects than in younger subjects. Patients up to age 80 have been safely treated with usual dosages.

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 μg/ml. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs (see Precautions, Drug Interactions).

INDICATIONS AND USAGE:

TAMBOCOR is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

TAMBOCOR is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of TAMBOCOR, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, TAMBOCOR, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients depending on their cardiac status and underlying cardiac disease (see Dosage and Administration).

The effects of TAMBOCOR in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including TAMBOCOR, has been shown to have a favorable effect on mortality or sudden death.

CONTRAINDICATIONS:

TAMBOCOR is contraindicated in patients with preexisting second- or third-degree AV block or with right bundle branch block when associated with a left hemiblock (bifascicular block) unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Proarrhythmic Effects.

TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias.

In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous

From age 20 to 60, plasma levels are only slightly higher with advancing age. Flecainide elimination from plasma is somewhat slower in elderly subjects than in younger subjects. Patients up to age 80+ have been safely treated with usual dosages.

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In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. Their frequency appears to be related to dose and to the underlying cardiac disease.

Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule (see Dosage and Administration).

Patients with less serious arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal.

The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).

Heart Failure.
TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of pre-

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Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose-related increases in PR, QRS, and QT intervals.

PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one-third of patients may develop new first-degree AV heart block (PR interval >0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study 9% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus caution should be used when such increases occur, and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 50% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythmia associated with TAMBOCOR-induced QT prolongation and bradycardia.

Other significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block or right bundle branch block associated with a left hemiblock occur, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally, threshold changes are within the range of multiprogrammable pacemakers and when these occur a doubling of either voltage or pulse width is usually sufficient to regain capture.

Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

PRECAUTIONS:

Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin, a 13% ±19% increase in plasma digoxin levels occurred at six hours postdose.

In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, plasma flecainide levels were increased about 20% and propto control values. In this formal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects; when the drugs were administered together, the effects were additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive. In TAMBOCOR clinical trials, patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.

Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction. Limited data in patients receiving known enzyme inducers (phenytoin, phenobarbital, carbamazepine) indicate only a 30% increase in the rate of flecainide elimination. In healthy subjects receiving cimetidine (1 gm daily) for one week, plasma flecainide levels increased by about 30% and half-life increased by about 10%.

When amiodarone is added to flecainide therapy, plasma flecainide levels may increase two-fold or more in some patients. If flecainide dosage is not reduced. (See Dosage and Administration.)

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgment of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with quinidine or diltiazem to recommend concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

Pregnancy. Pregnancy Category C. Flecainide has been shown to have teratogenic effects (club paws, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day, respectively; however, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. Limited data suggest that flecainide is excreted in human milk. Because of the drug's potential for serious adverse effects in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 16 years of age have not been established.

Hepatic Impairment. Since flecainide elimination from plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma level monitoring is required to guide dosage (see Plasma Level Monitoring); dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days).

ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR described in detail in Warnings section were new or exacerbated ventricular arrhythmias which occurred in 7% of patients, and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause or sinus arrest, about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/ml.

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Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.

Hepatic Impairment. Since flecainide elimination from plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma level monitoring is required to guide dosage (see Plasma Level Monitoring); dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days).

ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR, described in detail in Warnings section, were new or exacerbated ventricular arrhythmias which occurred in 7% of patients, and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/mL.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign post-marketing surveillance studies, there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure, and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects are based on a multicenter efficacy study utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table 1
Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 429 Patients at Any Dose (N=429)	Incidence by Dose During Upward Titration 200 mg/Day (N=293)	300 mg/Day (N=293)	400 mg/Day (N=100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance†	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400-600 mg/day, the incidence of these adverse experiences was similar, except for dizziness (32%) and visual disturbances (28%).

The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies: *Body as a Whole* – malaise, fever; *Cardiovascular* – tachycardia, sinus pause or arrest; *Gastrointestinal* – vomiting, diarrhea, dyspepsia, anorexia; *Skin* – rash; *Visual* – diplopia; *Nervous System* – hypoesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus; *Psychiatric* – anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients: *Body as a Whole* – swollen lips, tongue and mouth, arthralgia, bronchospasm, myalgia; *Cardiovascular* – angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension; *Gastrointestinal* – flatulence; *Urinary System* – polyuria, urinary retention; *Hematologic* – leukopenia, thrombocytopenia; *Skin* – urticaria, exfoliative dermatitis, pruritis; *Visual* – eye pain or irritation, photophobia, nystagmus; *Nervous System* – twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor; *Psychiatric* – amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dream, apathy.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the

eliminate TAMBOCOR as the possible causative agent.

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Headache	9.6%	4.5%	6.1%	9.0%
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Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	1.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
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In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400-600 mg/day, the incidence of these adverse experiences was similar except for dizziness (32%) and visual disturbances (28%).

The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies: *Body as a Whole* – malaise, fever; *Cardiovascular* – tachycardia, sinus pause or arrest; *Gastrointestinal* – vomiting, diarrhea, dyspepsia, anorexia; *Skin* – rash; *Visual* – diplopia; *Nervous System* – hypoesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus; *Psychiatric* – anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients: *Body as a Whole* – swollen lips, tongue and mouth; arthralgia, bronchospasm, myalgia; *Cardiovascular* – angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension; *Gastrointestinal* – flatulence; *Urinary System* – polyuria, urinary retention; *Hematologic* – leukopenia, thrombocytopenia; *Skin* – urticaria, exfoliative dermatitis, pruritis; *Visual* – eye pain or irritation, photophobia, nystagmus; *Nervous System* – twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor; *Psychiatric* – amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the T-wave, a reduction in myocardial rate and contractility, conduction disturbances, hypotension, and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: removal of unabsorbed drug from the gastrointestinal tract; administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol; mechanically assisted respiration; circulatory assists such as intra-aortic balloon pumping; and transvenous pacing in the event of conduction block. Because of the long plasma half-life of flecainide (12 to 27 hours in patients receiving usual doses) and the possibility of markedly non-linear elimination kinetics at very high doses, these supportive treatments may need to be continued for extended periods of time.

Hemodialysis is not an effective means of removing flecainide from the body. Since flecainide elimination is much slower when urine is very alkaline (pH 8 or higher), theoretically acidification of urine to promote drug excretion may be beneficial in overdose cases with very alkaline urine. There is no evidence that acidification from normal urinary pH increases excretion.

DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels, in patients with normal renal and hepatic function, may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore **increases in dosage should be made no more frequently than once every four days** since during the first 3 to 5 days of therapy the optimal effect of a given dose may not be achieved.

For sustained ventricular tachycardia patients, the recommended starting dose is 100 mg every 12 hours. The dose may be increased in increments of 50 mg

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For sustained ventricular tachycardia patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most such patients do not require more than 150 mg every 12 hours (300 mg daily) and the maximum dose is 400 mg daily.

For patients with symptomatic nonsustained ventricular tachycardia or disabling frequent premature ventricular complexes the recommended starting dose is 50 to 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg daily). If such a patient is still symptomatic due to the arrhythmia at 400 mg daily and the plasma level is below 0.6 μg/ml, the dosage may be cautiously increased to a maximum of 600 mg daily.

Use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and congestive heart failure, particularly during the first few days of dosing (see Warnings). Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12 hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients, efficacy at the lower dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction (see Warnings). The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg bid every four days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg daily) because higher doses are associated with a greater incidence of worsened CHF.

In patients with severe renal impairment (creatinine clearance of 35 ml/min/1.73 square meters or less), the initial dosage should be 100 mg once daily (or 50 mg bid). When used in such patients, frequent plasma level monitoring is required to guide dosage adjustments (see Plasma Level Monitoring). In patients with less severe renal disease, the initial dosage should be 100 mg every 12 hours. Plasma level monitoring may also be useful in these patients during dosage adjustment. In both groups of patients, dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days), observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change.

Based on theoretical considerations, rather than experimental data, the following suggestion is made when transferring patients from another antiarrhythmic drug to TAMBOCOR: allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting TAMBOCOR at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

When flecainide is given in the presence of amiodarone, reduce the usual flecainide dose by 50% and monitor the patient closely for adverse effects. Plasma level monitoring is strongly recommended to guide dosage with such combination therapy (see below).

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 μg/ml. The probability of adverse experiences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 μg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Plasma level monitoring is required in patients with severe renal failure or severe hepatic disease, since elimination of flecainide from plasma may be markedly slower. Monitoring of plasma levels is strongly recommended in patients on concurrent amiodarone therapy and may also be helpful in patients with congestive heart failure and in patients with moderate renal disease.

HOW SUPPLIED:

TAMBOCOR is supplied as white, round, scored tablets containing 100 mg of flecainide acetate and embossed with RIKER on one side and TR 100 on the other side.

Tambocor 100 mg/tablet is available in:
Bottles of 100 — NDC #0089-0307-10
Boxes of 100 in unit dose blister strips — NDC #0089-0307-16

Store at controlled room temperature 15°-30°C (59°-86°F) in a tight, light-resistant container.

TR-5 NOVEMBER 1986

Manufactured by
Riker Laboratories, Inc./3M
St. Paul, Minnesota 55144

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-83
HFN-232 (with labeling)
HFN-110/CHeal/9/10/86;9/19/86
sb/9/11/86;9/15/86;9/22/86;9/25/86;10/8/86
P/D: NRosenthal/9/16/86
SChun/9/16/86
CResnick/9/17/86
AThompson/9/16/86
HBergenstern/9/19/86;9/24/86

SUPPLEMENT APPROVED

NDA 18-800/S-001

Riker Laboratories, Inc.
Attention: Florence M. Wong, Pharm.D.
Building 270-3A, 3M Center
St. Paul, MN 55144-1000

Dear Dr. Wong:

We acknowledge receipt on September 3, 1986 of your September [illegible], 1986 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide) Tablets.

The supplemental application provides for the voluntary listing of inactive ingredients in your prescription product labeling and the following minor editorial changes to the package insert: rearrangement of the structural formula of the drug substance as requested by Dr. Nathan Rosenthal of this Division, correction of the spelling of hypoesthesia and paresthesia in the Adverse Reactions section, and the addition of the unit dose strips to the How Supplied section.

Most of the labeling changes that you have proposed are permitted by 21 CFR 314.70(c)(2) [formerly 21 CFR 314.8(d)] to be made prior to approval of the supplement. We understand that those changes have been made. The addition of new packaging (such as the unit dose strip) is not permitted to be effected prior to approval of the supplement. You submitted, however, draft labels in the original NDA and they were approvable.

We have completed the review of this supplemental application as submitted with final printed labeling and it is approved. Our letter of October 31, 1985 detailed the conditions relating to the approval of this application.

Please submit twelve copies of the final printed labels for the unit dose strip. Please mount seven of the copies on heavy weight paper or similar materials. Your transmittal letter should refer to this approved supplemental application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

TAMBOCOR®

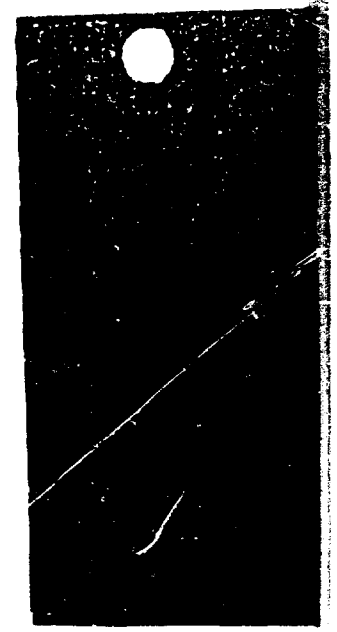
(flecainide acetate)

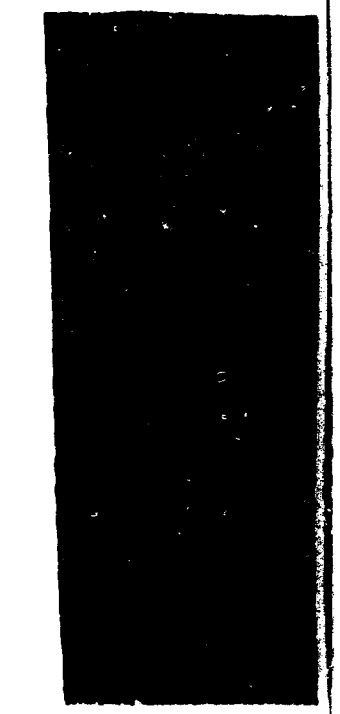
Tablets

DESCRIPTION

CLINICAL PHARMACOLOGY

Electrophysiology





accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one-fifth as potent) and the meta-O-dealkylated lactam of flecainide (non-active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found in urine. Only 5% of an oral dose is excreted in feces. In patients, free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 μg/ml).

The elimination of flecainide from the body depends on renal function (i.e., 30 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. (See Dosage and Administration.)

In patients with congestive heart failure (NYHA class III), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 11 hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar. (See Dosage and Administration.)

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 μg/ml. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs (see Precautions, Drug Interactions).

INDICATIONS AND USAGE:

TAMBOCOR is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

TAMBOCOR is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of TAMBOCOR, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, TAMBOCOR, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients depending on their cardiac status and underlying cardiac disease (see Dosage and Administration).

The effects of TAMBOCOR in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including TAMBOCOR, has been shown to have a favorable effect on mortality or sudden death.

CONTRAINDICATIONS:

TAMBOCOR is contraindicated in patients with pre-existing second- or third-degree AV block or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Proarrhythmic Effects.

TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias.

In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. The frequency appears to be related to dose and to the underlying cardiac disease.

Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was titrated at 200 mg/day with slow upward titration

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Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest) the incidence of proarrhythmic events was 4.3% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated pro*arrhythmic events resulted in death*, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. *Accordingly, it is extremely important* to follow the recommended dosage schedule (see Dosage and Administration).

Patients with less serious arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% *being fatal*.

The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).

Heart Failure.

TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. *Exacerbation of pre*existing CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg bid (see Dosage and Administration) and patients should be monitored carefully. Close attention must be *given to maintenance of cardiac* function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics, others may require dosage reduction or discontinuation of TAMBOCOR. *When feasible*, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/ml.

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Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose related increases in PR, QRS, and QT intervals.

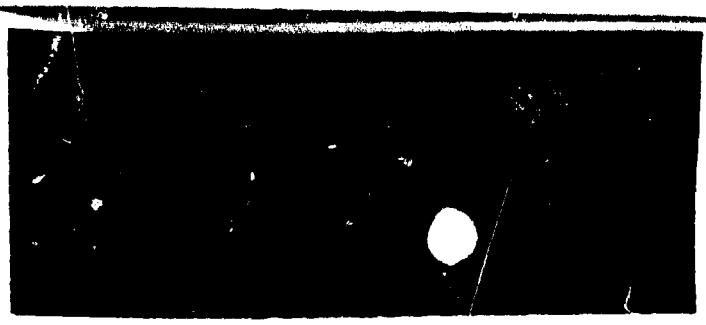
PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one-third of patients may develop new first-degree AV heart block (PR interval ≥0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study, 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur, and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythmia associated with Tambocor induced QT prolongation and bradycardia.

Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block or right bundle branch block associated with a left hemiblock occur, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration, and at regular intervals thereafter. Generally threshold changes are within the range of multiprogram-



Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

PRECAUTIONS:

Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin, a 13% - 15% increase in plasma digoxin levels occurred at six hours postdose.

In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, plasma flecainide levels were increased about 20% and propranolol levels were increased about 30% compared to control values. In this formal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects when the drugs were administered together the effects were additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive. In TAMBOCOR clinical trials, patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.

Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction.

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgment of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 3 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

Pregnancy. Pregnancy Category C. Flecainide has been shown to have teratogenic effects (club paws, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day, respectively, however, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. It is not known whether flecainide is excreted in human milk. Because many drugs are excreted in human milk and because of the drug's potential for serious adverse effects in infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.

Use in Patients with Hepatic Impairment. Studies to determine the effect of hepatic impairment upon the elimination of TAMBOCOR have not yet been completed. Because the drug undergoes extensive biotransformation, most likely in the liver, patients with significant hepatic impairment should not receive TAMBOCOR unless the potential benefits clearly outweigh the risks.

ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR (described in detail in Warnings) were new or exacerbated ventricular arrhythmias which occurred in 7% of patients and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresponsive ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause or sinus arrest about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events [illegible] with higher [illegible]

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ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR described in detail in *Warnings* section were new or exacerbated ventricular arrhythmias which occurred in 7% of patients, and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest, about 1.2% altogether (see *Warnings*). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/ml.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign post-marketing surveillance studies there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects are based on a multicenter efficacy study utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table 1
Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 429 Patients at Any Dose	Incidence By Dose During Upward Titration 200 mg/Day (N=426)	300 mg/Day (N=392)	400 mg/Day (N=199)
Dizziness*	18.9%	11.0%	10.6%	13.6%
Visual Disturbance†	15.9%	5.4%	12.0%	16.6%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	3.0%
Nausea	8.9%	4.9%	4.6%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.5%
Palpitation	6.1%	3.5%	3.3%	1.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.5%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400-600 mg/day the incidence of these adverse experiences was similar except for dizziness (32%) and visual disturbances (28%).

The following additional adverse experiences possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies: *Body as a Whole* – malaise, fever; *Cardiovascular* – tachycardia, sinus pause or arrest; *Gastrointestinal* – vomiting, diarrhea, dyspepsia, anorexia; *Skin* – rash; *Visual* – diplopia; *Nervous System* – hypoesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus; *Psychiatric* – anxiety, insomnia, depression.

The following additional adverse experiences possibly related to TAMBOCOR have been reported in less than 1% of patients: *Body as a Whole* – swollen lips, tongue and mouth, arthralgia, bronchospasm, myalgia; *Cardiovascular* – angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension; *Gastrointestinal* – flatulence; *Urinary System* – polyuria, urinary retention; *Hematologic* – leukopenia, thrombocytopenia; *Skin* – urticaria, exfoliative dermatitis, pruritis; *Visual* – eye pain or irritation, photophobia, nystagmus; *Nervous System* – twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor; *Psychiatric* – amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the T-wave, a reduction in myocardial rate and contractility, conduction disturbances, hypotension, and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine, isoproterenol; mechanically assisted respiration;

Chest Pain	**5.4%**	**3.1%**	**3.8%**	**1.0%**
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
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DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels in patients with normal renal and hepatic function may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore **increases in dosage should be made no more frequently than once every four days** since during the first 2 to 3 days of therapy the optimal effect of a given dose may not be achieved.

For sustained ventricular tachycardia patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most such patients do not require more than 150 mg every 12 hours (300 mg/day) and the maximum dose is 400 mg/day.

For patients with symptomatic nonsustained ventricular tachycardia, couplets or premature ventricular complexes the recommended starting dose is also 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day and the plasma level is below 0.6 μg/mL the dosage may be cautiously increased to a maximum of 600 mg/day.

Use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and congestive heart failure, particularly during the first few days of dosing (see Warnings). Therefore a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. [illegible] studies have been [illegible]

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Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients, efficacy at the lower dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction (see Warnings). The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg bid every four days. The maximum dosage should not exceed 300 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

In patients with renal impairment, the initial dosage should be 100 mg every 12 hours. Dosage increases should be made cautiously at intervals greater than 4 days, observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change. It is recommended that plasma level monitoring be used to guide dosage adjustments (see below).

Based on theoretical considerations, rather than experimental data, the following suggestion is made when transferring patients from another antiarrhythmic drug to TAMBOCOR: allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting TAMBOCOR at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 μg/ml. The probability of adverse experiences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 μg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Because elimination of flecainide from plasma may be slower in patients with severe chronic renal failure or severe congestive heart failure, plasma level monitoring may be especially helpful in these patients.

HOW SUPPLIED:

TAMBOCOR is supplied as white, round, scored tablets containing 100 mg of flecainide acetate and embossed with RIKER on one side and TR 100 on the other side.

Tambocor, 100 mg tablet, is available in:
Bottles of 100 — NDC #0089-0307-10
Boxes of 100 in unit dose blister strips — NDC #0089-0307-16

Store at controlled room temperature 15°-30°C (59°-86°F) in a tight, light-resistant container.

TR-3 MARCH 1986

Manufactured by:
Riker Laboratories, Inc./3M
St. Paul, Minnesota 55144

Summary Basis of Approval

JUL 25 1989

NDA 18-830

Applicant:
Riker Laboratories, Inc./3M
St. Paul, Minnesota 55144

Drug Generic Name:
Flecainide Acetate

Drug Trade Name:
Tambocor

I. Indications for Use:

Flecainide is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

Flecainide is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of flecainide, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, flecainide, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients depending on their cardiac status and underlying cardiac disease.

The effects of flecainide in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including flecainide, has been shown to have a favorable effect on mortality or sudden death.

II. Dosage form, route of administration and recommended dosage:

A. Dosage Form: Oral Compressed Tablet

B. Dosage Strength: 100 and 200 mg

C. Recommended Dosage: For patients with sustained ventricular tachycardia, no matter what their cardiac status, flecainide, like other antiarrhythmics, should be initiated in-hosptial with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions.

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels, in patients with normal renal and hepatic function, may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, increases in dosage should be made no more frequently than once every four days, since during the first 2 to 3 days of therapy the optimal effect of a given dose may not be achieved.

For sustained ventricular tachycardia patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day, and the plasma level is below 0.6 µg/ml, the dosage may be cautiously increased to a maximum of 600 mg/day.

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Intravenous lidocaine has been used occassionally with flecainide while awaiting the therapeutic effect of flecainide. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen. An occasional patient not adequately controlled by (or intolerant to) a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients efficacy at the lower dose should be evaluated.

Flecainide should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction. The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg bid every four days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

In patients with renal impairment, the initial dosage should be 100 mg every 12 hours. Dosage increases should be made cautiously, at intervals greater than 4 days, observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change. It is recommended that plasma level monitoring be used to guide dosage adjustments (see below).

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Plasma Level Monitoring: The large majority of patients successfully treated with flecainide were found to have plasma levels between 0.2 and 1.0 µg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Because elimination of flecainide from plasma may be slower in patients with severe chronic renal failure or severe congestive heart failure, plasma level monitoring may be especially helpful in these patients.

III. Manufacturing and Control:

A. Manufacturing and Controls

The synthesis of the new drug substance is described in the application in sufficient detail to permit a determination that the assigned chemical structure is valid and that the specifications and test methods for the new drug substance are suitable. The specifications include limits on total and individual impurities as determined by specific assay methods. Adequate information has been provided to explain the various steps involved in the synthesis, and the organic chemical reactions employed are reasonable for the synthesis of this type of chemical compound. Raw materials and intermediates are satisfactorily characterized and their purity well controlled.

Controls over the manufacturing procedures, including specifications and test methods for the new drug substance, excipients, and the drug product, give sufficient assurance of the identity, strength, quality, and purity of the drug product.

B. Stability

The stability of the drug substance has been characterized. Stability studies have been conducted on the products in the proposed container/closure systems under room temperature and accelerated conditions. The data support the use of a two year expiration time. The data were obtained using a stability-indicating assay method, whose suitability has been demonstrated.

In addition, the applicant has stated their intention to place initial production lots on stability studies when they become available.

C. Methods Validation

The analytical methods for control of the new drug substance and drug product have been independently validated by two FDA laboratories and found suitable for their intended purpose.

D. Labeling

The immediate container label and carton labels are in compliance with technical requirements pertaining to the following: established name, ingredients statement, control number, expiration date, prescription caution, applicant's name and address, and net contents statement. Likewise, the "Description" and "How Supplied" sections of the package insert are satisfactory with respect to the technical requirements of the regulations.

E. Establishment Inspection

Inspections of Riker Laboratories facilities in Northridge, California; Decatur, Alabama; and Loughborough, England have been performed to determine their compliance with Current Good Manufacturing Practice Regulations. A satisfactory report was received from the Office of Compliance, indicating no reason to withhold approval of the application.

F. Environmental Impact Analysis Report

A report on the impact on the environment was submitted. The manufacture of Tambocor tablets is expected to have little or no impact on the environment.

IV. Pharmacology

A. Antiarrhythmic Studies

Flecainide demonstrated antifibrillatory action both orally and parenterally in mice exposed to toxic concentrations of chloroform and showed greater potency than the reference antiarrhythmic agents, quinidine, lidocaine and procainamide. Intravenously administered flecainide had a wide spectrum of antiarrhythmic action in completely suppressing atrial and ventricular arrhythmias induced experimentally in pentobarbital anesthetized dogs by hydrocarbon-epinephrine, ouabain or aconitine administration and in conscious dogs by coronary ligation. Flecainide showed 100% effectiveness in suppressing these arrhythmias with average effective doses ranging from 1 mg/kg (against ouabain-induced tachycardia) to 7.2 mg/kg (against aconitine-induced atrial arrhythmia) and was approximately two to three times more potent than the reference agents.

Flecainide was effective in blocking atrial arrhythmias induced by direct application of methacholine chloride to the right atrium of open-chest, pentobarbital anesthetized dogs. An intravenous dose of 2.5 mg/kg was required to completely block the arrhythmia. An intravenous dose of approximately 5.0 mg/kg was required to convert an established atrial arrhythmia to sinus rhythm. An intravenous infusion of flecainide at the rate of 0.2 mg/kg/min in two dogs (average total of dose of 4.5 mg/kg) was effective in blocking the methacholine-induced arrhythmia for approximately 30 minutes.

Five dogs with stable ventricular tachycardia induced by ouabain were infused with flecainide (0.25 mg/kg/min) to a total intravenous dose of 18.0 to 50.0 mg. Based on an average weight of the dogs of 28.5 kg, the dose of flecainide administered was estimated to be 0.5 to 2.0 mg/kg. In three dogs no effect was obtained. In one dog there was a conversion to sinus rhythm and in one a conversion to A-V dissociation. When the study was repeated using a similar protocol, efficacy was demonstrated in four of five dogs treated with an average intravenous dose of 2.8 mg/kg.

When compared to some of the new antiarrhythmic compounds, e.g., disopyramide, tocainide, encainide, mexiletine and lorcainide, i.v. flecainide was one of the most effective, (in terms of % arrhythmias converted) in treating ectopic ventricular tachycardia induced by toxic doses of ouabain in male and female pentobarbital anesthetized dogs. Only encainide showed greater potency than flecainide in treating this arrhythmia. All compounds showed minor effects on arterial blood pressure. Disopyramide, encainide and lorcainide showed greater bradycardic effects than the other compounds.

Five and 10.0 mg/kg doses of flecainide, injected directly into the duodenum of pentobarbital anesthetized dogs, suppressed ectopic ventricular tachycardia induced by ouabain with a 100% conversion rate achieved at the higher dosage. Time to onset of suppression and duration of suppression were also dose related (at 10.0 mg/kg all arrhythmias were fully suppressed within about 30 minutes with response lasting about two hours). In conscious dogs with arrhythmias induced by ouabain, intraduodenally administered flecainide generally suppressed the arrhythmia within 15 minutes and for greater than one hour after a 10.0 mg/kg dose (67% conversion rate). Flecainide administered by intramuscular injection at doses of 5.0 and 10.0 mg/kg was also effective in suppressing arrhythmias induced by ouabain (about an 80% conversion rate at 10.0 mg/kg). The onset of action was approximately 20 minutes and the duration of action was generally greater than one hour, irrespective of dose level.

Ventricular arrhythmias induced by coronary artery ligation were suppressed by flecainide administration either by oral gavage or by intraduodenal injection at a dose of 10.0 mg/kg (100% conversion at 15.0 mg/kg i.d.). Prolonged antiarrhythmic activity (greater than one hour) was observed only after

intraduodenal administration. Flecainide administered in gelatin capsules was effective in suppressing this arrhythmia; however, a dose of 20.0 mg/kg was required (for a 100% conversion rate). At 10.0 mg/kg, transient suppression of the arrhythmia was observed in 1/4 dogs tested and traces of flecainide were found in the stomach and duodenum indicating incomplete absorption in these experiments. Flecainide, administered by intramuscular injection at a dose of 10.0 mg/kg, was generally effective in suppressing ventricular arrhythmias induced by coronary artery ligation with conversion achieved 50% of the time. The onset of action was less than 15 minutes while the duration of action was generally less than 30 minutes.

Pretreatment of coronary ligated dogs with reference cardiovascular compounds revealed that propranolol, phentolamine, procainamide and quinidine seemed to enhance the antiarrhythmic potency of flecainide, whereas digoxin and diphenylhydantoin seemed to diminish its antiarrhythmic potency. Slight cumulative toxicity was observed with the combinations of flecainide with chlordiazepoxide, diphenylhydantoin, procainamide, quinidine or lidocaine. The combinations of flecainide with propranolol or digoxin showed greater cumulative toxicity resulting in death after small to moderate doses of flecainide (average of 7.0 mg flecainide/kg fatal in three of three propranolol pretreated dogs with deaths attributed to respiratory depression; average of 14.5 mg flecainide/kg fatal in two of four digoxin pretreated dogs with deaths attributed to ventricular fibrillation). These same doses of flecainide produced no serious toxic effects in control flecainide experiments.

A meta-o-dealkylated metabolite of flecainide was effective on intravenous administration in suppressing ectopic ventricular tachycardia induced by ouabain; however the metabolite was considerably less potent than flecainide in treating this arrhythmia (average converting dose 5.0 mg/kg vs less than 2.0 mg/kg for flecainide). The metabolite showed rather weak antiarrhythmic action compared to flecainide when administered intravenously to coronary artery ligated dogs (at an average dose of 5.0 mg/kg) with ventricular arrhythmias.

A second metabolite of flecainide, the meta-o-dealkylated lactam, was not effective (at a dose of 10.0 mg/kg i.v.) in suppressing ectopic ventricular tachycardia induced by ouabain in pentobarbital anesthetized dogs.

B. Electrophysiological Studies

In isolated dog Purkinje fibers, a bath concentration of 1.0 µg/ml of flecainide had the following electrophysiological effects: alterations in the contour of the action potential included a decrease in the rising velocity, a shortening of the plateau (phase 2 repolarization), a decrease in the overshoot and no change in the duration; the effective refractory period was lengthened; local premature responses were abolished; the

rate of spontaneously beating fibers was decreased (a concentration of 2.0 µg/ml rendered these fibers quiescent); no effect on the slope of diastolic depolarization (phase 4) was observed in concentrations up to 5.0 µg/ml; there was a decrease in the ability of fibers to undergo depolarization; the period during an action potential when premature responses could be elicited was shortened; the increased slope of diastolic depolarization and other changes induced by ouabain (2.1×10^{-7}M) and epinephrine (1.0 µg/ml) were abolished at concentrations of 2.0 to 10.0 µg/ml of flecainide. The electrophysiological effects of flecainide in isolated atrial and ventricular muscle fibers were similar to those observed in Purkinje fibers except that the duration of the ventricular action potential was increased. Flecainide did not alter the changes in the ventricular action potential induced by relative hypoxia.

In open-chest pentobarbital anesthetized dogs, flecainide infused intravenously at 0.1 and 0.25 mg/kg/min had the following electrophysiological effects: conduction was depressed in all tissues of the heart and the degree of depression was related to the plasma concentration of the drug; depression of conduction was most pronounced in the His-Purkinje system and in the ventricular muscle. Flecainide did not greatly depress sinus node function or junctional rhythms even at high plasma concentrations (up to 10 µg/ml and 8 µg/ml, respectively). Ectopic atrial and ventricular rates were slowed by flecainide and this slowing was related to plasma concentrations of the drug. The slowing of ectopic ventricular rate was less than that reported for lidocaine, but similar to that reported for propranolol. Mean aortic blood pressure was not greatly changed even at high plasma concentrations of flecainide. Flecainide increased ventricular fibrillation threshold; however, the increase was not consistent and was of lesser magnitude than values reported for lidocaine or propranolol. Results of experiments carried out in pentobarbital anesthetized open chest dogs indicate that flecainide may be more effective in increasing ventricular fibrillation threshold during premature ventricular beats than during supraventricular pacing.

In pentobarbital anesthetized open chest dogs, flecainide, at plasma concentrations of 0.4 to 0.7 µg/ml, prolonged atrioventricular conduction. Both flecainide and ouabain slowed intra-atrial conduction, ventricular activation time and A-V nodal conduction during atrial fibrillation. Used in combination, the effects of the two drugs were additive. Propranolol pretreatment potentiated the actions of flecainide by further prolonging intra-atrial conduction, A-V nodal conduction and His-Purkinje conduction. A-V conduction may be slowed to such an extent that A-V block could be a complication.

Intravenous doses of 5.0 or 10.0 mg/kg of flecainide administered to pentobarbital anesthetized closed chest dogs significantly decreased sinus rate and prolonged His-Purkinje conduction. No significant effect was seen on either intra-atrial or atrioventricular conduction. Ouabain and propranolol induced conduction changes were variably affected by flecainide. However, these changes were proportionate to the changes of flecainide alone. Hence, conduction abnormalities induced by digitalis and propranolol were not exaggerated.

C. Myocardial Studies

When tested in isolated guinea pig atria, flecainide showed greater myocardial depressant action than either quinidine or lidocaine. No cholinergic receptor stimulant or beta-adrenergic receptor blocking actions were observed.

Studies in isolated cat papillary muscle on the effects of flecainide on sodium kinetics, sodium and potassium content and contractile characteristics showed that higher concentrations of flecainide increased the half-time (t 1/2) of the faster of two sodium influx kinetic pools, depressed the developed tension and increased the stimulation threshold in a dose-related manner. It is believed that, because of the crudeness of the technique used and inadequate stabilization of the muscle preparations, the true changes in sodium flux caused by flecainide were not seen in these experiments.

Flecainide had a mild negative inotropic action after 1.0 mg/kg iv in the open chest vagotomized dog. However, subsequent higher doses generally had a slight positive inotropic effect. The 1.0 mg/kg iv dose also produced an apparent slight decrease in ventricular function. There was no further decrease with higher doses of flecainide; rather, there was some recovery of the apparent loss of function after the first dose. A mild negative inotropic response to flecainide was also observed with relatively large intracoronary doses in the isolated perfused rabbit heart.

In a comparative cardiovascular study in open chest, vagotomized, pentobarbital anesthetized male and female dogs, encainide had greater hypotensive and bradycardic effects than either flecainide or disopyramide at an intravenous dose of 5.0 mg/kg. Flecainide had a mild negative inotropic effect at 5.0 mg/kg, whereas both disopyramide and encainide showed negative inotropism at 3.0 mg/kg and greater negative inotropism than flecainide at 5.0 mg/kg.

D. Cardiovascular Studies

Evidence of depressed nerve conduction and/or ganglionic blockade was observed in anesthetized dogs where attenuation of responses to carotid occlusion, right vagal stimulation and cardiac nerve stimulation were demonstrated after intravenously administered flecainide, 5.0 mg/kg body weight.

Flecainide infused (15 mg/min) intravenously in conscious dogs at doses of 1.0 mg/kg/day for 14 consecutive days showed no significant electrocardiographic changes. Increasing the daily dose to 5.0 or 15.0 mg/kg resulted in increases in heart rate, PR interval, QRS duration, QT interval and T-wave amplitude (effects were of dosage dependent severity) during dosing on day 14 (not on days 1, 4 or 7). Values returned to normal following termination of the infusion. There was a significant (p less than 0.05) positive correlation between plasma concentrations (determined 15 minutes after completion of infusion) and electrocardiographic changes. Retching and/or emesis and marked muscle tremors were frequently observed in all of the high dose animals. There were no deaths.

At 5.0 mg/kg of flecainide, administered intravenously to anesthetized dogs, there was no apparent effect on cardiovascular hemodynamics including mean aortic, pulmonary arterial and central venous pressures, cardiac output and total peripheral resistance.

In experiments designed to measure changes in coronary arteriovenous oxygen differences and plasma potassium levels in normal pentobarbital anesthetized dogs and in conscious coronary ligated dogs (24 hours post ligation), a 5.0 or 7.5 mg/kg intravenous dose of flecainide did not alter either coronary arteriovenous blood gas or plasma potassium concentrations.

No apparent vasodilatory activity was observed for flecainide given intra-arterially in doses up to 1.2 mg in the dog perfused hind limb at constant blood flow. At an effective intravenous antiarrhythmic dose of 5.0 mg/kg, flecainide had no apparent effect on regional blood flow in carotid, femoral, renal and superior mesenteric vascular beds. Coronary blood flow in isolated perfused rabbit heart showed minimal variable changes at relatively high intracoronary doses of flecainide.

Large cumulative intravenous doses of flecainide administered to pentobarbital anesthetized dogs by constant infusion gradually depressed heart rate and blood pressure and finally caused respiratory failure and death. The lead II electrocardiographic changes observed during flecainide infusion were an increased amplitude of the T-wave and a decreased amplitude of the QRS

complex. Similar cardiopulmonary effects were seen with lidocaine and quinidine; however, the average fatal dose of flecainide was considerably less than the fatal doses of lidocaine and quinidine (infusion rates for all drugs 1 mg/kg/min). Some idea of the relative margin of safety of flecainide may be assessed from a ratio of the fatal intravenous dose found in this study to the average effective antiarrhythmic intravenous dose derived from three experimentally induced arrhythmias in the pentobarbital anesthetized dog. The table below shows values computed for this ratio (or relative safety margin) for flecainide, lidocaine and quinidine and indicates that flecainide may have greater safety potential than either lidocaine or quinidine.

	Fatal Dose mg/kg	Effective Dose mg/kg	Dose Fatal/Effective
Flecainide	31.0	3.9	7.9
Lidocaine	60.0	9.3	6.5
Quinidine	86.0	11.7	7.4

Procainamide was considerably less toxic than the other compounds including flecainide and though it showed some similar cardiovascular effects, they were generally less severe. Procainamide has been omitted from the above table as it was not fatal in the one dog in which it was infused at 1 mg/kg/min. At 2 mg/kg/min it was fatal in only 1/4 dogs (total dose of 30 mg/kg). Chronic pretreatment with 5.0 mg/kg daily doses of flecainide for 14 days resulted in a greater sensitivity to the toxic effects of an acute intravenous infusion (1 mg/kg/min) of flecainide on the 15th day with average fatal dose reduced by 29%.

E. Other Pharmacological Studies

In pentobarbital anesthetized male and female dogs with neuromuscular blockade by succinylcholine chloride and mechanical ventilation with room air, intravenous flecainide (5.0 or 10.0 mg/kg) did not block bronchoconstriction induced by intravenous histamine or methacholine.

Local anesthetic action similar to lidocaine was demonstrated for flecainide administered topically to the rabbit cornea. When given intramuscularly flecainide showed regional nerve block of equal intensity but of longer duration than lidocaine in the mouse sciatic nerve preparation.

In isolated smooth muscle tissues (trachea, ileum, uterus and seminal vesicle) taken from rats and guinea pigs, flecainide demonstrated a relatively weak nonspecific spasmolytic action.

Dose-related CNS depression was observed in rats administered flecainide intraperitoneally. Death was observed at 100.0 mg/kg. Male and female mongrel dogs administered flecainide orally showed mild CNS depression and mild tachycardia at 10.0 and 20.0 mg/kg. Vomiting was the limiting factor for the administration of higher oral doses of flecainide to dogs. A slight delayed weight loss was observed in dogs treated with flecainide at all oral doses.

Flecainide did not block electrically induced arterial thrombosis in the pentobarbital anesthetized male rat at an intravenous dose of 5.0 mg/kg body weight.

F. Preclinical Metabolism

Metabolic studies with flecainide in laboratory animals have been conducted with intravenous and/or oral dosage in dogs, rats, mice, cats, monkeys, and swine. Results and conclusions on the primary metabolic aspects of flecainide from these various animal studies are summarized below.

The results from comparative radiochromatographic (TLC) metabolite fraction analyses indicate that flecainide undergoes more routes of biotransformation (more metabolite fractions) in each of the three chronic toxicity animal species (dog, rat, and mouse) than in humans. While at least seven or eight metabolites are detectable in the urine of all three animal species, only two major metabolites and two or three minor ones are detectable in human urine. Although fewer metabolites are found in human urine, all of the metabolites in human urine are also present in the urine of all three animal species; in addition, the two major metabolites in human urine and plasma (both the meta-O-dealkylated metabolite and the meta-O-dealkylated lactam of flecainide) are also major metabolites in the urine from each of the three animal species. Conjugation of flecainide metabolites (glucuronide and/or sulfate) is a major route of biotransformation in all four species. Overall, these results indicate that the three chronic toxicity animal species were exposed to all of the same metabolites of flecainide as are present in human urine and plasma; from a biotransformation viewpoint, the evaluation of chronic drug toxicity in these animal species is a reasonable assessment of flecainide safety for humans.

After multiple oral dosing of pregnant rats with carbon-14 labelled flecainide, the presence of radioactivity in fetal and embryo-placenta tissues on gestation Days 10 and 15 indicates that the lack of teratogenic effects in teratogenicity studies with flecainide in rats cannot be attributed to lack of exposure of the fetuses to flecainide and/or its metabolites during the period of organogenesis.

Following a single intravenous dose of carbon-14 labelled drug to rats, flecainide and/or its metabolites (radioactivity) distribute extensively to many tissues, but not extensively to the brain; subsequently, carbon-14 is eliminated at a relatively rapid rate. Although cardiac tissue levels of unchanged flecainide are 11- to 12-fold higher than plasma levels, the levels of flecainide in heart and plasma decline at the same rate.

In rats, dogs, cats, and monkeys, flecainide and/or its metabolites (carbon-14) do not appear to be retained in any of the tissues, except for pigmented ocular tissues. In contrast to albino rats (non-pigmented eye), levels of carbon-14 (flecainide and/or its metabolites) are relatively high in the uveal tract of the three species (dog, cat, and monkey) with pigmented eye tissues as compared with non-pigmented eye tissues, other tissues, and plasma. However, long-term toxicity studies in dogs (12-18 months), baboons (six months), albino rats (two years), and mice (18 months) have revealed no evidence of ocular toxicity and no ocular toxicity has been found in humans with administration of flecainide for periods of 12 months and longer.

In the cat, procainamide and/or its metabolites (carbon-14) are also present at relatively high levels in pigmented eye tissues and are also retained. Since procainamide is an antiarrhythmic for which there is a record of extensive chronic use in humans without ocular toxicity, these procainamide results provide additional evidence to include with the growing literature that indicates a lack of relationship between drug binding to pigmented eye tissues and ocular toxicity. Overall, there is no evidence that the presence and retention of flecainide and/or its metabolites in pigmented ocular tissues is of clinical consequence.

After oral dosage, flecainide absorption is prompt and nearly complete in humans, dogs, rats, and mice, based on comparison of oral/IV plasma level data and/or urinary excretion data. In contrast to humans, flecainide undergoes substantial presystemic biotransformation (first-pass effect) in dogs; plasma AUC's of flecainide after oral dosage to dogs are about 50% of those after IV dosage. First-pass effect was not assessed in other animal species. For toxicity assessment, drug-diet feeding used for rodents provides extensive absorption and the solid dosage forms used for dogs provide nearly complete drug absorption.

In comparison to humans, the plasma half-life of unchanged flecainide (Table 1) is relatively short in dogs (about 1 hour), rats (about 2 hours), cats (about 1 hour), swine (about 1 hour), and monkeys (about 4 hours). Although the difference in plasma half-life for flecainide in humans as compared with laboratory

animals is quantitatively striking, it is similar to the differences reported for several other drugs. For flecainide, no definitive, direct explanation for this difference can be given; however, available comparative data (presystemic biotransformation and excretion data) for dogs and rats indicate that this difference in plasma half-life between humans and animals most probably results, at least in part, from differences in rates of flecainide biotransformation (probably hepatic) and, perhaps, in the extent of biliary excretion. Apparently, these animal species possess drug-metabolizing-enzyme systems that can biotransform flecainide at a faster rate than humans.

Flecainide and/or its metabolites (radioactivity) are excreted in both urine and feces of dogs, rats, and monkeys; the drug appears to undergo extensive biliary elimination in dogs and rats. Only about 1 to 2% of a single dose is excreted in dog urine as unchanged flecainide (Table 1); in comparison, excretion of unchanged drug in rat urine accounts for about 25% of the dose and in mouse urine accounts for about 11 to 13% of a single dose.

Table I

Comparative Pharmacokinetics and Excretion for Unchanged Flecainide in Humans and Laboratory Animals

Species	Healthy Human	Beagle Dog	Albino Rat	Albino Mouse	Mongrel Cat	Yorkshire Swine	Rhesus Monkey
Pharmacokinetics of Unchanged Flecainide							
Dose (mg/kg)[a]	0.5-3.5	5.0	5.0	5.0	5.0	2.0	5.0
Dose Route	Oral & IV	Oral & IV	Oral & IV	Oral & IV	IV	IV	IV
Time to Peak Plasma Level (hrs)[b]	≈3 hrs (0.5-6 hrs)	≈1 hr (0.5-3 hrs)	0.5 hr	-[c]	-[c]	-[c]	-[c]
Plasma Half-Life	13 hrs (7-22 hrs)	≈1 hr (55-85 min)	≈2 hrs (95-130 min)	-[c]	≈1 hr (45-85 min)	≈1 hr	4 hrs (2-5 hrs)
Excretion of Unchanged Flecainide							
Dose (mg/kg)	0.6-3.5	4.0	5.0	5.0	-[c]	-[c]	-[c]
Dose Route	Oral	IV	IV	Oral & IV	-	-	-
Urinary (% dose)	27% (10-50%)	1-2%	≈25%	11 & 13%	-	-	-
Collection Period (hours)	48-144	24	24	24			

[a] Single doses.
[b] Oral dosage.
[c] Not available.

G. Acute Toxicity

Symptoms following acute oral or parenteral administration of flecainide to mouse, rat, dog or cat included, at the higher doses tested, tremors, ataxia, dyspnea and convulsions. Also observed in dogs and cats (only two of the latter species studied) was emesis. Deaths were attributed to respiratory depression and arrest. Surviving animals recovered within hours.

Species	Sex	Route	No. Gps. No./Gp.	Dose Range (mg/kg)	Maximum Non-lethal (mg/kg)	LD_{50}(95%CL) (mg/kg)
Mouse	M	p.o.	4/10	100-400	100	190(151-239)
Mouse	M	i.v.	3/10	20-25	20-23	24(23-25)
Rat	F	p.o.	5/10	100-800	200-400	567(422-763)
Rat	M	p.o.	7/10	250-630	250	498(452-549)
Rat	F	i.v.	4/10	16-50	16-20	23(21-25)
Rat	M	i.v.	5/10	10-50	10-16	20(17-23)
Dog	M&F	p.o.	3/2	25-100	25-50	50*#
Dog	M&F	i.v.	3/2	15-30	15-20	20*

* gross estimate. LD50 not calculated.
# aqueous solution. When drug administered in capsules median lethal dose was over 200 mg/kg (no deaths at any of tested levels, 20-200 mg/kg).

H. Chronic Toxicity

Chronic studies were carried out in baboons, dogs, mice and rats. The studies of longest duration in each of these species are outlined below.

	*	**	***	****
Study:	18 Month Mouse	24 Month Rat	18 Month Dog	6 Month Baboon
Maximum Exposure Evaluated:	60 mg/kg/day for 18 months	60 mg/kg/day for 24 months	20 mg/kg b.i.d. for 18 months	15 mg/kg b.i.d. for 6 months
Animals/ Dose Level:	70/sex	50/sex	4/sex #	2/sex
Mode of Admin.:	diet	diet	tablets	fruit juice

* Charles River CD-1/ICR; 42-44 days of age at start
** Charles River Crl:COBS(WI)BR; 37-39 days of age at start
*** beagles; 7.8-14.3 kg at start
**** Senegalese; 5.5-10 kg 4 days prior to initiation of dosing
\# Not reflected in this number were an additional 2 dogs/sex which were added to the high dose group (only) for the purpose of an interim necropsy @ 12 months. One female and one male from this interim necropsy group plus one female and one male scheduled for terminal necropsy were not dosed during a 2 week recovery interval following 9 months of dosing to determine reversibility of ECG effects.

The only finding associated with treatment in the mouse was a slight reduction in body weight gain relative to controls. This effect was much more pronounced in rats where mean body weight decrement at conclusion of study ranged from 11-30% of control weight (dose-dependent effect with all dosage levels affected). An increased incidence of interstitial cell adenoma in testes at high dose levels in the rat was attributed to increased survival in that group. All of the flecainide-treated male groups had better survival (dose related) than the control male group. (An apparent improvement in female survival at the highest dosage level was of borderline significance). There was a dose-related increased incidence of urinary incontinence in the high and intermediate dosage male groups. There was a decreased incidence of focal degeneration and fibrosis of heart and of chronic nephritis in high dose males and females. A decreased incidence of pituitary chromophobe adenoma was recorded in all treated female groups (dose dependent). Overall incidence of tumor bearing animals was lower in these groups. In high dose females there was a decreased incidence of focal degeneration and hemmorhage of adrenal, and of mammary fibroadenomas.

There was one high dosage death in each of the non-rodent studies. Toxic signs were not observed preceding death and tissue examinations were unremarkable. Expected (and reversible) EKG changes were noted in dogs (EKGs not recorded in baboons). Other findings in dogs included peripheral flushing (all treated groups) which gradually decreased in occurrence after the initial 3-4 months of study and a mean body weight loss or failure to gain weight which occurred at high and intermediate dosage levels during the last six months of study. Mild morphologic changes in the lung (focal inflammation and hemosiderin-containing macrophages) were present (as early as 12 months) in both the intermediate and high dosage levels. These changes were closely linked with elevation in CPK enzyme activity. Other than the one death there were no remarkable findings in baboons.

I. Effects on Reproduction

Segment II studies (for teratogenic potential) were carried out in mice, rats and rabbits.

Species	Route	Period of Admin.	Dosage Levels (mg/kg/day)	Females/ Dose Level
Mouse (OF1)	p.o.	gestation days 6-15	0,5,20,80	28
Mouse (OF1)	i.v.	gestation days 6-15	0,1,2.5,5	25-26
Rat (CRCD)	p.o.	gestation days 6-16	0,10,20,50	21-24
Rat (CRCD)	p.o.	gestation days 6-15	0,10,20,50	22-29
Rabbit (NZ*)	p.o.	gestation days 6-18	0,10,20,25,30,35	15-26
Rabbit (NZ*)	i.v.	gestation days 6-18	0,1,2,4	16-19
Rabbit (DB#)	p.o.	gestation days 6-18	0,10,20,30	15-17

* NZ = New Zealand # DB = Dutch Belted

Adverse effects were observed with oral administration in New Zealand rabbits with increased resorptions noted at 25 or more mg/kg and teratogenic findings (clubbed paws, heart changes, sternebral and vertebral abnormalities) observed at 30 or more mg/kg. Similar findings were not reported with the i.v. route of administration or with oral dosing in the Dutch Belted rabbit. In both rat studies the highest dosage level was associated with a significant increase in the number of fetuses with one or more bipartite bodies in the vertebrae.

A combined fertility/general reproduction and peri/post-natal study was carried out in the (CRCD) rat (up to 50 mg/kg/day administered from before breeding to weaning). There were no adverse effects on fertility, reproductive performance, late fetal development or growth of pups during lactation. The F1

pups (exposed in utero during gestation and during lactation via milk) exhibited no adverse effects of flecainide on growth, CNS development or subsequent reproductive performance (second generation study in which no further treatment was administered).

J. Mutagenicity

Neither Ames test nor mouse lymphoma test (up to 8,000 mcg/plate in former, up to 500 mcg/ml in latter; both tests conducted with and without metabolic activation) revealed a clearly significant effect of flecainide on the number of revertants, although an equivocal finding (max effect at 4,000 mcg/plate with less than 100% increase in revertants) with Salmonella strain TA 1535 (only without metabolic activation) was reproducible. Nor was the drug associated with cytogenetic abnormalities in a bone marrow cytogenetic study in which rats were dosed for five days at levels of up to 20 mg/kg/day.

V. Medical

The approval of flecainide rests on the analysis of 38 studies in 923 patients and 354 subjects. A total of 546 patients have been exposed to the drug for at least 30 days, 274 of these patients for at least one year and 99 patients for at least two years. Information on clinical pharmacology was obtained in 26 studies, and information on efficacy and safety was obtained in 12 studies.

Safety information was obtained in an additional 201 patients in clinical studies outside the U.S. (Germany, France, United Kingdom and Norway). Sixty-nine (34%) of these patients were followed for more than one year.

The approval is further supported by analysis of spontaneous adverse reaction reporting in the United Kingdom where flecainide has been marketed since September 1983 with an estimated 1,300 patient-years exposure, and in Germany where flecainide has been marketed since September 1982 with an estimated 65,000 patient-years exposure.

A. Clinical Pharmacology and Metabolism

A list of the studies in which the clinical pharmacology and metabolism of flecainide has been studied is contained in the following Table. This Table lists the purposes, investigator, study design, number of subjects or patients, and the duration of therapy and doses used in each study.

The clinical electrophysiology of flecainide has been defined by both the intravenous and oral routes in studies conducted in the U.S. In addition, a number of studies have been conducted outside the U.S. and reported in the published literature. The clinical hemodynamic effects of the drug have been investigated in patients after single intravenous doses and in both patients and subjects after single oral doses. Assessment of the effects of flecainide on left ventricular function in patients has also been made in conjunction with some of the efficacy studies on the drug.

The pharmacokinetics, metabolism and bioavailability of flecainide have been defined in nine studies in healthy subjects and pharmacokinetics were determined in one multicenter study in patients with premature ventricular contractions. Additionally, the effects of renal insufficiency and congestive heart failure on the single dose kinetics of flecainide have been determined in separate studies in patients with each disease state.

Drug-drug interactions of flecainide have been systematically investigated in two studies in healthy subjects; one investigated the potential interaction with digoxin, and the other studied the effects of propranolol and flecainide when given concurrently.

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818V-001	Drug safety & pharmacokinetics in healthy male subjects	D. Hunninghake	Open	9 subjects	Single iv dose 2 @ 0.5 mg/kg over 5 min 2 @ 1.0 mg/kg over 5 min 2 @ 1.5 mg/kg over 5 min 2 @ 2.0 mg/kg over 5 min 1 @ 5,7.5,10,12.5 mg at 2 hour intervals
R-818V-003	Safety & effect of flecainide on cardiodynamics in patients undergoing diagnostic catheterization	P. Miller	Open	12 patients	Single iv dose 4 @ 0.5 mg/kg over 5-10 min 2 @ 0.75 mg/kg over 5-10 min 3 @ 1.0 mg/kg over 5-10 min 3 @ 1.5 mg/kg over 5-10 min
R-818V-005	Determine rate & extent of absorption of flecainide. Obtain pharmacokinetic data, assess safety & tolerance in healthy male subjects	G. Lewis	Open	16 subjects	Single oral & iv doses 4 @ 60 mg oral 7 days later 60 mg iv 4 @ 120 mg oral 7 days later 120 mg iv 4 @ 180 mg oral 6 weeks later 200 mg oral 4 @ 240 mg oral only
R-818V-015	Effect of flecainide on intracardiac conduction system & sinus node function when administered as a single intravenous dose to patients	R. Helfant	Open	15 patients	Single iv doses of 1.0 mg/kg administered over 5-10 min.

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONTINUED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-018	Determine plasma levels of flecainide during seven days of oral dosing. Assess multiple-dose pharmacokinetics of flecainide. Determine safety & tolerance of multiple oral doses of flecainide in subjects	G. Lewis	Open	16 subjects	Seven days of dosage 4 @ 80 mg bid 4 @ 120 mg bid 4 @ 150 mg bid 4 @ 180 mg bid
R-818V-022	Determine the effect of intravenous flecainide on right and left ventricular performance using radionuclide angiography in patients with suspected or diagnosed heart disease	R. Helfant M. Bodenheimer	Open	20 patients	Single iv dose 4 @ 1.0 mg/kg over [illegible] min 5 @ 1.5 mg/kg over 5-13 min 10 @ 2.0 mg/kg over 5-13 min 1 @ 0.7 mg/kg over 5-13 min
R-818V-023	To compare the effects of flecainide & vehicle on left ventricular function using catheter tip sensors in patients with suspected or diagnosed left ventricular disease.	M. Hodges	Double-blind vehicle controlled parallel study	2 patients	Single iv dose 1 @ 2.0 mg/kg 1 @ vehicle control

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONTINUED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-024	Compare the effects of oral flecainide and placebo on left ventricular function using non-invasive techniques.	M. Hodges	Double-blind, placebo-controlled two period crossover	10 subjects 20 patients	Single oral dose 250 mg
R-818-026	Compare relative rate & extent of flecainide absorption between a tablet & capsule formulation.	G. Lewis	Open, randomized two period crossover	16 subjects	Single dose 200 mg of each formulation
R-818-030-01	Dose ranging efficacy of oral flecainide in patients with PVCs. Plasma pharmacokinetics during washout. Short-term (2 weeks) efficacy.	J. Anderson	Open, placebo-controlled.	9 patients	100 mg bid for 3 days; then 200 mg bid for 3 days, if needed; then 250 mg bid for 3 days, if needed. Two-weeks of bid dosage with efficacious regimen.
R-818-030-02	Dose ranging efficacy of oral flecainide in patients with PVCs. Plasma pharmacokinetics during washout. Short-term (2 weeks) efficacy.	M. Hodges	Open, placebo-controlled.	10 patients	100 mg bid for 3 days; then 200 mg bid for 3 days, if needed; then 300 mg bid for 3 days, if needed. Two-weeks of bid dosage with efficacious regimen.

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONTINUED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-030-03	Dose ranging efficacy of oral flecainide in patients with PVCs. Plasma pharmacokinetics during washout. Short-term (2 weeks) efficacy.	R. Woosley	Open, placebo-controlled.	11 patients	100 mg bid for 3 days; then 200 mg bid for 3 days, if needed; then 250 mg bid for 3 days, if needed. Two-weeks of bid dosage with efficacious regimen.
R-818-038	Determine effect of chronic renal impairment on flecainide elimination. Assess influence of hemodialysis on flecainide elimination. Determine if dosage adjustments are necessary in this patient population.	R. Cutler	Open	10 patients with varying degrees of chronic moderate renal failure. 10 patients with end stage renal disease	Single oral dose 200 mg
R-818-039	Pharmacokinetics & cardiodynamics of flecainide in healthy subjects & in patients with congestive heart failure.	J. Francioso	Open	9 subjects 10 patients	Single oral dose 200 mg

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONTINUED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-041	Effects of oral flecainide & propranolol administered alone & concurrently on cardiac function in healthy male subjects.	J. Holtzman	Open	10 subjects	Total of nine days of dosage 200 mg bid
R-818-045	Effects of flecainide on plasma digoxin levels when given concurrently to subjects.	G. Lewis	Open	15 subjects	Five days of oral dosage 200 mg bid
R-818-049	Comparative oral absorption of three flecainide dosage formulations & the effect of food on drug absorption.	A. Cohen	Open, randomized four period crossover	18 subjects	Single dose 200 mg of each formulation; 200 mg as tablet with food
R-818-050-03	Metabolic disposition of carbon-14 labeled flecainide in subjects	A. Cohen	Open	4 subjects	Single dose 200 mg ^{14}C-labeled flecainide

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONTINUED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-041	Effects of oral flecainide & propranolol administered alone & concurrently on cardiac function in healthy male subjects.	J. Holtzman	Open	10 subjects	Total of nine days of dosage 200 mg bid
R-818-045	Effects of flecainide on plasma digoxin levels when given concurrently to subjects.	G. Lewis	Open	15 subjects	Five days of oral dosage 200 mg bid
R-818-049	Comparative oral absorption of three flecainide dosage formulations & the effect of food on drug absorption.	A. Cohen	Open, randomized four period crossover	18 subjects	Single dose 200 mg of each formulation; 200 mg as tablet with food
R-818-050-03	Metabolic disposition of carbon-14 labeled flecainide in subjects	A. Cohen	Open	4 subjects	Single dose 200 mg ^{14}C-labeled flecainide

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONTINUED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-053-01	Effects of oral flecainide on the inducibility of ventricular tachycardia during electrophysiologic provocation	J. Stewart	Open	2 patients	200 mg tid on day 1, then bid for three to five days
R-818-053-02	Effect of oral flecainide on the inducibility of ventricular tachycardia during electrophysiologic provocation	J. Anderson	Open	15 patients	200 mg tid on day 1, then four to six days of therapy 200 mg bid
R-818V-054-01	Effects of iv flecainide on left ventricular function (invasive).	B. Singh	Double-blind randomized vehicle controlled parallel study	18 patients	Single iv dose 6 @ 1.0 mg/kg 6 @ 2.0 mg/kg 6 on vehicle
R-818V-054-02	Effects of iv flecainide on left ventricular function (invasive).	P. Troup	Double-blind randomized vehicle controlled parallel study	2 patients	Single iv dose 1 @ 2.0 mg/kg 1 @ vehicle control

CLINICAL PHARMACOLOGY AND METABOLISM STUDIES (CONCLUDED)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818V-058-01	Effects of iv flecainide on left ventricular function in patients with reduced ejection fractions (25-45%) (invasive)	B. Singh	Open	10 patients	Single iv dose 5 @ 1.0 mg/kg 5 @ 2.0 mg/kg
R-818-061-01	Plasma level-dose proportionality and absolute bioavailability in healthy male subjects	M. Zinny	Open, randomized four period crossover	12 subjects	Single oral doses of 100, 200, and 300 mg as tablet when fasting and single iv dose of 100 mg
81-152-PRO-BE-002	Effect of food and antacid on flecainide absorption in subjects	T. Tjandramaga	Open, three period crossover	10 subjects	Single oral doses of 200 mg as tablet when fasting, with food, and with antacid

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Vik-Mo H, Ohm OJ, Lund-Johansen P: Electrophysiologic effects of flecainide acetate in patients with sinus nodal dysfunction. Am J Cardiol 50:1090-1094, 1982.

1. Clinical Electrophysiology

a. Routine Electrophysiological Studies

Studies carried out to determine the electrophysiologic effects of flecainide have shown the following:

- Marked effects on conduction in all parts of the heart which are most prominent in the His-Purkinje system and ventricle.

- Effects on refractoriness are less prominent than those on conduction.

These effects of intravenous flecainide on the intracardiac conduction system were examined in an open-label study of 15 patients with known or suspected cardiac disease, who were undergoing diagnostic catheterization (Study 015). Flecainide lengthened the conduction intervals (AH, HV, and PA), but only demonstrated statistically significant increases in the AH and HV intervals at 20 minutes postdosing (Table 2). Plasma flecainide levels at this time averaged 502 ng/ml (range 134-1784 ng/ml).

These observations were confirmed in a published open-label study of 47 patients using intravenous doses of 2.0 mg/kg (Hellestrand et al). All patients were undergoing routine electrophysiological study for investigation of symptoms or evidence of recurrent arrhythmias or cardiac conduction disturbances. No change was noted in sinus cycle length; PA, AH and HV intervals were prolonged significantly. The duration of the QRS complex increased an average of 23% (range 0% to 79%). The QT interval showed a slight prolongation, but this was entirely due to the increase in QRS duration. Changes in refractoriness were small and were significant only in the ventricular effective refractory period. Plasma flecainide levels, obtained during the time electrophysiological measurements were being made, averaged 335 ng/ml (range 85-785 ng/ml).

Findings were similar in an open-label study of 27 patients undergoing diagnostic catheterization conducted in Germany (Seipel et al). The effects of flecainide in patients with normal baseline values are presented in Table 3. Dose-related increases in AH and HV intervals were observed after intravenous injection of 1.0 mg/kg, or 2.0 mg/kg; increases were also noted in HRA-A and V-RVA intervals, although these did not appear to be particularly dose-related. Only the change in ventricular effective refractory period was statistically significant at both doses. In contrast, there were only small and often

insignificant increases (5% to 15% of control values) in the refractoriness of the atria and AV node. Average plasma flecainide levels obtained with the 1.0 mg/kg dose (n=17) were 366 ± 161 ng/ml at 5 min. and 146 ± 52 ng/ml at 20 min. After 2 mg/kg given as a bolus (n=6) levels were 851 ± 17 ng/ml at 5 min. and 306 ± 4 ng/ml at 20 min. Four patients received the 2.0 mg/kg dose as a 1.0 mg/kg bolus plus a 1.0 mg/kg infusion given over 20 minutes. Plasma flecainide levels from this regimen were 397 ± 266 ng/ml after 5 minutes and 343 ± 81 ng/ml at 20 minutes. Initial plasma levels from 1.0 mg/kg doses and all levels from 2.0 mg/kg doses are within the range accepted as effective for suppression of PVCs (200-1,000 ng/ml). These investigators found no significant effects on sinus node function in this study even in six patients with sinus node dysfunction. However, a Norwegian study found that flecainide depressed sinus node function in 11 patients with pre-existing sinus node dysfunction (Vik-Mo, et al).

The effects of oral flecainide were also studied in 14 patients with inducible ventricular arrhythmias (Study 053-02). Therapeutic response in this open-label study was evaluated using programmed electrical stimulation and effects on intracardiac conduction were measured. Flecainide was given orally, 200 mg or 150 mg bid, for 4-6 days after baseline EP testing. Plasma levels of flecainide at the time of repeat testing averaged 773 ± 222 ng/ml, comparable to those associated with suppression of PVCs. Flecainide significantly increased intracardiac conduction times as well as the ventricular refractory period (Table 4). This indicates that the electrophysiologic effects of flecainide are similar by both the oral and intravenous routes.

As a consequence of its effects on intracardiac conduction, flecainide produces dose-related effects on intervals measured on the surface electrocardiogram. This is illustrated by the changes in ECG intervals (both as absolute values and percentages) produced after three days of flecainide therapy in the dose-ranging trial (Study 030) at 100 mg bid, 200 mg bid and 250 or 300 mg bid. An analysis of the mean interval changes on day three of dosing at each dose level is displayed in Table 5 for the 10 patients who received all three dose levels.

These data indicate that prolongations of the PR and QRS intervals were experienced which became more pronounced as the dose was increased every three days. The QT interval remained fairly constant after an initial small increase at 100 mg bid; JT interval (QT-QRS), however, increased slightly at 100 mg bid and 200 mg bid, but to a lesser extent at the highest dose. No patients discontinued from the study because of interval changes.

It may be concluded that, in initial flecainide therapy, an apparent positive relationship exists between the daily dose and the increases produced in PR and QRS intervals.

Flecainide has profound effects on myocardial conduction, with minimal influence on refractoriness; in accord with its in vitro electrophysiological actions, it affects primarily depolarization, with scant effects on repolarization. As with all Class I agents, its effects on conduction are magnified when cardiac conduction is impaired.

Table 2

Study: B-8.8-015-01
Investigator: R. Melfant, MD

EFFECT OF FLECAINIDE, 1.0 mg/kg IV ON INTRACARDIAC CONDUCTION IN PATIENTS

MEASUREMENT	CONTROL	MEAN DIFFERENCE FROM CONTROL ± STD DEV		
		Minutes Post Dose		
		10	20	30
PA INTERVAL (msec)	24.5	n = 13 0.69 ± 7.50	n = 14 0.93 ± 7.59	n = 13 1.46 ± 6.35
AH INTERVAL (msec)	97.3	n = 14 5.07 ± 10.25	n = 15 6.13 ± 8.68*	n = 15 3.93 ± 8.66
HV INTERVAL (msec)	47.3	n = 14 4.36 ± 7.84	n = 15 6.13 ± 8.93*	n = 15 5.00 ± 9.82

*Significantly different from control, P<0.05

INVESTIGATOR: L. SEIFEL, MD

Table 3

EFFECTS OF FLECAINIDE, 1.0 OR 2.0 MG/KG IV, ON INTRACARDIAC CONDUCTION AND REFRACTORINESS IN PATIENTS WITH NORMAL BASELINE VALUES

INTRAVENOUS DOSE MG/KG	N	Percentage Change From Control Values							
		HRA-A	A-H	H-V	V-RVA	ERP-A	FRP-AVN	ERP-AVN	ERP-V
1.0	12	+10.4	+13.5	+15.7	+29.1*	+4.3	+8.0	+15.0	+5.6
	P =	<0.05	<0.001	<0.001	<0.005	NS	<0.05	NS	<0.05
2.0	6	+9.0	+24.4	+40.2	+16.5	+16.0	+3.4	+12.4**	+10.5
	P =	NS	<0.005	<0.001	<0.05	<0.01	NS	NS	<0.01

*N=5
**N=4

HRA-A = CONDUCTION TIME, HIGH TO BASAL RIGHT ATRIUM
A-H = CONDUCTION TIME, BASAL ATRIUM TO HIS BUNDLE
H-V = CONDUCTION TIME, HIS BUNDLE TO RIGHT VENTRICULAR ACTIVATION
V-RVA = CONDUCTION TIME, VENTRICULAR SEPTAL ACTIVATION TO DEPOLARIZATION OF RIGHT VENTRICULAR APEX
ERP-A = EFFECTIVE REFRACTORY PERIOD OF ATRIUM
FRP-AVN = FUNCTIONAL REFRACTORY PERIOD OF AV NODE
ERP-AVN = EFFECTIVE REFRACTORY PERIOD OF AV NODE
ERP-V = EFFECTIVE REFRACTORY PERIOD OF VENTRICLE

Table 4

Study: B-818-853-02
Investigator: J. Anderson, MD

ELECTROPHYSIOLOGICAL EFFECTS OF FLECAINIDE, PO, IN PATIENTS WITH VENTRICULAR TACHYCARDIA

	n=	MEAN (msec) ± Std Dev	
		Control	Flecainide
Sinus Cycle	14	965 ± 207	942 ± 190
Sinus Cycle Length Pacing&	13	600	600
PA Interval	13	38 ± 11	38 ± 10*
PA Interval, Pacing	13	39 ± 11	37 ± 8
AH Interval	12	116 ± 34	142 ± 31**
AH Interval, Pacing	12	113 ± 35	144 ± 40
HV Interval	12	50 ± 11	70 ± 22**
HV Interval, Pacing	12	53 ± 12	73 ± 24
Atrial ERP	13	283 ± 28	308 ± 55
AVN ERP	13	456 ± 142	611 ± 108
Ventricular ERP	13	263 ± 27	288 ± 25**

& Pacing cycle length, 600 msec
* significantly different from control, $p<0.05$
** significantly different from control, $p<0.01$
*** significantly different from control, $p\leq0.001$

Table 5

Absolute and Percent Changes for ECG Intervals after Three Days of Therapy in Study 030 Dose-Ranging Study for the Ten Patients Who Received all Three Dose Levels

Mean Percent Increase From Baseline				Mean Absolute Increase From Baseline (sec)		
	Dose (mg bid)			Dose (mg bid)		
	100	200	250/300	100	200	250/300
PR	7.9%	14.9%	24.2%	0.013	0.024	0.038
QRS	12.8%	17.9%	27.1%	0.010	0.014	0.022
QT	3.9%	6.1%	7.0%	0.015	0.022	0.026
JT*	1.4%	2.8%	1.4%	0.005	0.008	0.004

*JT = QT minus QRS

b. Studies Using Programmed Electrical Stimulation (PES)

A limited amount of data are available on the ability of oral flecainide to prevent the induction of ventricular tachycardia (V-Tach) during programmed electrical stimulation (PES). A number of investigators, at their option, have studied the effect of multiple oral doses of flecainide on the inducibility of V-Tach upon retesting after institution of therapy, under open-label protocol R-818-057 Amended. Results from this show that (Table 6) 7/23 patients were fully protected, 7/23 were partially protected and 9/23 were fully inducible after flecainide. Fifteen of the 23 patients were discharged on flecainide. Mean plasma levels (Table 6) were within the therapeutic range and did not differ between responders and partial or non-responders.

Seventeen patients with inducible ventricular tachycardia due to a variety of cardiac diagnoses were studied under protocol R-818-053 (Table 6). Experience in this open-label study was slightly more favorable. Ventricular tachycardia was fully prevented in 9/17 patients, partially prevented in 4/17 patients and was fully inducible in 4/17 patients after four to six days of multiple dose therapy with flecainide. Ten of the 17 patients continued long term flecainide treatment. Again plasma levels of flecainide did not differ significantly between groups (Table 6).

From the experience in these two studies, oral flecainide would appear to be effective in preventing the induction of ventricular tachycardia in approximately 40% (range 30%-53%) of patients, and partially effective in another 25% (range 24-26%) of patients. These results in this procedure compare very favorably with the experience with other Class I drugs.

2. Clinical Hemodynamics

Hemodynamic studies on flecainide have shown the following:

- Flecainide possesses a measurable negative inotropic effect.
- In healthy subjects or in the compensated patient, overall left ventricular pump function is maintained after flecainide administration.
- Flecainide has no significant effects on systemic vascular resistance.

TABLE 6

EFFECT OF ORAL FLECAINIDE ON INDUCIBILITY OF VENTRICULAR TACHYCARDIA BY PROGRAMMED ELECTRICAL STIMULATION

STUDY NO	RESPONSE	NO. PTS / PATIENTS STUDIED	TOTAL DAILY DOSE MEAN ± SD (range)	DAYS ON FLECAINIDE PRIOR TO PES MEAN ± SD (range)	PLASMA LEVEL AT TIME OF PES NG/ML MEAN ± SD (range)	NO. PTS DISCHARGED ON FLECAINIDE
R-818-057* Amended	V-TACH FULLY PREVENTED	7/23	286 ± 69 (200-400)	8.9 ± 1.8 (6.0-11.0)	626 ± 239† (365-1015)	7
	V-TACH PARTIALLY PREVENTED	7/23	317 ± 41† (300-400)	8.0 ± 3.8 (1.0-14.0)	651 ± 252 (252-1045)	7
	FAILURE	9/23	300 ± 87 (200-400)	10.2 ± 5.5 (3.0-17.0)	534 ± 277 (208-1112)	5
R-818-053**	V-TACH FULLY PREVENTED	9/17	289 ± 105 (200-400)	4.7 ± 0.8 (4.0-6.5)	769 ± 240 (377-1081)	8
	V-TACH PARTIALLY PREVENTED	4/17	350 ± 191 (200-600)	5.1 ± 0.8 (4.5-6.0)	881 ± 252 (654-1152)	2
	FAILURE	4/17	325 ± 96 (200-400)	3.8 ± 1.2 (2.0-4.5)	705 ± 56 (654-755)	0

*MULTIPLE INVESTIGATORS

**INVESTIGATORS - J. STEWART, MD; J. ANDERSON, MD

†N=6

Single Dose Studies. Several single dose IV studies were conducted in patients to determine the effect of flecainide on left ventricular function (Studies 003, 022, 023, 054). Table 7 shows results from a double-blind vehicle-controlled study which shows a slight negative inotropic effect for flecainide under these conditions. In this controlled study of patients undergoing diagnostic catheterization, the mean changes from baseline for hemodynamic parameters did not differ significantly from those of the vehicle group at any time interval (p greater than 0.05). However, mean ejection fractions tended to decrease more in patients receiving flecainide, and the direction of the changes in other indices (PAWP and LVEDP) was consistent with a negative inotropic effect for the drug compared with drug vehicle.

A similar but open-label, study (058) in patients undergoing diagnostic catheterization, who had impaired left ventricular function demonstrated comparable effects on hemodynamic parameters (Table 8). Changes from baseline in ejection fraction in this study, which lacked a vehicle control group, were statistically significant.

A double-blind noninvasive study (024) comparing the effects of oral flecainide and placebo on left ventricular function (using M-mode and 2-D echocardiography and systolic time intervals) in subjects and patients with cardiac disease confirmed that flecainide reduces myocardial contractility slightly, but also showed that overall pump function is maintained. M-mode indices and systolic time interval changes were consistent with a mild negative inotropic effect. Changes in ejection fraction were most pronounced at early time periods when plasma levels were rising.

Multiple Dose Studies. To substantiate the results of the single dose studies, noninvasive multiple dose hemodynamic measurements were obtained as adjuncts to the dose ranging studies (030-01,02,03) in patients with PVCs. Table 9 shows the results of these studies, which showed no effect on ejection fraction as measured echocardiographically.

Patients with radionuclide ejection fractions (RNEFs) less than 30% at baseline were required to have followup ejection fractions performed at subsequent visits in the acute and chronic study of ventricular tachycardia (057 amended). Multiple dose therapy with flecainide did not change the mean ejection fraction in this group of patients during three months of monitoring (Table 10).

TABLE 7

Study: R-818V-054-02
Investigator: B.N. Singh, MD, D.Phil.

Hemodynamic Effects of Flecainide in Patients Determined During Diagnostic Catheterization - Double-blind Study With Vehicle Control

	Mean ± Standard Deviation		
	Vehicle (N=6)	Flecainide 1 mg/kg (N=6)	Flecainide 2 mg/kg (N=6)
Cardiac output (L/min)--baseline	5.40 ± 1.1	5.35 ± 0.8	5.48 ± 1.3
30 minutes after dose	4.80 ± 0.8	4.98 ± 0.7	5.05 ± 1.6
Systemic vascular resistance (dynes/sec/cm)--baseline	1451 ± 397	1456 ± 531	1387 ± 446
30 minutes after dose	1595 ± 433	1518 ± 385	1573 ± 684
Left ventricular ejection fraction--baseline	0.60 ± 0.07	0.61 ± 0.15	0.65 ± 0.06
20 minutes after dose	0.58 ± 0.06	0.56 ± 0.13	0.59 ± 0.06
Left ventricular end diastolic pressure (mmHg)--baseline	19.7 ± 4.2	20.0 ± 5.2	15.2 ± 4.1
30 minutes after dose	18.5 ± 5.4	21.5 ± 4.9	16.5 ± 4.6
Pulmonary wedge pressure (mmHg)--baseline	11.5 ± 4.2	12.2 ± 1.6	11.0 ± 2.0
30 minutes after dose	10.5 ± 4.3	13.7 ± 3.3	11.5 ± 3.3

None of the differences is significantly different ($p>0.05$) from those of the vehicle group.

TABLE 8

Study: R-818V-058-02
Investigator: B.N. Singh, MD, D.Phil.

Hemodynamic Effects of Flecainide in Patients With Reduced Ejection Fractions Determined During Diagnostic Catheterization - Open Label Study Without Vehicle Control

	Mean ± Standard Deviation	
	Flecainide	
	1 mg/kg (N=5)	2 mg/kg (N=5)
Cardiac output (L/min) -- baseline	4.68 ± 0.34	5.00 ± 0.84
30 minutes after dose	4.25 ± 0.31†	4.44 ± 1.00*
Systemic vascular resistance (dynes/sec/cm) before	1667 ± 315	1423 ± 323
30 minutes after dose	1984 ± 521	1635 ± 460
Left ventricular ejection fraction--baseline	0.33 ± 0.07	0.32 ± 0.06
20 minutes after dose	0.28 ± 0.07*	0.27 ± 0.06*
Left ventricular end diastolic pressure (mmHg)--baseline	24.6 ± 9.0	20.2 ± 7.4
30 minutes after dose	25.6 ± 8.4	19.6 ± 6.0

*$p<0.01$, significantly different compared to predose values
†$p<0.05$, significantly different compared to predose values

Table 9

Effect of Flecainide on Ejection Fractions in Patients With PVCs After Daily Administration for 14 Days (Median Daily Dose of 400 mg)

Investigator	Study No	No. Patients	Ejection Fraction	
			Baseline	During Therapy
Anderson	030-01	9	63.0 ± 6.1[a]	65.2 ± 6.5[a]
Hodges	030-02	10	55.4 ± 12.0[a]	59.5 ± 9.3[a]
Duff	030-03	10	52.0 ± 8.0[b]	53.0 ± 12.0[b]

[a] Determined using M-mode echocardiography.
[b] Determined using 2-dimensional echocardiography.

Table 10

Study 057 Amended (Acute and Chronic Ventricular Tachycardia): Followup Results for Patients With Baseline RNEFs < 30%

	RNEF Values			
	Baseline	Week 1	Month 1	Month 3
	19%	11%	9%	11%
	22%	24%		25%
	17%	19%	[b]	
	29%	24%	31%	30%
	22%	25%	[b]	
	18%	19%	[b]	
	29%	30%		27%
	15%	16%		18%
	25%	41%[a]		34%
	20%	27%		21%
	23%	24%	17%	19%
	20%	28%	[b]	
	27%	22%		25%
	16			15%
Mean ± SD	21.6 ± 4.6	23.9 ± 7.3	19.0 ± 11.1	22.5 ± 7.0

[a] Week 2 RNEF
[b] Patient discontinued

3. Metabolism

Comprehensive metabolic information on flecainide has been obtained in humans and laboratory animals. Results and conclusions from studies in humans on the principal metabolic aspects of flecainide are summarized below by topic and in Drug-Drug Interactions. Results from metabolism studies in animals are summarized in the preclinical metabolism section.

Metabolic information for flecainide on absorption, pharmacokinetics, biotransformation, and excretion was obtained in nine open-label studies in healthy human subjects and pharmacokinetic data for patients with premature ventricular contractions were obtained in a multicenter efficacy study. In addition, the effects of renal failure and congestive heart failure on the pharmacokinetics and excretion of flecainide were assessed in separate single dose open-label studies in patients with each disease state. The potential metabolic interactions of flecainide with digoxin and propranolol were evaluated in separate multiple dose open-label studies in healthy subjects with each other drug.

a. Oral Absorption

After oral administration of the tablet formulation, peak plasma levels of flecainide are attained at about three hours, on average, with a range of one to six hours.

Figure 1 shows a plot of mean plasma levels versus time for 18 subjects after a single, 200 mg oral dose (Study R-818-049-01). As shown, plasma levels of flecainide increase promptly after dosage with the tablet, with a peak level attained at three hours. In comparison to a solution of flecainide in the same subjects, absorption is only slightly slower from the tablet than the solution, and the extent of absorption is comparable (not statistically different) for the two dosage forms (Table 11).

When plasma level data after oral dosage are compared to data after intravenous dosage in the same subjects (Study 005-01), the extent of absorption of unchanged flecainide into the systemic circulation (absolute bioavailability) was shown to be greater than 90% (Table 11). Thus, flecainide does not undergo any consequential presystemic biotransformation (first-pass effect) during absorption in humans. In addition, when flecainide is given with a meal, food does not appreciably affect absorption (Studies 049-01

Figure 1A (Electronic Plot)

Mean Plasma Flecainide Levels After 200 mg
Oral Dose (18 Subjects)
Bioavailability Study (049)

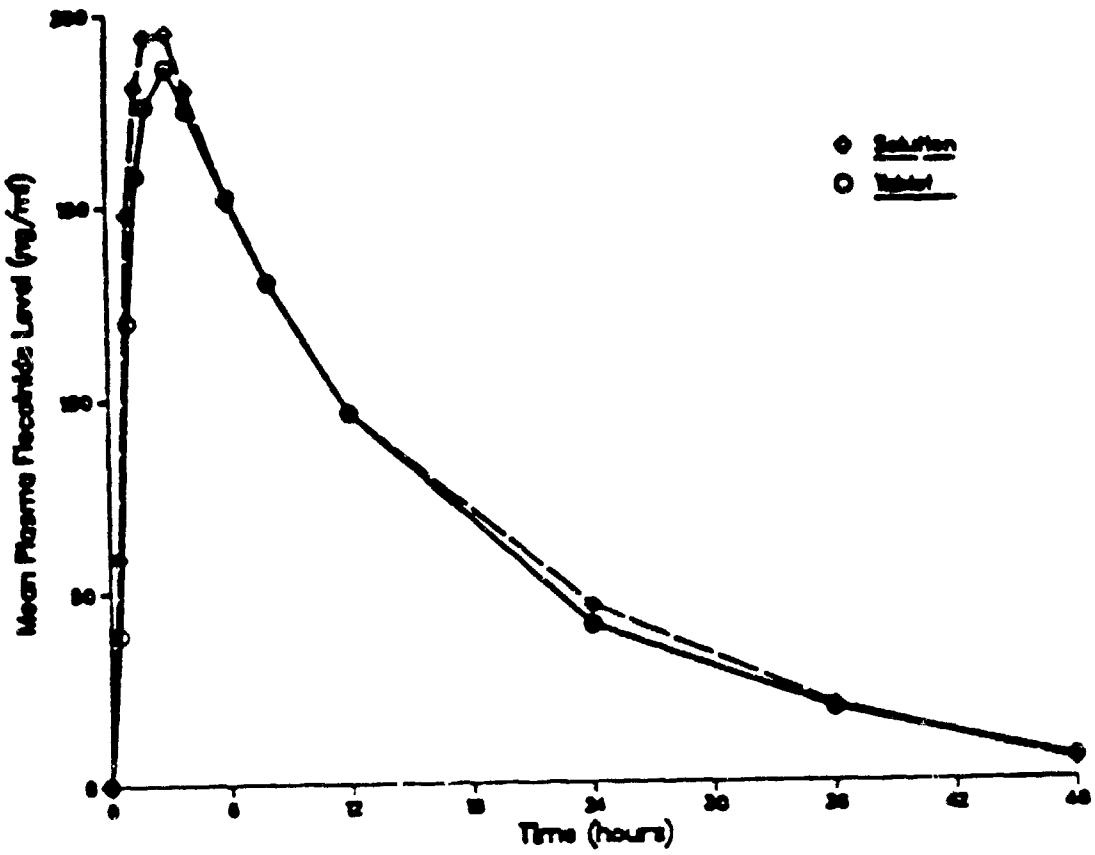


Figure 1B (Semilog Plot)

Mean Plasma Flecainide Levels After 200 mg
Oral Dose (18 Subjects)
Bioavailability Study (049)

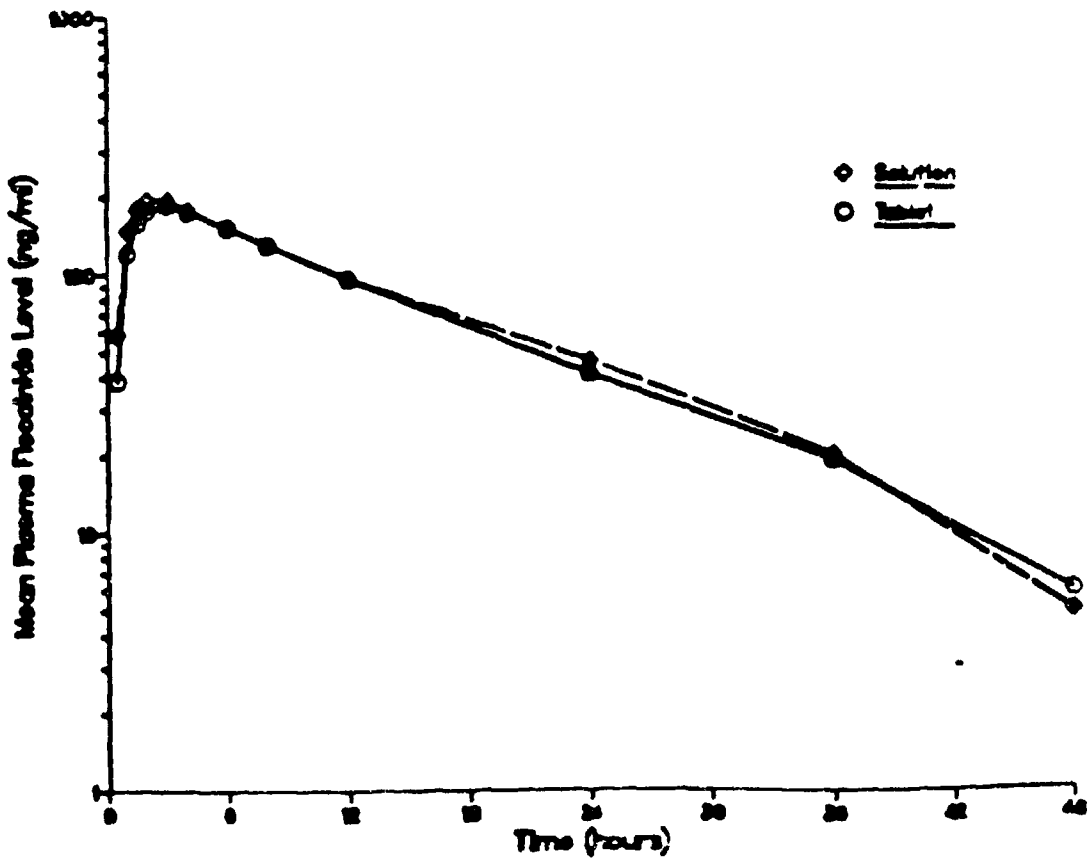


Table 11

Absorption in Healthy Human Subjects

Absolute (005) and Relative (049) Bioavailability Studies

Study Number	Dose[a]	N[b]	Formulation Reference	Time to Peak Level (hours)[c] Reference	Time to Peak Level (hours)[c] Solid Dosage Form	Plasma Half-life (hours)[c] Reference	Plasma Half-life (hours)[c] Solid Dosage Form	Plasma AUC (0 to Infinity) Ratio[c]: Solid Dosage Form/ Reference	Difference[d]
005	60 or 120 mg	8	IV	N/A	2.6±0.8	14±4	14±4	0.95±0.21	n.s.
049	200 mg	18	Solution	2.2±0.8	2.8±1.1	11±2	10±3	0.93±0.17	n.s.

[a] All single doses.

[b] All subjects were male.

[c] Mean ± Standard Deviation.

[d] Results of statistical comparison of treatment difference in plasma AUC values (n.s. indicates $p > 0.05$).

Figure 2A (Rectilinear Plot)

Mean Plasma Flecainide Levels After 200 mg Oral Dose With Meal and Fasted (18 Subjects) Bioavailability Study (049)

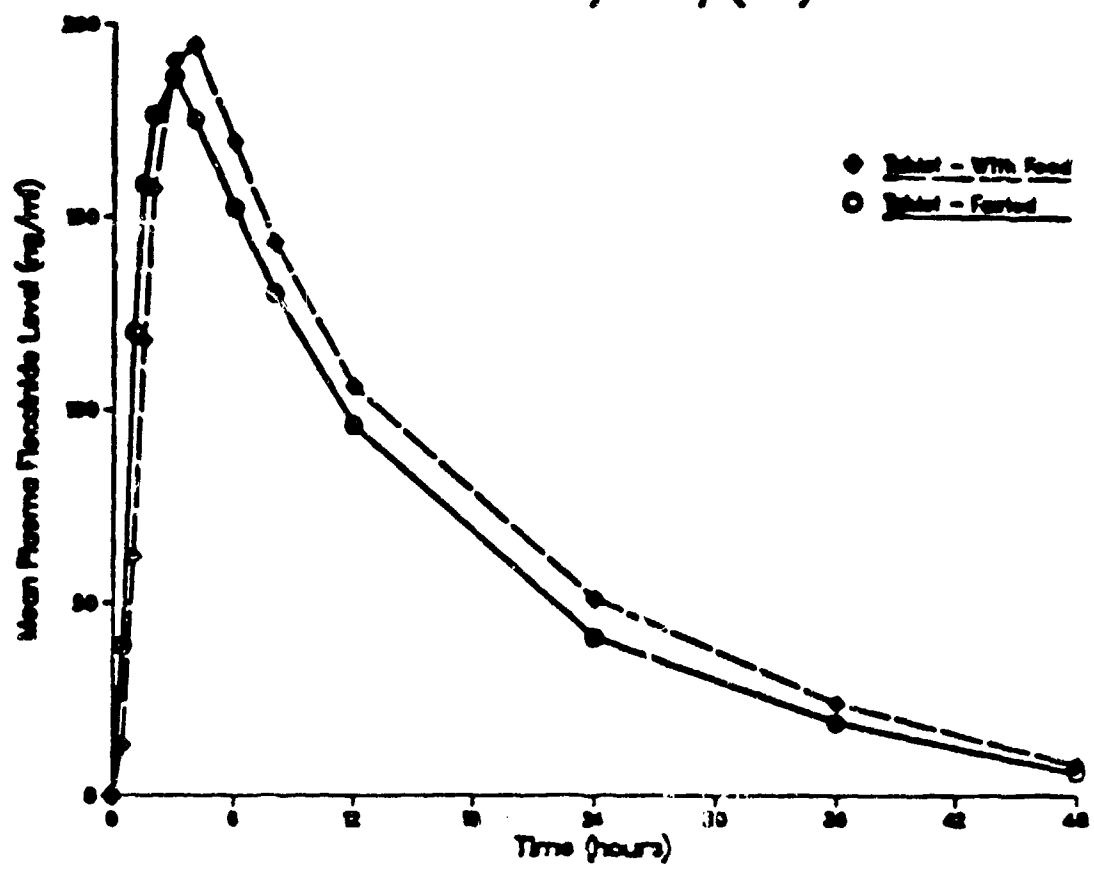


Figure 2B (Semilog Plot)

Mean Plasma Flecainide Levels After 200 mg Oral Dose With Meal and Fasted (18 Subjects) Bioavailability Study (049)

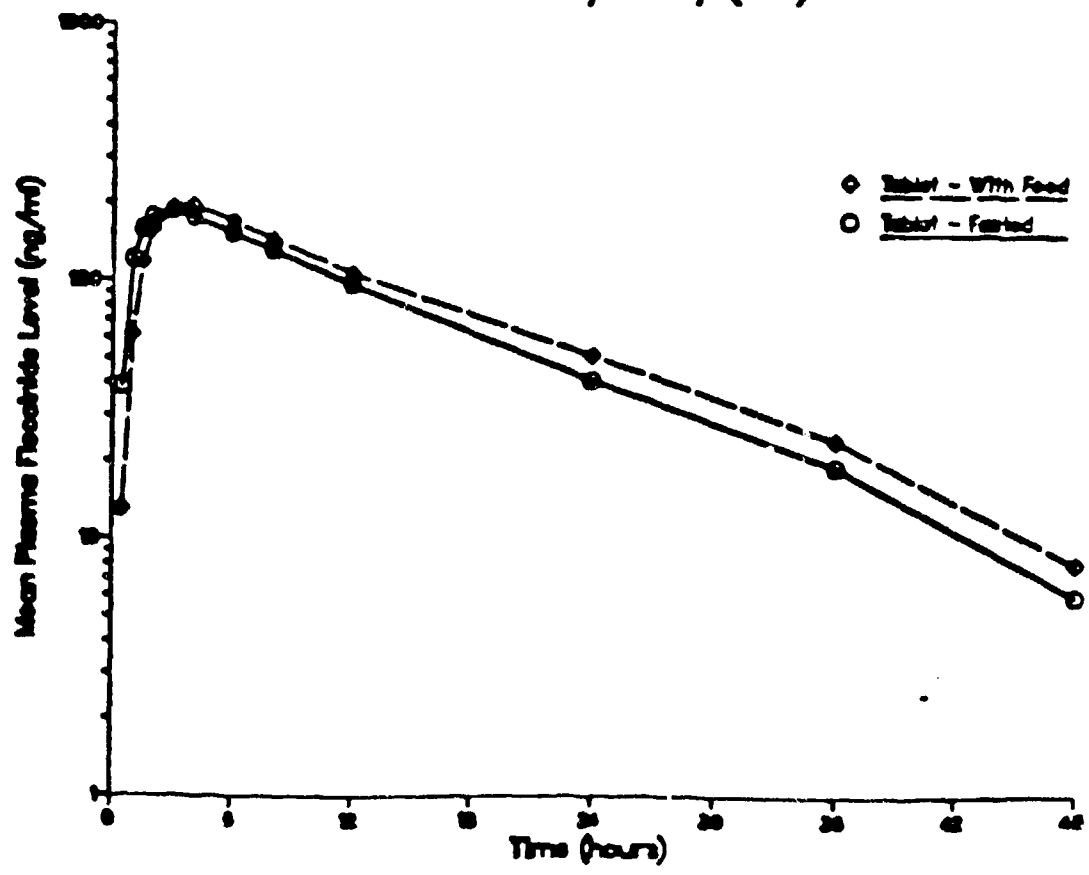


Figure 3A (Rectilinear Plot)

Mean Plasma Flecainide Levels After 200 mg
Oral Dose With Antacid and Fasted (9 Subjects)
Absorption Study (81-152)

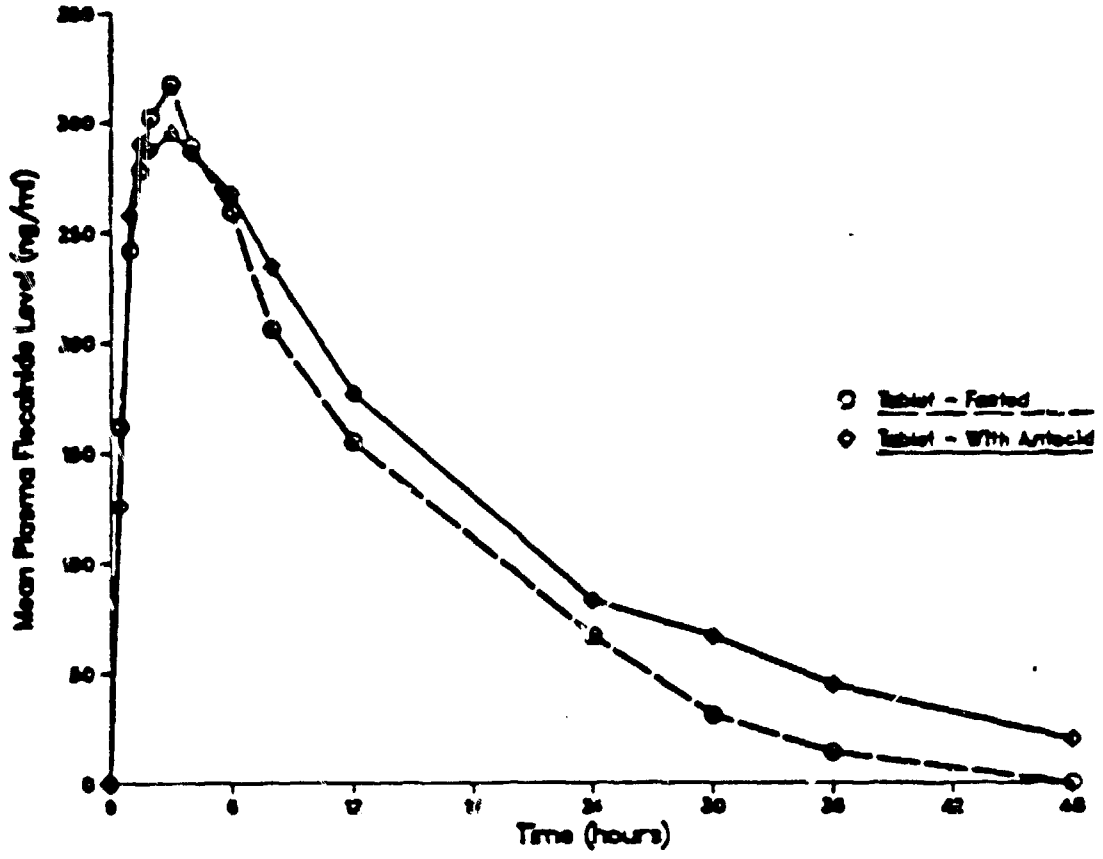
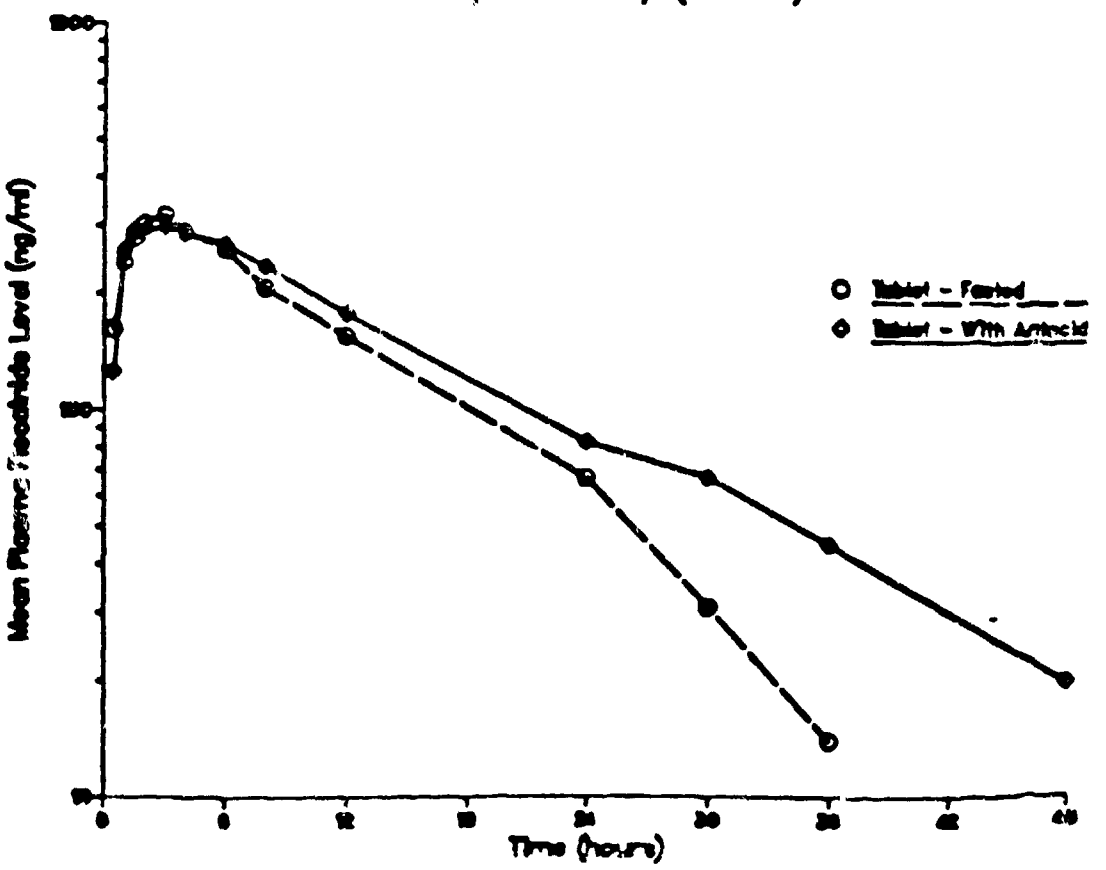


Figure 3B (Semilog Plot)

Mean Plasma Flecainide Levels After 200 mg
Oral Dose With Antacid and Fasted (9 Subjects)
Absorption Study (81-152)

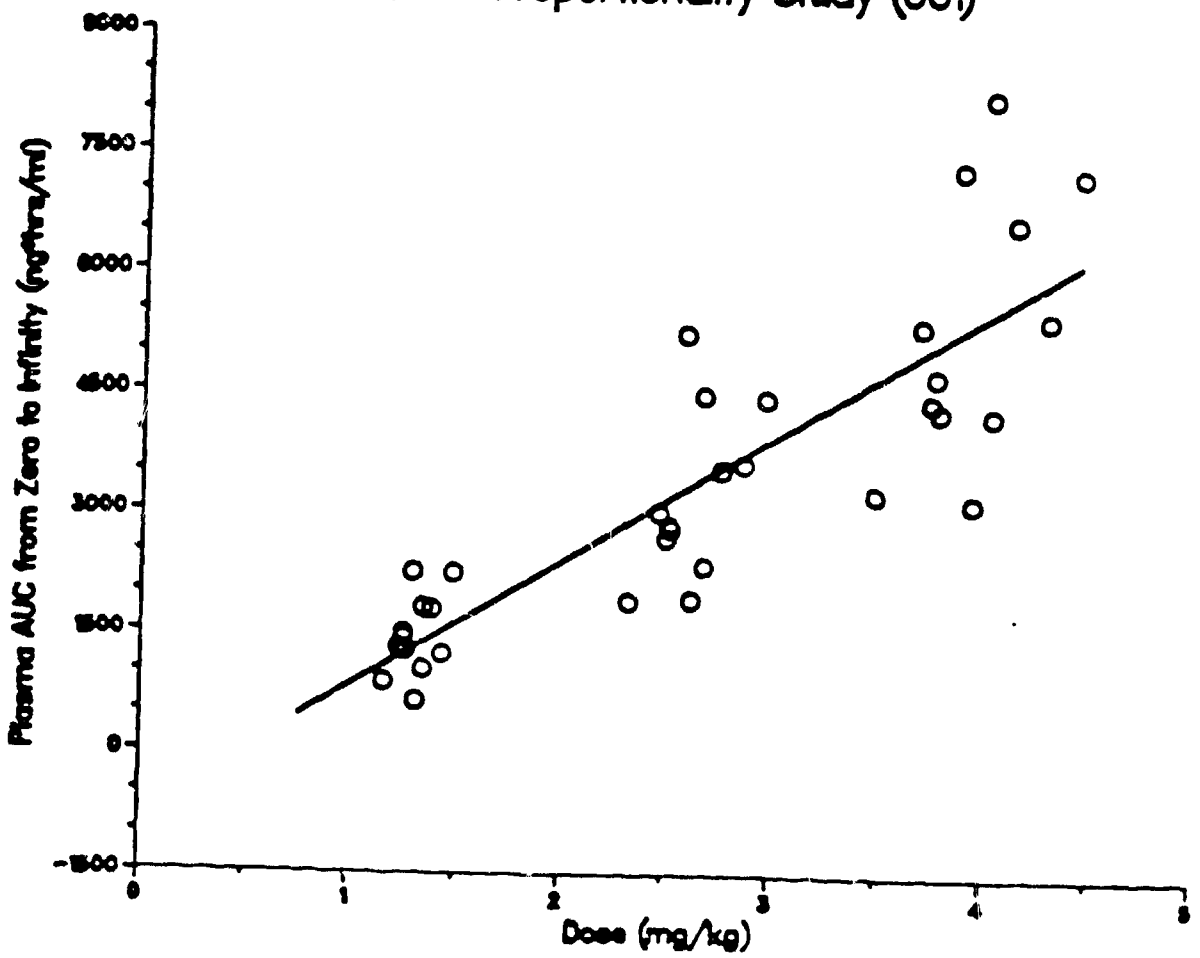


and 81-152-FRO-BE-002); the rate of absorption is only slightly slower, but the extent of absorption is not altered (Figure 2). Similar results (Figure 3) were found when flecainide is given with an antacid (Study 81-152-FRO-BE-002).

Within the range of usual therapeutic doses, plasma levels of flecainide are nearly proportional to dose levels. In an intrasubject comparison study (Figure 4), plasma levels (AUCs) of drug deviate upward from direct proportionality by only about 10 to 15% per 100 mg dose increment (Study 061-01).

Figure 4

Plasma AUC Versus Dose Following Single Oral Doses of 100, 200 and 300 mg (12 Subjects) Dose Proportionality Study (061)



b. Plasma Pharmacokinetics

For 30 patients with chronic PVCs and an average age of 54 years (Table 12), the apparent plasma half-life of flecainide averages about 20 hours, with a range of 12 to 27 hours, after multiple oral dosage regimens (Multicenter Study 030); eight of these patients had evidence of left ventricular dysfunction, including four with CHF. With the long half-life, plasma levels of flecainide are sustained, which allows twice daily dosage for treatment of most patients. Plasma pharmacokinetic data for younger healthy human subjects, (half-life and clearance) are summarized in Table 13.

With multiple dosage, flecainide accumulates to steady-state plasma levels within three to five days, based on its long half-life. This is illustrated in Figure 5. Shown are mean plasma levels of flecainide in four different subjects at two dose levels over a seven day period of dosage (Study 018-01); doses are indicated by the arrows and dosage regimens are either 180 mg bid or 80 mg bid. As expected, plasma levels increase to steady-state levels in a few days; this is evident by about the third day. In addition, measured plasma levels at steady-state are in good agreement with those predicted by superposition from first dose data. Also in this study (018-01), similar results were found for eight other subjects (four at 120 mg bid and four at 150 mg bid).

Once at steady-state with multiple dosage in patients, no more (or unexpected) accumulation of drug in plasma occurs during chronic therapy over long periods of time. For 78 patients with up to 43 months of flecainide therapy (mean, 19 months), trough plasma levels of flecainide remain reasonably constant with time on drug. Overall, regression analyses show a slight nonsignificant (p greater than 0.05) decrease in trough plasma level (adjusted for dose changes) over time. For a daily dose of 400 mg, the average decrease is estimated to be about 1.5 ng/ml per month on therapy.

Information (Table 13) on the relationship of the plasma pharmacokinetics of flecainide to dose is available from three studies (005-01, 018-01, and 061-01). In two intersubject comparison studies (005 and 018), plasma half-life is not related to dose level and plasma levels (AUCs) are proportional to dose. In study 018-01 (Table 13), plasma half-life is somewhat longer after 7 days of dosage (mean, 16 hours) than after the first dose (mean, 13 hours), but plasma clearance is not different after multiple dosage. In an intrasubject comparison study (061), plasma half-life tends to be somewhat longer with

increasing doses (Table 13) and plasma clearance appears to be modestly slower (on average, about 10% per 100 mg dose increase). In addition, plasma levels (AUCs) deviate slightly upwards from direct proportionality to dose (Figure 4). Overall, the data indicate that the plasma pharmacokinetics of flecainide are reasonably linear (not greatly affected by dose or plasma concentration) over the range of usual therapeutic doses.

The elimination of drug from plasma is only slightly reduced in older patients; when trough plasma levels are related to age, levels ranging up to about 1,500 ng/ml are only about 3 to 4 ng/ml greater per year of age, for a population of patients receiving an average total daily dose of about 300 mg and ranging in age from about 20 years to over 80 years.

Table 12

Plasma Phermacokinetics for Patients with Premature Ventricular Contractions
Dose-Ranging Study (030)

Study Number	Dose[a]	N[b]	Plasma Half-life (hours) Mean±S.D.	Plasma Half-life (hours) Range	Plasma Clearance (ml/min/kg) Mean±S.D.	Plasma Clearance (ml/min/kg) Range
030-01	100-250 mg bid Wash-out	9	19±4	14-26	-- [c]	--
030-02	100-300 mg bid Wash-out	10	20±5	12-27	-- [c]	--
030-03	100-250 mg bid Wash-out	11	20±4	13-27	6.2±2.8	3.1-12.6

[a] Twice daily oral dosage for 3 to 12 days.

[b] Both sexes.

[c] Blood sampling schedule did not permit determination of plasma clearance.

Table 13

Plasma Pharmacokinetics for Healthy Human Subjects
Pharmacokinetic and Metabolism Studies

Study Number	Dosage Route	Dose[a]	N[b]	Plasma Half-life (hours) Mean±S.D.	Plasma Half-life (hours) Range	Plasma Clearance (ml/min/kg) Mean±S.D.	Plasma Clearance (ml/min/kg) Range
001	IV	0.5-2.0 mg/kg	8	11±2	7-15	-- [c]	--
005	IV	0.6-1.7 mg/kg	8	14±4	7-19	7.6±2.5	4.6-12.1
005	Oral	60-240 mg	16	14±4	7-22	7.9±2.7	4.1-13.7
026	Oral	200 mg	16	12±2[d]	8-16[d]	9.8±2.7[d]	6.0-14.1[d]
039	Oral	200 mg	9	14±3	10-18	10.2±3.8	5.4-17.0
049	Oral	200 mg	18	11±2[e]	7-14[e]	15.2±4.6[e]	7.8-22.0[e]
050	Oral	200 mg	4	16±5	9-21	6.1±2.3	4.2- 9.4
061	Oral	100 mg	12	10±3	5-16	17.0±6.7	9.6-34.3
061	Oral	200 mg	12	11±3	7-20	14.7±4.3	8.2-22.7
061	Oral	300 mg	12	12±3	7-20	13.3±3.8	8.1-20.9
018	Oral	80-180 mg	16	13±3	9-19	7.3±2.3	4.1-11.7
018	Oral	80-180 mg bid[f]	16	16±4	9-23	6.9±2.7	4.1-14.5

[a] All single doses, except as indicated for Study 018.

[b] All subjects were male, except for 1 female in Study 050.

[c] Blood sampling schedule did not permit determination of plasma clearance.

[d] Average values for 2 single doses (capsule and tablet) in each subject.

[e] Average values for 3 single doses (capsule, tablet, and solution) in each subject.

[f] Twice daily dosage for 7 days.

Table 13

Plasma Pharmacokinetics for Healthy Human Subjects

Pharmacokinetic and Metabolism Studies

Study Number	Dosage Route	Dose[a]	N[b]	Plasma Half-life (hours) Mean±S.D.	Plasma Half-life (hours) Range	Plasma Clearance (ml/min/kg) Mean±S.D.	Plasma Clearance (ml/min/kg) Range
001	IV	0.5-2.0 mg/kg	8	11±2	7-15	-- [c]	--
005	IV	0.6-1.7 mg/kg	8	14±4	7-19	7.6±2.5	4.6-12.1
005	Oral	60-240 mg	16	14±4	7-22	7.9±2.7	4.1-13.7
026	Oral	200 mg	16	12±2[d]	8-16[d]	9.8±2.7[d]	6.0-14.1[d]
039	Oral	200 mg	9	14±3	10-18	10.2±3.8	5.4-17.0
049	Oral	200 mg	18	11±2[e]	7-14[e]	15.2±4.6[e]	7.8-22.0[e]
050	Oral	200 mg	4	16±5	9-21	6.1±2.3	4.2- 9.4
061	Oral	100 mg	12	10±3	5-16	17.0±6.7	9.6-34.3
061	Oral	200 mg	12	11±3	7-20	14.7±4.3	8.2-22.7
061	Oral	300 mg	12	12±3	7-20	13.3±3.8	8.1-20.9
018	Oral	80-180 mg	16	13±3	9-19	7.3±2.3	4.1-11.7
018	Oral	80-180 mg bid[f]	16	16±4	9-23	6.9±2.7	4.1-14.5

[a] All single doses, except as indicated for Study 018.

[b] All subjects were male, except for 1 female in Study 050.

[c] Blood sampling schedule did not permit determination of plasma clearance.

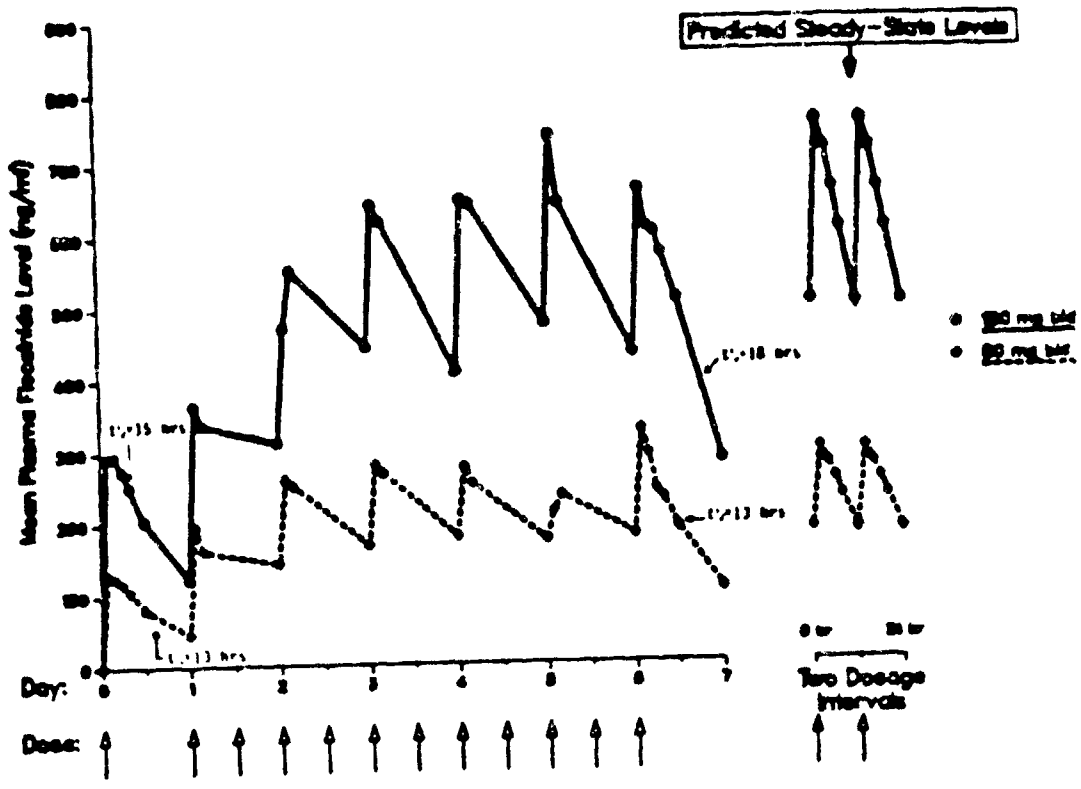
[d] Average values for 2 single doses (capsule and tablet) in each subject.

[e] Average values for 3 single doses (capsule, tablet, and solution) in each subject.

[f] Twice daily dosage for 7 days.

Figure 5A (Rectilinear Plot)

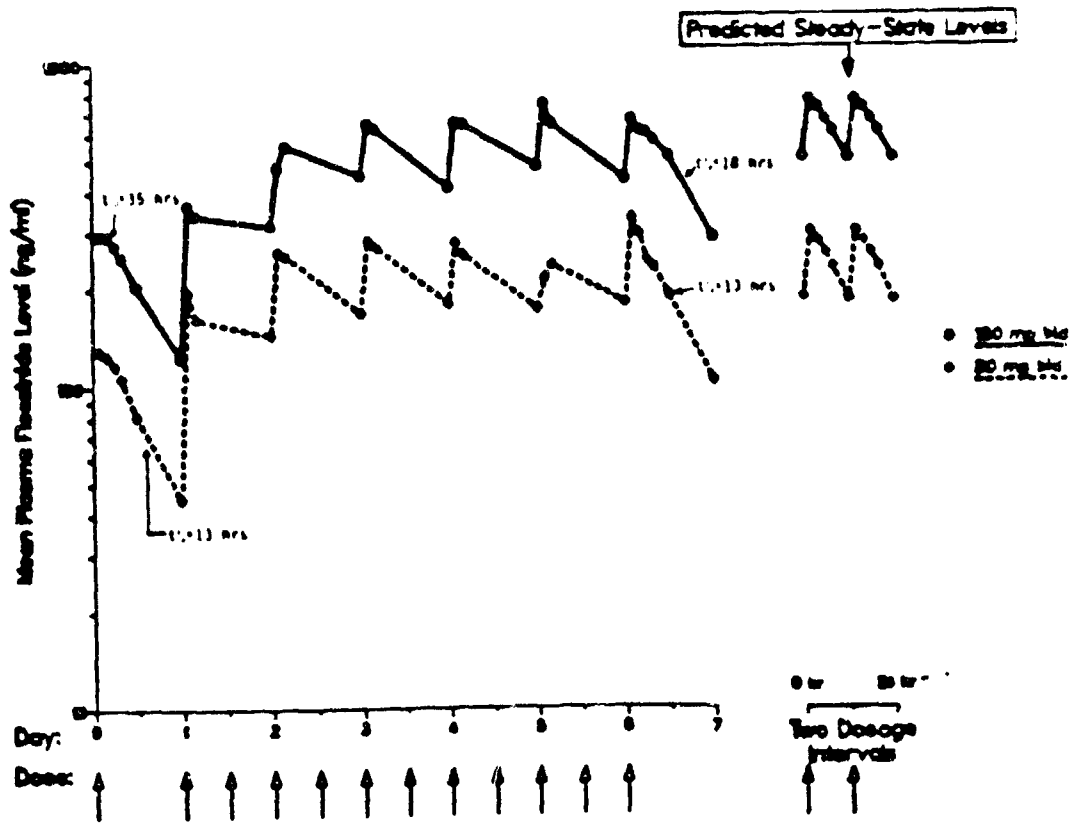
Mean Plasma Flecainide Levels During Multiple Oral Dosage (4 Subjects)*
Multi-Dose Pharmacokinetic Study (018)



* Four different subjects at each dose

Figure 5B (Semilog Plot)

Mean Plasma Flecainide Levels During Multiple Oral Dosage (4 Subjects)*
Multi-Dose Pharmacokinetic Study (018)



* Four different subjects at each dose

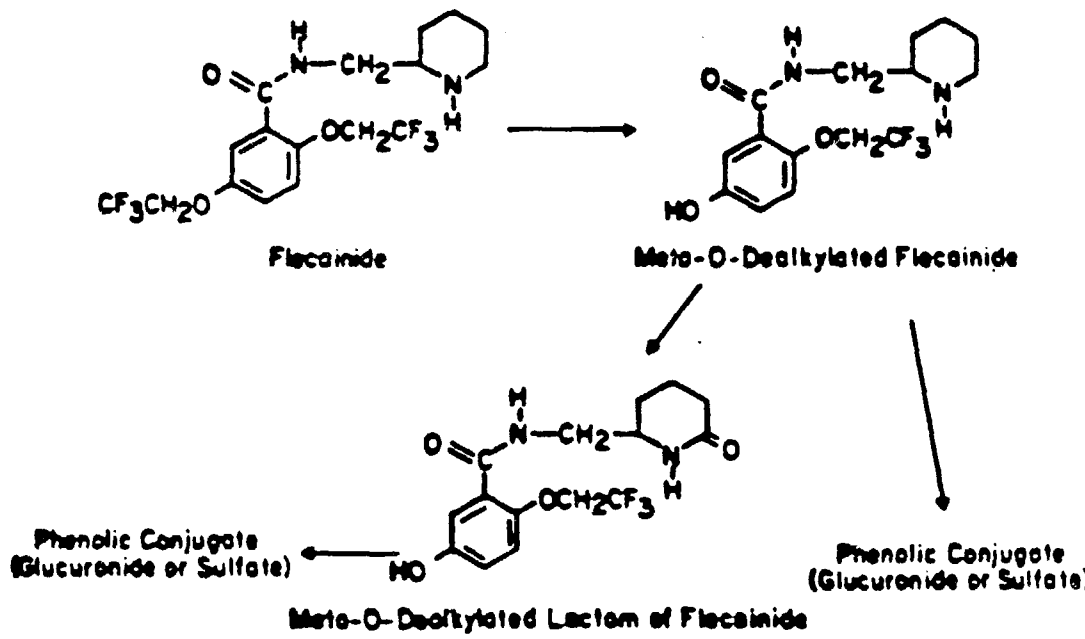
c. Biotransformation

In addition to urinary excretion of unchanged drug, flecainide undergoes extensive biotransformation in humans. Only two major metabolites, however, are found in human urine and plasma.

Figure 6 shows the major pathways of flecainide biotransformation in humans. Flecainide undergoes O-dealkylation, selectively in the meta (or 5) position of the molecule, to form meta-O-dealkylated flecainide; this phenolic metabolite is extensively conjugated as either the glucuronide or sulfate. In addition, the piperidine ring undergoes oxidative metabolism to form the lactam of the meta-O-dealkylated metabolite; this second major phenolic metabolite is also extensively conjugated.

FIGURE 6

Major Pathways of Flecainide Biotransformation in Humans



Both of these two major metabolites are found primarily in the conjugated form in both urine and plasma of humans. In addition, these two metabolites were tested in animal models; results indicate that they have a lack of or markedly reduced antiarrhythmic and electrophysiologic actions, when compared to flecainide. Also, free (unconjugated) plasma levels of these metabolites are very

low (less than 50 ng/ml) in humans, even after multiple dosage to patients, when plasma levels of flecainide are in the therapeutic range of 200 to 1,000 ng/ml and higher. Thus, the metabolites of flecainide are not likely to contribute any consequential pharmacologic activity.

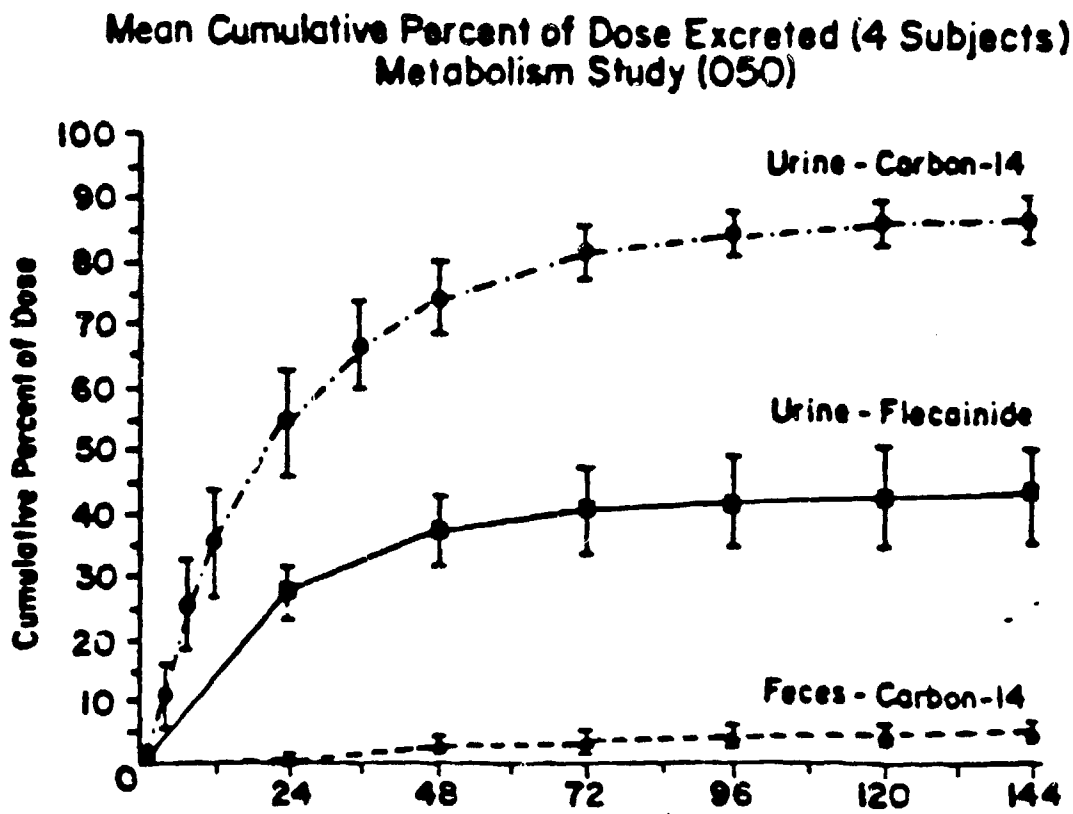
As an indicator of the relevance of laboratory animal toxicity results to flecainide safety for humans, urinary metabolite fractions were compared using radiochromatographic (TLC) analyses. Results show that the three chronic toxicity species (dogs, rats, and mice) were exposed to all human metabolites; in addition, the two major human metabolites are also major metabolites in all three animal species. Thus, the laboratory evaluation of chronic toxicity in these animal species is a reasonable assessment of flecainide safety for humans.

d. Excretion of Flecainide and Its Metabolites

After an oral dose of carbon-14 labelled drug, flecainide and its metabolites (carbon-14) are primarily excreted in human urine; only a small proportion of the dose is found in feces.

Shown in Figure 7 are mean data for four subjects who received an oral, 200 mg dose of carbon-14 labelled flecainide (Study 050-03); cumulative percent of dose is plotted versus time. As indicated, most of the carbon-14 is excreted in urine (on average, 86% of the dose) while little of the carbon-14 (5% of the dose) is excreted in feces. Thus, biliary elimination of flecainide is apparently not extensive in humans. In addition, there is extensive excretion of unchanged flecainide in human urine, as well as extensive urinary excretion of metabolites as indicated by the difference between carbon-14 and flecainide.

FIGURE 7



As shown, a substantial amount of unchanged flecainide is excreted in human urine. Data for a larger group of subjects from several studies shows that the range is from about 10 to 50% of the dose, with a mean of 27%. In addition, urinary excretion of the two major metabolites, in both the free and conjugated forms, accounts for most of the balance of the dose in urine.

Also, the renal clearance of unchanged flecainide averages about 175 ml/min and accounts for about 25% of total body clearance. Compared to normal inulin clearance values, these data suggest that flecainide undergoes some active renal secretion.

e. Effect of Disease States on Pharmacokinetics and Excretion

Congestive Heart Failure Table 14 shows results from a study in patients with congestive heart failure after a single, 200 mg oral dose (Study 039-01). In this table, plasma pharmacokinetic and urinary excretion data for ten patients with CHF (primarily New York Heart Association functional Class III) are compared to data for nine healthy subjects, who were age and weight matched, and free of cardiac disease.

TABLE 14

Plasma Pharmacokinetics and Urinary Excretion
Congestive Heart Failure Study (039)

	CHF Patients (N=10)[a]		Healthy Subjects (N=9)	
Plasma Pharmacokinetics:				
Half-life (hours)	19	(14-26)	14	(10-18)
Clearance (ml/min/kg)	8.1	(3.1-13.4)	10.2	(5.4-17.0)
Urinary Excretion:				
Extent (% dose)	24.1	(13.4-58.8)	24.7	(11.8-43.3)
Clearance (ml/min)	133		176	

[a] 9 in NYHA Class III and 1 in Class II.

As shown, plasma half-life, on average, is about 35% longer in CHF patients, and plasma clearance is about 20% slower than in the subjects. Overall, the rate of elimination of flecainide from plasma is about 25% slower in patients with CHF than for control healthy subjects. In addition, the extent of unchanged flecainide excretion in urine is not altered, but renal clearance of flecainide i somewhat slower (about 25%) in patients with CHF. Therefore, patients with congestive heart failure may require somewhat lower maintenance doses, particularly if their left ventricular dysfunction is severe.

Chronic Impairment of Renal Function Results from a study in two groups of patients with renal disease after a single, 200 mg oral dose are shown in Table 15 (Study 038-01). Plasma pharmacokinetic and urinary excretion data for 10 patients with moderate renal failure (creatinine clearances of 4 to 41 ml/min/m^2) and 10 patients with

end-stage renal disease (creatinine clearances of 2 ml/min/m^2 or less) are compared to data for healthy, young subjects with normal renal function from several other studies.

TABLE 15

Plasma Pharmacokinetics and Urinary Excretion
Renal Failure Study (038)

	Moderate Patients[a] (N=10)		End-Stage Patients[b] (N=10)		Healthy Subjects (N=79)	
Plasma Pharmacokinetics:						
Hal life (hours)	17	(12-26)	26	(9-58)	13	(7-22)
Clearance (ml/min/kg)	6.7	(2.2-13.9)	5.1	(1.5-10.0)	10	(4-20)
Urinary Excretion:						
Extent (% dose)	15.3	(5.7-29.8)	0.8	(0-3.1)	27	(10-50)
Clearance (ml/min)	90		<4		175	

[a] Creatinine clearance of 4 to 41 ml/min/m^2.
[b] Creatinine clearance of 0 to 2 ml/min/m^2.

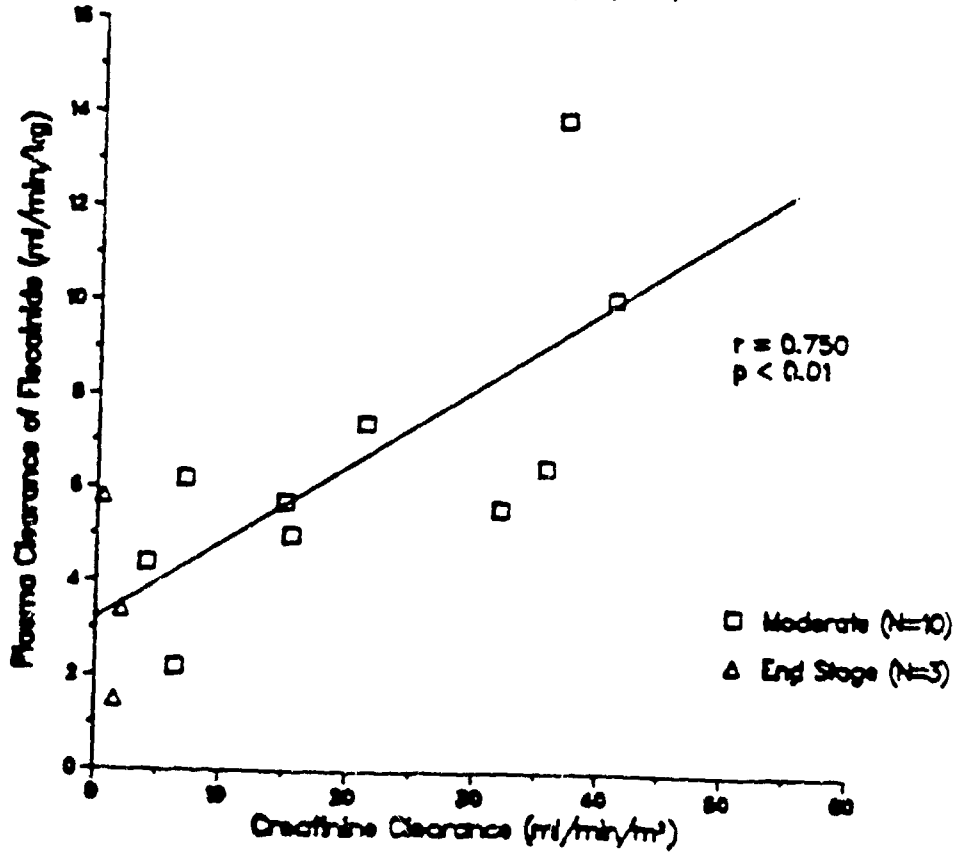
For patients with moderate renal failure, plasma half-life, on average, is about 30% longer and plasma clearance is about 35% slower than for healthy subjects; overall, flecainide elimination from plasma is about 30% slower than for subjects with normal renal function. In addition for the moderate group, the extent of flecainide excretion in urine is less extensive (about 40%) and renal clearance is slower (about 50%); on average, the excretion of flecainide in urine is about 45% less.

For patients with end-stage renal disease, plasma half-life is longer and clearance is slower than for the moderate group; this was particularly the case for two patients with end-stage renal disease, who had half-lives of about two days. Thus, the elimination of flecainide from plasma is markedly slower in some end-stage patients. In addition, the extent of urinary excretion is markedly less and renal clearance of flecainide is markedly slower in the end-stage group.

Although plasma and renal clearance of flecainide are correlated with creatinine clearance, the latter alone (creatinine clearance) is not predictive of flecainide clearance in a given patient; Figure 8A shows a plot of plasma clearance of flecainide versus creatinine clearance (Study 038-01) for the 10 patients with moderate renal failure and three patients with end-stage renal disease (creatinine clearance could not be determined in the other seven end-stage patients). Since flecainide is also extensively biotransformed (in addition to being excreted unchanged in urine), there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. For patients with more severe renal impairment, lower maintenance doses may be required. Upward dosage titration should be undertaken cautiously, bearing in mind that it may take longer to achieve a new steady-state plasma level in these patients.

FIGURE 8A

Relationship Between Plasma Clearance of Flecainide and Creatinine Clearance Renal Failure Study (038)



Hemodialysis does not effectively remove unchanged flecainide from the body (only about 1% of the dose). Removal of metabolites by hemodialysis, however, is more substantial (about 10% of the dose as total meta-O-dealkylated flecainide).

f. Plasma Protein Binding

The plasma protein binding of flecainide has been assessed in vitro using equilibrium dialysis. Results indicate that flecainide is not extensively bound to human plasma proteins (only about 40%, on average). In addition, the binding is independent of total plasma drug level over a wide range that includes and markedly exceeds therapeutic concentrations.

No consequential effect or interaction on binding has been found with other drugs that are protein bound. Also, flecainide binding is not greatly increased in patients after an acute myocardial infarction, at a time when alpha$_1$-acid glycoprotein levels are elevated. Thus, consequential changes in free (unbound) drug levels in vivo would not be expected with concomitant drugs or with changes in plasma proteins.

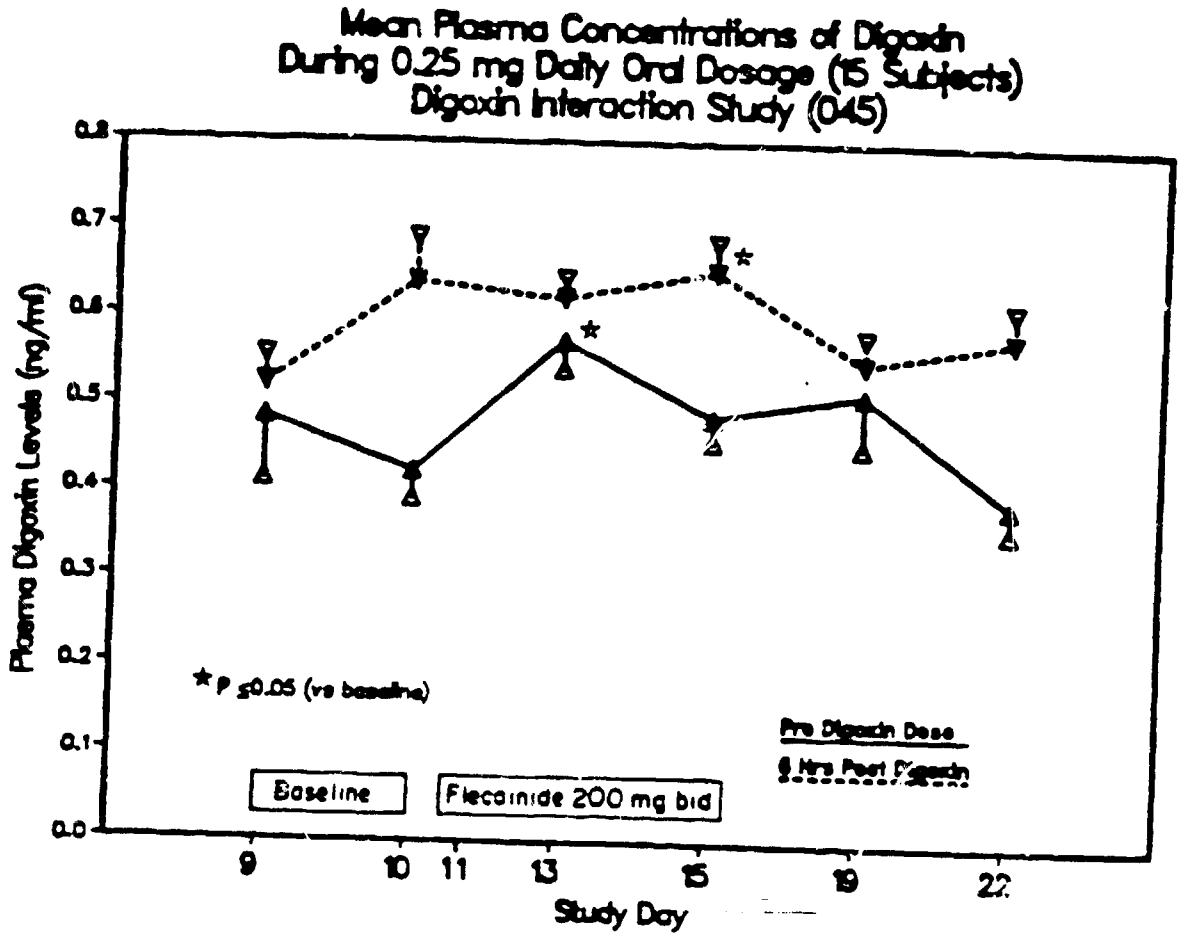
4. Drug-Drug Interactions

a. Digoxin

The effect of multiple dosage of flecainide (200 mg bid for five days) on steady-state plasma levels of digoxin has been assessed (Study R-818-045-01). As shown in Figure 8B, coadministration of therapeutic doses of flecainide was found to cause a small, but sometimes statistically significant, increase in plasma digoxin levels when values on days 13 and 15 were compared with baseline (average of days 9 and 10) values.

On average, digoxin levels were 13% higher at six-hours postdose; this is markedly less than that reported for quinidine.

FIGURE 8B



No increase was noted in the incidence of side effects reported by the subjects in this study, nor were unexpected adverse reactions observed. Increases were noted in the PR interval when both drugs were administered concurrently, but these were of the magnitude generally reported for flecainide given by itself. The small changes in digoxin levels should be of little clinical consequence for most patients on chronic digoxin therapy.

b. Propranolol

In another study (041-01), the pharmacodynamic and pharmacokinetic interactions of flecainide (200 mg bid) and propranolol (80 mg tid) were assessed. Each drug alone demonstrated a mild negative inotropic effect, the negative inotropic effects of flecainide and propranolol being comparable in this study. The coadministration of the two drugs produced effects that were, at most, additive. Effects on PR interval were less than additive. During

coadministration, plasma levels were elevated about 30% for propranolol and about 20% for flecainide as compared to control levels. These somewhat higher levels were associated with no greater than additive pharmacodynamic effects, and the plasma half-lives of both drugs did not appear to be affected by coadministration. While these effects were of little clinical consequence in the healthy subjects in this study, there remains the possibility of exaggerated negative inotropic effects in patients with reduced left ventricular function.

ACUTE AND CHRONIC CONTROLLED STUDIES

Protocol	No of Sites	Study Design	Condition(s) Studied	No of Qualifying Patients Enrolled	Completed	Conclusions
030 Dose-Ranging Trial	3	Single-blind trial, 3 day dosing of flecainide 200, 400, and 600 mg/day followed by open-label 2-week trial in responders	Chronic PVCs, nonsustained VT	35	30	Flecainide was highly effective in suppressing PVCs and nonsustained ventricular contractions. 31/35 patients achieved ≥ 80% suppression: 9 required 200 mg/day, 15 required 300 mg/day or 400 mg/day, and 7 required 500 mg/day or 600 mg/day.
032 Flecainide (F) - Quinidine (Q) Comparison Trial	16	Double-blind, parallel, randomized, 4 week trial comparing flecainide 200-300 mg bid with quinidine 300 to 400 mg qid	Chronic PVCs, nonsustained VT	F = 141 Q = 139/280	F = 119 Q = 114/233	Oral flecainide (200 to 300 mg every 12 hours) compared with oral quinidine (300 to 400 mg every six hours) showed greater suppression of PVCs and nonsustained VT.
057 Amended, Acute Chronic Study of Ventricular Tachycardia	14	Open-label, long-term safety and efficacy study using an initial dose of 100 mg bid with controlled upward titration of dosage	Refractory ventricular tachycardia and significant cardiac disease	96	47 ongoing (mean, 8 months)	An initial dose of 100 mg bid with careful upward titration to optimize efficacy and tolerance is appropriate when treating patients with severe heart disease and associated complex ventricular arrhythmias.
060 Flecainide - Disopyramide Comparison Trial (Norway)	4	Double-blind, crossover, randomized, placebo-controlled trial comparing flecainide 200 mg bid with disopyramide 150 qid for a 7 week duration	Chronic PVCs, Nonsustained VT	32	26	Flecainide (400 mg per day) when compared to Disopyramide (600 mg per day) was more effective in the suppression of simple and complex PVCs.

ACUTE AND CHRONIC CONTROLLED STUDIES

Protocol	No of Sites	Study Design	Condition(s) Studied	No of Qualifying Patients Enrolled	Completed	Conclusions
030 Dose-Ranging Trial	3	Single-blind trial, 3 day dosing of flecainide 200, 400, and 600 mg/day followed by open-label 2-week trial in responders	Chronic PVCs, nonsustained VT	35	30	Flecainide was highly effective in suppressing PVCs and nonsustained ventricular contractions. 31/35 patients achieved ≥ 80% suppression: 9 required 200 mg/day, 15 required 300 mg/day or 400 mg/day, and 7 required 500 mg/day or 600 mg/day.
032 Flecainide (F) - Quinidine (Q) Comparison Trial	16	Double-blind, parallel, randomized, 4 week trial comparing flecainide 200-300 mg bid with quinidine 300 to 400 mg qid	Chronic PVCs, nonsustained VT	F = 141 Q = 139/280	F = 119 Q = 114/233	Oral flecainide (200 to 300 mg every 12 hours) compared with oral quinidine (300 to 400 mg every six hours) showed greater suppression of PVCs and nonsustained VT.
057 Amended, Acute Chronic Study of Ventricular Tachycardia	14	Open-label, long-term safety and efficacy study using an initial dose of 100 mg bid with controlled upward titration of dosage	Refractory ventricular tachycardia and significant cardiac disease	96	47 ongoing (mean, 8 months)	An initial dose of 100 mg bid with careful upward titration to optimize efficacy and tolerance is appropriate when treating patients with severe heart disease and associated complex ventricular arrhythmias.
060 Flecainide - Disopyramide Comparison Trial (Norway)	4	Double-blind, crossover, randomized, placebo-controlled trial comparing flecainide 200 mg bid with disopyramide 150 qid for a 7 week duration	Chronic PVCs, Nonsustained VT	32	26	Flecainide (400 mg per day) when compared to Disopyramide (600 mg per day) was more effective in the suppression of simple and complex PVCs.

CHRONIC SAFETY AND EFFICACY TRIALS

Protocol	No of Sites	Study Design	Condition(s) Studied	No of Qualifying Patients Enrolled	No ongoing/ Duration of Therapy	Conclusions
031 Chronic followup of Dose-Ranging Trial	3	Open-label, long-term followup of responders from 030 trial	Chronic PVCs, nonsustained VT	29	23 patients at 24 mos	Flecainide continued to be effective in suppressing ventricular arrhythmias, without limiting side effects in 23/29 patients who completed at least 24 mo the of long-term therapy.
033 Chronic followup of Flecainide - Quinidine Comparison Trial	16	Open-label, long-term followup of patients from 032 trial	Chronic PVCs, nonsustained VT	198	117 patients at 6 to 24 mos	For the 117 (59%) patients who completed 6 to 24 months of long-term therapy (mean exceeding one year), flecainide continued to be successful in suppressing ventricular arrhythmias without limiting side effects.
035 Chronic Controlled Trial/Ventricular Ectopy (Netherlands)	4	Open-label, 8-day inpatient period followed by long-term followup of responders	Chronic PVCs, nonsustained VT	66	37 patients at 12-28 mos	Flecainide continued to be effective in suppressing ventricular arrhythmias without limiting side effects in patients treated approximately 17 months (median, 15 months).
COMPASSIONATE-USE TRIALS						
028	45	Open-label long-term safety and efficacy trial	Refractory ventricular tachycardia	228	89 patients for a mean of 13.5 mos	Flecainide was an effective antiarrhythmic in this refractory population. 39% of patients were effectively treated for a mean of 13.5 months. Flecainide did appear to be associated with potentially serious cardiac side effects.
057	13	Open-label long-term safety and efficacy trial	Refractory ventricular tachycardia significant, cardiac disease	39	14 patients for a mean of 11.6 mos	Flecainide was effective in 14 of 39 high risk patients for 10 to 12 months; this trial was suspended in November 1982. An amended protocol of this study was initiated which used lower initial doses, upward dose titration, and plasma level monitoring (057, Amended).

OTHER STUDIES

Protocol	No of Sites	Study Design	Condition(s) Studied	No of Qualifying Patients Enrolled	Completed	Conclusions
019 Efficacy, tolerance, and plasma levels of flecainide in patients	3	Open-label, inhospital, divided doses within a six hour period to a total dose of 240 mg	Non-life-threatening cardiac arrhythmias	25	25	Antiarrhythmic effects were demonstrated in patients with useable data.
053 Effect on intracardiac conduction and induced ventricular tachycardia	2	Open-label, 200 mg bid, 4 to 6 days inhospital	Ventricular tachycardia	17	16	From the induction of ventricular tachycardia, flecainide protected 9/17 (53%) patients, partially protected 4/17 (24%) patients, and failed in 4/17 (24%) of patients. This indicates that flecainide is safe and effective in the suppression of VT as evaluated by PES testing.
056 Effect of multiple oral doses on the inducibility of VT during EP testing	1	Open-label, inhospital, safety and efficacy trial for VT inducibility by EP testing	Ventricular tachycardia	8	8	EP testing results have not been evaluated. Safety analyses showed that a loading dose regimen should not be recommended.

B. Efficacy

1. Controlled Trials

This section discusses:

a. A dose-ranging trial (Study 030) performed in 35 patients with simple and complex ventricular ectopy. This study identified doses that significantly suppressed (greater than 80%) PVCs in this population, and supported the recommended effective and maximum doses used in subsequent trials. Data from this trial that are used to support the relationship of plasma level to drug effect and to support the adequacy of a bid dosing regimen are discussed separately in Section D (Dosing Rationale).

b. A double-blind efficacy comparison trial (Study 032) in which 280 patients with ventricular ectopy were randomized to either flecainide or the commonly prescribed antiarrhythmic drug, quinidine.

c. An efficacy and safety study (amended 057 Study) of flecainide treatment in 96 patients with ventricular tachycardia most of whom had significant coexisting cardiac disease, risk of congestive heart failure and various conduction disturbances, and who were refractory to or intolerant of marketed or investigational antiarrhythmic drugs. In this trial, patients were initially treated with the lowest recommended dose of flecainide, then had limited and controlled dose adjustments based on efficacy and safety evaluations.

d. A double-blind crossover comparison study (Study 060) in 32 patients with ventricular ectopy who received both flecainide and disopyramide, in a randomized order.

a. Dose-Ranging Trial (Study 030)

STUDY DESIGN: Three centers participated in this study. Forty patients with chronic ventricular arrhythmias were screened and 35 patients qualified for participation in this study to determine the range of effective multiple oral dosage regimens for flecainide in suppressing PVCs (part 1) and to determine safety and continued effectiveness of the dosage regimen determined effective for each patient in part 1 for a two-week period (part 2). Pharmacokinetic parameters and plasma level efficacy relationships were studied to establish dosing rationale.

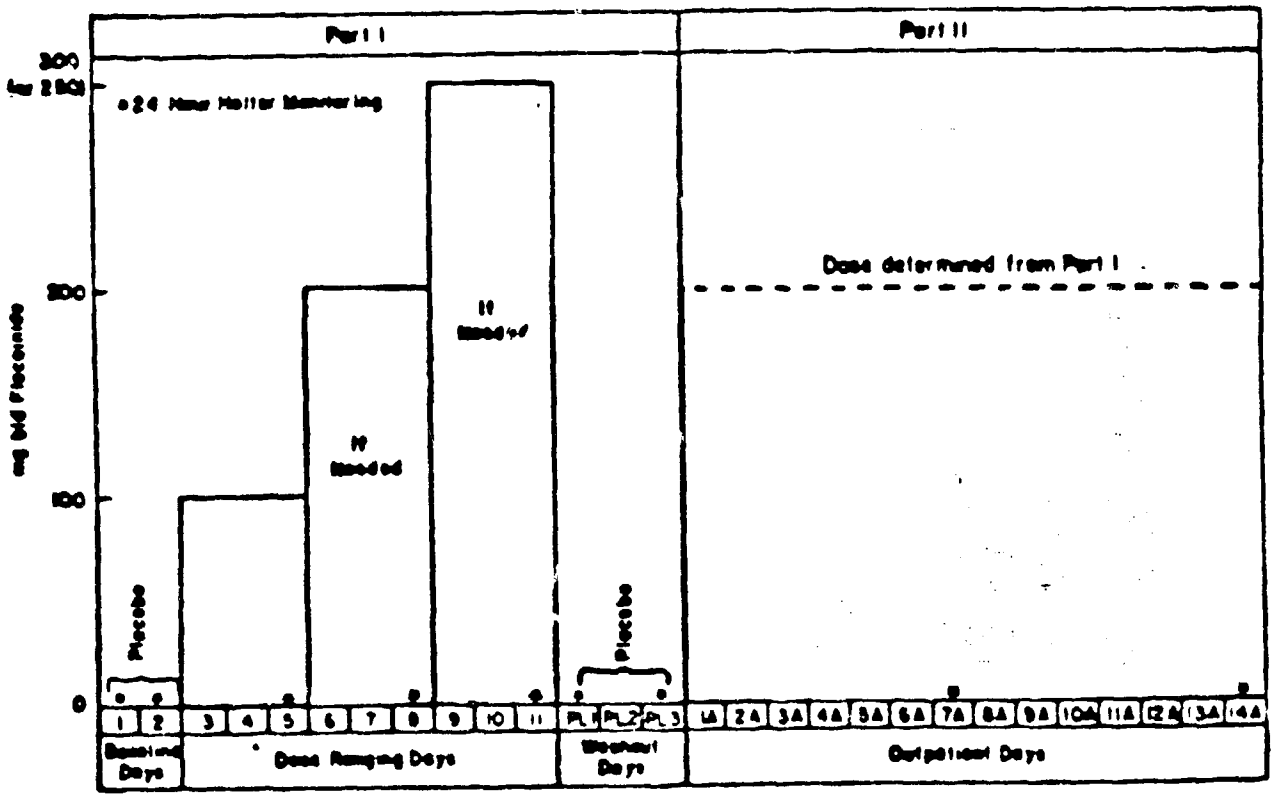
Patients with a history of chronic stable PVCs (greater than 600/12 waking hours), including unifocal, multifocal and nonsustained salvos of three or more PVCs could be entered into the study. Patients were excluded if they had digitalis intoxication arrhythmias, grade 2 or greater A-V block, a recent myocardial infarction, bundle branch block, unstable angina, ventricular tachycardia with a history of syncope or presyncope, or Class III or IV CHF.

Study design is displayed in Figure 9. Although there is no concurrent control, the washout period allows assessment of spontaneous improvement; Holter tapes are read by persons not involved in a trial and are thus effectively blinded.

Figure 9

Dose-Ranging Study (030)

STUDY DESIGN



Part 1 (single blind, inpatient) started with two days of placebo dosing followed by three days of flecainide dosing at each dose level (100 mg bid, 200 mg bid and either 250 or 300 mg bid) until greater than 80% suppression of the patient's placebo control PVC frequency was obtained, unless precluded by the occurrence of limiting side effects. Decisions by the investigator to increase dosage or to proceed to part 2 were made using 12-hour Trendscriber data (suppression of PVCs greater than or equal to 80% in comparison with placebo). Twenty-four-hour Holter recordings performed on the third day of each dosing regimen provided the basis for analysis of arrhythmia suppression.

A placebo washout period of three days was performed between parts 1 and 2.

In part 2 (open label, outpatient), patients were continued for an additional two weeks to assess multiple dose safety and efficacy on the previously determined effective and safe dose. Non-responders (patients having less than 80% suppression of PVCs) at the highest dose used in part 1 were not continued into part 2. Holter recordings were performed on the seventh and fourteenth days of part 2.

RESULTS: Eighteen males and 17 females entered the study. Ages ranged from 27 to 72 years with a mean of 54.1 years. These patients were treated with a mean of 2.5 previous antiarrhythmic agents (range 0 to 8). Table 16 lists the distribution of cardiac diagnoses.

Thirty-two of 35 qualifying patients completed part 1 of this study, 31 (89%) achieving greater than or equal to 80% suppression of PVCs. Nine of 35 patients (26%) required 100 mg bid; 14 (40%) required 200 mg bid, and seven (20%) required 250 or 300 mg bid. One patient who did not respond to 100 mg bid received 100 mg tid and achieved greater than 80% suppression. One patient completed part 1 without achieving 80% suppression of PVCs. This patient, therefore, did not enter part 2.

Three patients discontinued during part 1. One patient discontinued at 200 mg bid due to stomach pain, headache, abdominal cramps, and nausea; one due to an increase in PVCs on Trendscriber at 100 mg bid; one due to a nondrug-related transient ischemic attack.

Of the 31 patients who qualified for entry into part 2 (greater than or equal to 80% suppression of PVCs in part 1) 30 entered and all completed this two week outpatient portion of the study. The remaining patient was mistakenly determined to be a nonresponder by Trendscriber; Holter data later showed 82% suppression at 300 mg bid. Of the 30 patients entered in part 2, 26 achieved greater than or equal to 80% suppression of PVCs at the end of the two-week outpatient portion of the study. Three other patients achieved 63% to 79% suppression and one patient's Holter was not analyzable. The mean and median percent suppression of baseline PVCs and repetitive beats (couplets and nonsustained VT) are given in Tables 17 and 18, respectively.

Figure 10 shows the mean number of PVCs/hour for the 32 patients who completed part 1 of the study. The figure shows the mean PVCs/hour at baseline, at the effective dose, at washout, and on outpatient days 7 and 14. Figure 11 shows the same information for repetitive PVCs (couplets plus VT beats) for these 32 patients. The off-on-off-on pattern, as well as the very large response seen, leaves no doubt, despite lack of a concurrent control group, that the change in VPB rates is drug-related.

CONCLUSION: Flecainide was effective in this population of patients with chronic ventricular ectopy. Eighty-nine percent of qualifying patients (31/35) responded to daily doses of 200 to 600 mg/day with greater than or equal to 80% suppression. Eighty-seven percent (26/30) of patients entering the outpatient phase of the study achieved greater than or equal to 80% suppression of PVCs at two weeks. Flecainide was well tolerated in this population with only two patients discontinuing because of drug-related adverse effects.

TABLE 16

Cardiac Diagnoses

	Number of Patients[a]	% of Patients (n = 35)
Atherosclerotic heart disease	14	40%
Previous MI	5	14%
Cardiomyopathy	3	9%
Valvular disease	11	31%
Hypertensive heart disease	7	20%
Primary rhythm disorder	3	9%
History of CHF	4	11%

[a] Patients may have more than one cardiac diagnosis.

TABLE 17

Efficacy Summary

Mean and Median Percent Suppression of Baseline PVCs

Center	Dose-Ranging Effective Dose Mean	Dose-Ranging Effective Dose Median	Outpatient Day 7A Mean	Outpatient Day 7A Median	Outpatient Day 14A Mean	Outpatient Day 14A Median
01	94.9%	99.6%	96.1%	99.8%	95.3%	98.8%
	(n=10)		(n=9)		(n=9)	
02	96.3%	100%	94.1%	99.6%	93.2%	100%
	(n=11)		(n=10)		(n=9)	
03	96.9%	97.2%	92.6%	95.9%	95.8%	98.2%
	(n=11)		(n=11)		(n=11)	
Overall	96.1%	98.8%	94.2%	98.8%	94.9%	98.8%
	(n=32)		(n=30)		(n=29)	

TABLE 18

Efficacy Summary - Couplets and Nonsustained VT

Mean and Median Percent Suppression of Baseline Couplets and Nonsustained VT

	Dose-Ranging		Outpatient			
	Effective Dose		Day 7A		Day 14A	
Center	Mean	Median	Mean	Median	Mean	Median
01	98.5% (n=9)	100%	98.4% (n=8)	100%	92.8% (n=8)	100%
02	87.2% (n=11)	100%	92.5% (n=10)	100%	96.0% (n=9)	100%
03	99.9% (n=11)	100%	99.5% (n=11)	100%	99.2% (n=11)	100%
Overall	98.2% (n=31)	100%	96.8% (n=29)	100%	96.4% (n=28)	100%

Center 01 had one patient with zero couplets and zero nonsustained VT beats at both baseline and followup visits.

Figure 10

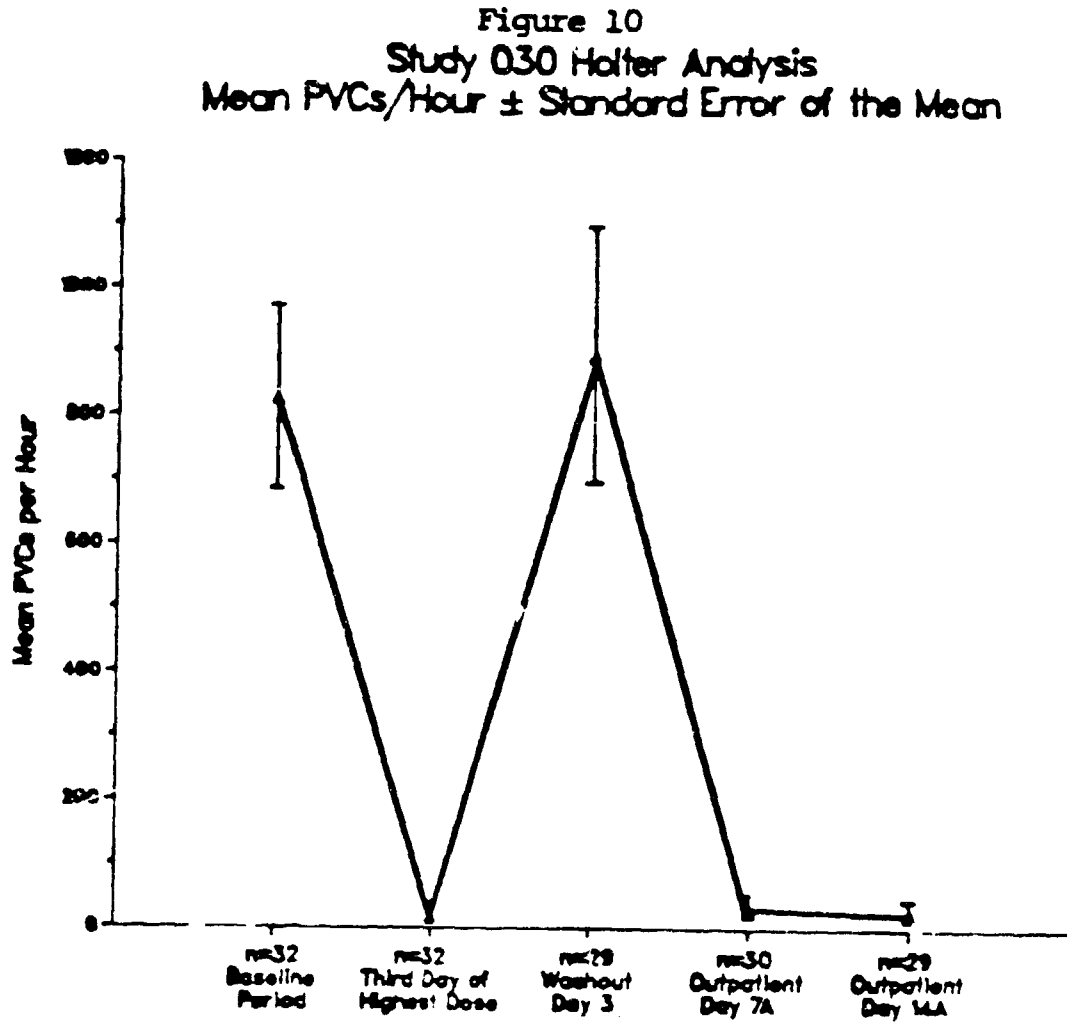
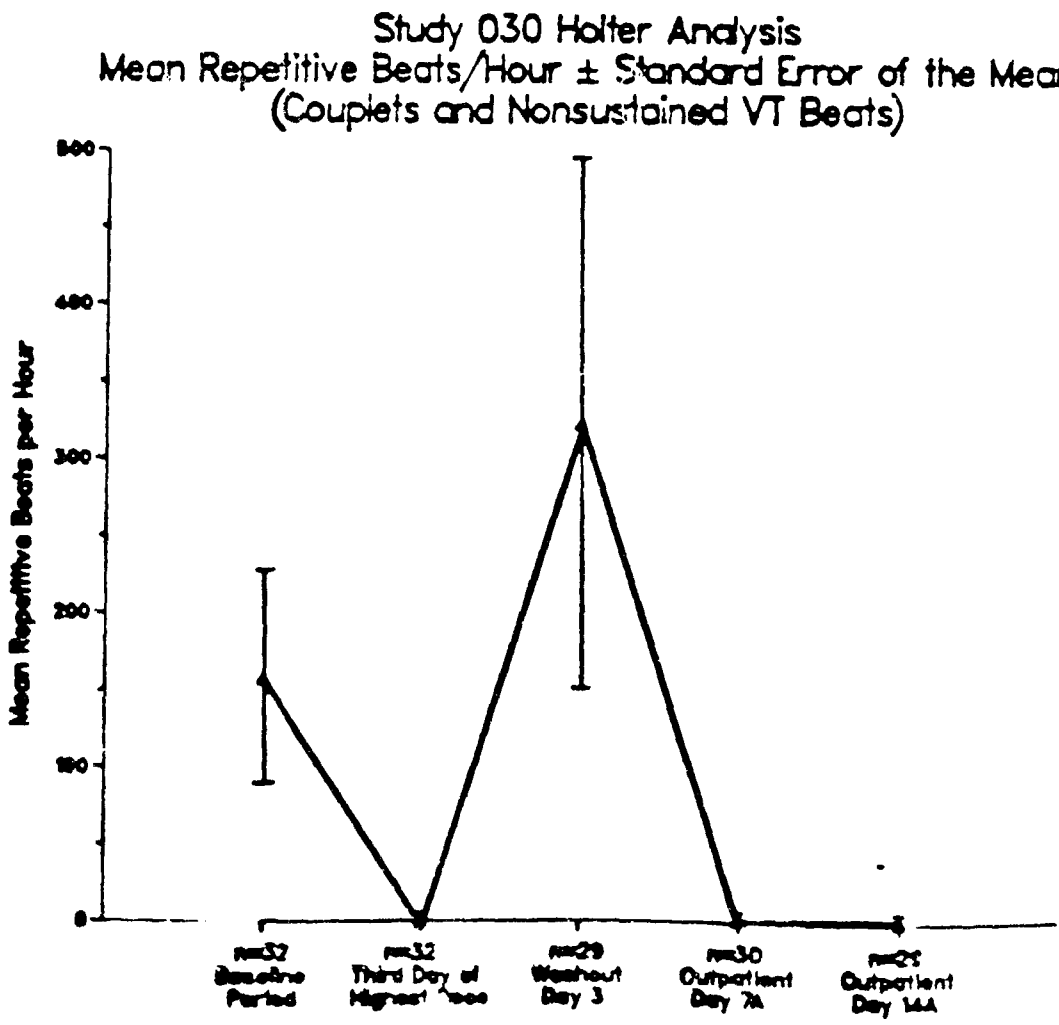


Figure 11



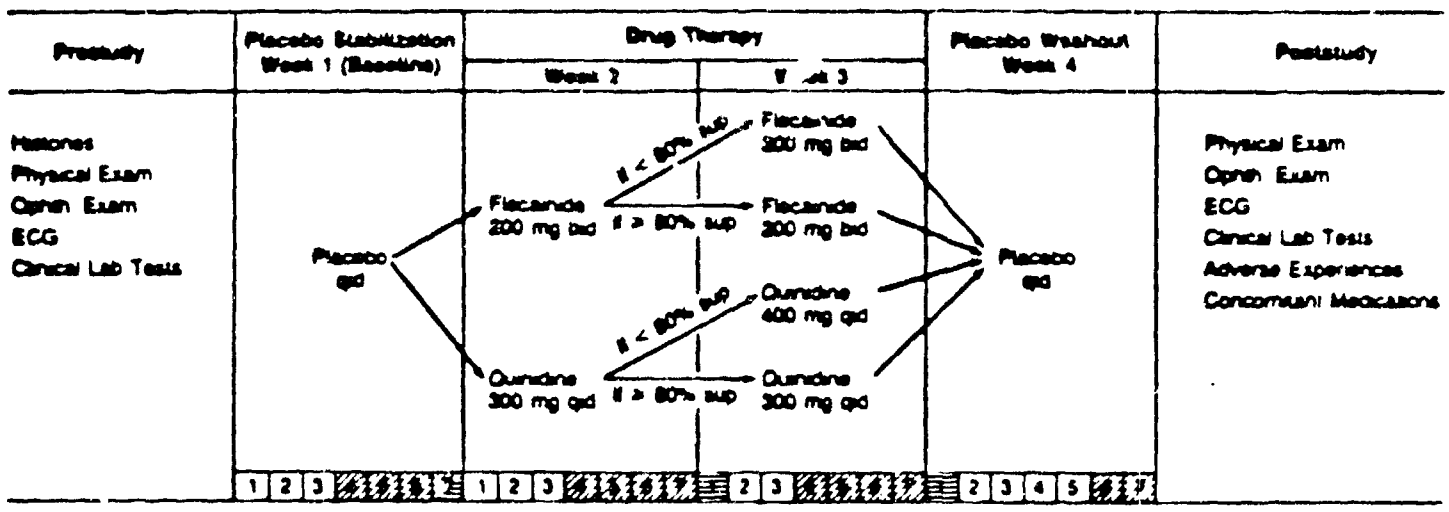
b) Flecainide-Quinidine Comparison Trial (Study 032)

STUDY DESIGN: Investigators at 16 sites participated in this study to determine the comparative safety and efficacy of multiple, oral dose administration of flecainide acetate and quinidine sulfate under double-blind conditions in patients with chronic premature contractions (PVCs), which included singled and paired premature beats and runs of ventricular tachycardia (V-tach).

This double-blind, parallel, randomized study included two weeks of active drug therapy, bounded before and after by placebo periods, each seven days long. (See Figure 12.)

Figure 12

Flecainide/Quinidine Comparison Study (032)
Study Design



Patients could be enrolled if they had ventricular arrhythmias that required antiarrhythmic therapy (greater than 30 PVCs/hr on placebo) and could be treated as outpatients. Patients were excluded from the study if they had digitalis intoxication arrhythmias, grade 2 or greater A-V block, bundle branch block combined with 1^{o} A-V block, severe hemodynamically compromising arrhythmias, unstable angina, a recent myocardial infarction, Class III or IV CHF, a cardiac pacemaker, or a known idiosyncratic reaction or known serious toxicity to either quinidine or flecainide.

In the two-week, drug therapy period, each patient received either flecainide or quinidine. To maintain a double-blind design, each patient receiving flecainide took active drug twice a day (6 a.m. and 6 p.m.) alternating with placebo twice a day (noon and midnight) to create a qid dosage regimen. Each patient receiving quinidine took active drug four times a day (6 a.m., noon, 6 p.m. and midnight).

During the first week of drug treatment, patients received either flecainide 200 mg bid or quinidine 300 mg qid. Twenty-four hour Holter recordings obtained on the fifth or sixth day of active therapy were compared to baseline (placebo) results. The percentage of suppression of PVCs achieved determined the dose of drug each patient received during the next week of treatment. Unless precluded by limiting adverse experiences, a patient who experienced greater than or equal to 80% suppression of the baseline PVC frequency continued on the lower dose of drug. Conversely, if a patient experienced less than 80% suppression of baseline PVCs, with no limiting adverse experiences, the patient received a higher dose of active drug during the second week of treatment; either flecainide 300 mg bid or quinidine 400 mg qid. Additional Holter monitoring was performed during this week to evaluate suppression of PVCs.

A seven-day placebo washout period concluded the study. Final Holter monitoring determined the level of return of PVCs. Each patient who qualified for and participated in this study was subsequently allowed to receive long-term flecainide or quinidine therapy in an open fashion (Study 033).

RESULTS: The 16 study centers screened a total of 342 consenting patients of whom 280 qualified for the study. The main reasons for disqualification of 62 patients were: failure to show an average of 30 PVCs/hr at baseline (43/62 patients) and positive ANA titer at baseline (7/62) - both were protocol violations; miscellaneous reasons (12/62) included placebo intolerance, intercurrent illness, and logistical and technical problems.

The 280 qualifying patients included 198 males and 82 females with a mean age of 58.5 years. One hundred forty-one patients received flecainide and 139 received quinidine. Demographic characteristics were comparable between groups with the exception of race ($p = 0.049$); there were more whites in the quinidine group (127/139 or 91%) than the flecainide group (117/141 or 83%). There were no significant differences (p less than 0.05) in baseline arrhythmia profiles between drug groups. Baseline means ($\pm$ one standard deviation) for qualifying patients by drug group were as follows:

Table 19
Baseline Arrhythmia Profiles
Flecainide-Quinidine Comparison Study (032)

	Flecainide	Quinidine
PVCs/hr	419 $\pm$ 448	429 $\pm$ 423
Paired beats/hr	27 $\pm$ 65	20 $\pm$ 46
V-tach beats/hr	7 $\pm$ 26	6 $\pm$ 19

Baseline cardiac diagnosis are in Table 20.

TABLE 20

FLECAINIDE-QUINIDINE COMPARISON TRIAL (STUDY 032)
BASELINE CARDIAC DIAGNOSES

	No. of Flecainide Patients[a] (%) (N=141)	No. of Quinidine Patients[a] (%) (N=139)
Atherosclerotic heart disease	73 (52%)	72 (52%)
Previous MI	42 (30%)	44 (32%)
Cardiomyopathy	16 (11%)	14 (10%)
Valvular disease	22 (16%)	30 (22%)
Hypertensive heart disease	50 (35%)	42 (30%)
Primary rhythm disorder	16 (11%)	19 (14%)

[a]Patients may have more than one cardiac diagnosis.

Of the qualifying patients, 233 completed the study. Of the 47 noncompleting patients, 40 discontinued because of adverse experiences (19 in the flecainide group and 21 in the quinidine group), including one flecainide patient without prior history of ventricular tachycardia who developed a new wide complex VT on the high dose and a second patient who had increased PVCs and new nonsustained VT. In addition four patients developed ECG changes leading to discontinuation (increased or new 1^0 AV block or widened QRS and PR intervals) and three developed junctional escape rhythms, in two cases with severe syncope due to sinus node dysfunction. Two patients developed worsened CHF, leading to discontinuation. Two quinidine patients developed ventricular tachycardia (both had prior history of VT) and one, CHF with increased PVCs. Four patients died, three of documented acute myocardial infarctions (all taking quinidine) and one suddenly out-of-hospital while taking placebo, 36 hours after taking flecainide for two weeks. The adverse experiences leading to withdrawal from flecainide were principally the cardiac experiences listed, as well as dizziness, blurred vision and nausea. Quinidine was discontinued principally because of diarrhea, nausea and vomiting. The discontinued patients and reasons for discontinuation are listed in Tables 20A and 20B. Other adverse experiences will be described in the safety section below.

The main basis for efficacy comparisons between flecainide and quinidine was the percent suppression of baseline PVCs which included 1) the total number of premature beats, 2) premature beats occurring in pairs (paired beats), and 3) premature beats occurring in runs of three or more (V-tach beats).

Forty-four percent (54/122) of the patients on quinidine who entered the second week of drug therapy required the higher dose compared to 18% (23/127) of the flecainide patients (p less than 0.0001).

The mean percent suppressions of PVCs by flecainide were 83.6% in the first week of therapy and 91.0% in the second week of therapy, versus 58.5% and 39.2% for quinidine, respectively. The median percent suppressions of PVCs by flecainide were 99.4% at week two and 99.5% at week three, versus 80.3% and 84.7% for quinidine at weeks two and three, respectively. The two-way analysis of variance on the ranks of percent suppression showed flecainide more effective than quinidine during both weeks two and three in suppressing PVCs (p less than 0.0001), paired beats (p less

TABLE 20A

QUALIFYING PATIENTS WHO DISCONTINUED WHILE TAKING FLECAINIDE (WEEKS 2 AND 3)

Center	Pt No.	Dose mg bid	Last Study Day	Reasons
02 Hodges	7	200	W3D2	Congestive heart failure
	23	200	W2D2	Severe syncope, fatigue, weakness, and junctional bradycardia.
03 Cook	7	200	W2D2	Grand mal seizure - vasovagal episode
04 Farnham	5	200	W3D3	Blurred vision, dizziness, first degree AV block worsened
	15	200	W2D7	First degree AV block, bradycardia
	20	200	W2D7	First degree AV block, dizziness
05 Hart	9	300	W3D5	Loss of equilibrium, dyspnea, fatigue
	10	200	W2D7	Severe weakness, diaphoresis, near syncope
06 Kalmanschn	10	200	W2D4	Palpitations and moderate dizziness
	14	200	W3D6	Severe fainting, nausea, dizziness, bradycardia, junctional rhythms
08 Lee	3	300	W3D7	Noncompliance
	6	300	W3D3	Ventricular tachycardia
	13	200	W2D4	Dizziness, peripheral blurring of vision, severe headache
10 Antlitz	3	200	W2D5	Congestive heart failure exacerbated
	4	200	W2D4	Dry mouth, nausea, numb hands and feet, disoriented
11 Marcus	2	200	W3D1	Widening of QRS and PR intervals
12 Morganroth	4	300	W3D2	Shortness of breath, nausea, junctional rhythm
	23	200	W2D3	Nervousness, dizziness, blurred vision, shortness of breath
13 Oshrain	19	200	W2D7	Blurred vision
17 Platt and Rosin	11	200	W3D1	Severe dizziness
	17	300	W3D6	Increase in PVCs, new, non-sustained V Tach

TABLE 20B

QUALIFYING PATIENTS WHO DISCONTINUED WHILE TAKING QUINIDINE (WEEKS 2 AND 3)

Center	Pt No.	Dose mg qid	Last Study Day	Reasons
01 Beller	6	400	W3D3	Vomiting, nausea, cramps
02 Hodges	28	300	W2D2	Acute thrombosis - patient died
03 Cook	3	300	W2D3	Severe diarrhea
	5	300	W3D5	Fever, diarrhea, tinnitus, rash, backache
	9	400	W3D2	Nausea, shortness of breath, rapid heart beat
04 Farnham	1	300	W2D2	Acute myocardial infarction - patient died two days later
	8	300	W2D6	Personal - noncompliance
	9	300	W2D2	Diarrhea, nausea, "sick"
05 Hart	8	300	W2D7	Gastric disturbances, ankle edema, precipitated CHF, increase in PVCs
07 Laidlaw	3	300	W2D4	Severe shortness of breath and wheezing, diarrhea
	15	300	W2D4	Acute myocardial infarction - patient died
	22	300	W3D4	Severe diarrhea
08 Lee	1	300	W2D3	Nausea, diarrhea
	5	400	W3D5	Severe nausea, vomiting, diarrhea, headache
	18	300	W2D5	Severe nausea and diarrhea
11 Marcus	1	300	W2D2	Diarrhea
	4	300	W2D7	Swelling, red hands; fatigue; peripheral edema; increased stools
12 Morganroth	13	400	W3D5	Severe nausea and dizziness
13 Oshrain	5	300	W3D4	Rash; axillary adenopathy, abnormal LF
14 Reid	5	300	W2D2	Tremor, fever, diarrhea, headache
	9	300	W2D6	Ventricular tachycardia, ventricular fibrillation
	12	300	W3D5	Vomiting, diarrhea, soft stools, tinnitus, fever, thrombocytopenia
	13	300	W3D1	Ventricular tachycardia
	18	300	W2D7	Cramps, sinus tachycardia, diarrhea, dehydration
17 Platt and Rosin	26	300	W2D7	Severe dizziness, nausea, vomiting, blurred vision

than 0.001) and V-tach beats (p less than 0.01). None of these analyses found significant differences between centers. Except for one center at week three, median percent suppression was greater for flecainide than quinidine in all 16 centers at both weeks two and three. In the one other instance, both drugs showed a median of 100% suppression.

At the end of the two week drug therapy period, a comparison between the flecainide and quinidine groups showed the following for percent suppression of PVCs, paired beats, and V-tach beats.

Table 21
Suppression of Arrhythmias In
Flecainide-Quinidine Trial

Percent Suppression	Flecainide Patients	Quinidine Patients	P-Value Between Drugs
PVCs			
100%	16%(19/118)	3%(3/110)	<0.001
≥95%	75%(88/118)	34%(37/110)	<0.0001
≥80%	85%(100/118)	57%(63/110)	<0.0001
Paired Beats			
100%	70%(73/105)	41%(41/99)	<0.0001
≥95%	85%(89/105)	60%(59/99)	<0.0001
V-tach Beats			
100%	79%(57/72)	55%(37/67)	<0.01
≥95%	86%(62/72)	66%(44/67)	<0.01

In addition to the above comparisons, 68% (80/118) of the flecainide patients had at least 80% suppression of PVCs plus complete (100%) suppression of paired beats and V-tach beats versus 33% (36/110) for quinidine (p less than 0.0001).

CONCLUSION: The doses of 200 mg to 300 mg bid of flecainide, and the doses of 300 mg to 400 mg qid of quinidine were equally tolerated in patients treated for chronic ventricular ectopy; discontinuations because of side effects were approximately equal, but quite common, (about 15%), and different in nature, quinidine causing

intolerable diarrhea, nausea, and vomiting, flecainide causing more symptomatic bradycardia, A-V block, and one well-documented pro-arrhythmic event, a new VT in a patient with no prior VT history. At these doses, flecainide showed greater suppression (p less than 0.0001) of simple and complex PVCs and nonsustained ventricular tachycardia compared to quinidine.

c) Open-Label Study of Patients With Ventricular Tachycardia (Study 057 amended)

STUDY DESIGN: Investigators at 14 sites participated in this open-label study to evaluate the safety and efficacy of oral flecainide acetate in patients with refractory ventricular arrhythmias and significant coexisting cardiac disease. The study was modified from a trial (Study 057) of similar design with a more aggressive initial titration after early deaths were seen in that study (see below under 3b) and in the compassionate use Study 028.

In order to receive flecainide in this study, patients were required to have significant ventricular arrhythmias, especially VT (greater than or equal to six beats in a row at a rate of greater than or equal to 100 beats/min). If there was no history of VT, the patient was required to have more than 10 PVCs per hour and be refractory to previous therapy. Investigators were encouraged to enter patients who had associated cardiac disease (BBB or IVCD; Class III or IV CHF) in conjunction with their arrhythmia.

Patients were excluded from the study if they exhibited any of the following: digitalis intoxication arrhythmias, second or third degree heart block, atrial flutter or fibrillation without a ventricular arrhythmia QRS greater than 0.15 or PR greater than 0.28 sec, recent unstable MI, or pacemaker dependent rhythm. Patients were to be monitored for at least 7 days in-hospital.

Patients underwent baseline determinations after discontinuing all previous antiarrhythmic therapy for a minimum of four drug half-lives. Each patient was to complete 24 hours of baseline Holter monitoring. Patients with a history of VT had to have VT documented by rhythm strip, electrocardiogram (ECG), or Holter monitoring within two weeks prior to starting flecainide. Baseline radionuclide ejection fraction (RNEF) and 12-lead ECG with interpretation were obtained on each patient. The RNEF had to to be repeated at discharge if it was less than 30% initially. At the investigator's discretion, patients with conduction abnormalities underwent standard electrophysiologic testing.

The initial starting dose was 100 mg bid. Upward dosage adjustments could be made if after four days efficacy was not achieved. Upward adjustments, however, were limited to 50 mg bid increments every four days to a maximum dose of 200 mg bid. These dosing requirements were lower than those most commonly used to treat similar patients in the compassionate-use protocols (200 mg bid initial dose, 300 mg bid maximum). Plasma flecainide trough levels were required on the fourth day of each dose level. The protocol did not specify an upper or lower plasma level limit, but the investigators tried to maintain trough plasma levels within the therapeutic range of 200 to 1,000 ng/ml.

The investigator's decision to discharge the patient from the hospital on flecainide was considered the best global assessment of effectiveness. This decision was based on one or more of the following: 1) Holter monitoring (required at baseline and at discharge), 2) telemetry, 3) PES testing (optional), 4) exercise stress testing (optional), and 5) the patient's history, symptoms, and response to previous therapy. The investigator performed interval evaluations for safety and efficacy on patients at the time of hospital discharge, one month and three months after initiating flecainide, and at quarterly intervals thereafter. In addition, the sponsor retrospectively established effectiveness criteria for patients released including (1) 100% suppression of VT by Holter, (2) 80% suppression of PVCs by Holter, and (3) non-inducibility of VT by PES or stress testing.

RESULTS: The first 96 patients (68 male, 28 female; mean age 61 years) enrolled into this ongoing study form the database for this summary.

Baseline demographic data (Table 22) were typical for these types of patients: 94 patients had a history of VT, 49 (51%) had a history of sustained VT and 45 (47%) had nonsustained VT; 2 patients (2%) were treated for PVCs; 43 (45%) patients had a history or evidence of CHF at baseline, and 30 (33%) had baseline RNEFs less than or equal to 30%; 49 patients had a history of conduction disturbances. The 96 patients had failed a mean of 4.4 previous antiarrhythmic agents prior to this study. There was a significant difference (p less than 0.05) in the mean number of previous antiarrhythmics between the sustained (4.9) and nonsustained (3.9) VT patient groups.

Table 23 summarizes efficacy results. In the judgement of the investigators, flecainide was effective in 73% (70/96) of patients during the initial in-hospital evaluation; these patients were discharged from the hospital on flecainide. Forty nine percent (47/96) of patients enrolled in the study remain ongoing for a mean of eight months (range 4.5 to 12 months). Of the 47 patients ongoing, 46 are free of symptomatic VT; one patient developed nonsustained VT associated with dizziness. The investigator chose to continue this patient on flecainide therapy due to marked decrease in frequency of his arrhythmia.

Of the patients with a history of sustained VT, 29/49 (59%) were discharged from the hospital on flecainide, and 22/49 (45%) are ongoing. Of the patients with a history of nonsustained VT, 39/45 (87%) were discharged from the hospital on flecainide, and 23/45 (51%) are ongoing.

Fifty patients had a baseline Holter tape and a Holter tape obtained prior to discharge. The median PVC suppression was 91.4%; 36/50 (72%) patients had at least 80% suppression of PVCs. Forty-three of the 50 patients had VT on baseline Holter tapes; 33/43 (77%) had complete suppression of VT; 10/43 (23%) patients had VT on their discharge Holter tape. No patient with zero VT beats at baseline had VT beats on their discharge Holter tape.

Twenty-three of the 96 patients had PES testing on oral flecainide. Flecainide provided complete suppression of VT on PES testing in 7/23 (30%) of these patients and five of seven remain ongoing. One of the suppressed patients died. Flecainide provided partial suppression in an additional 7/23 (30%) patients and three of these patients remain ongoing. Flecainide did not suppress VT during PES testing in 9/23 (39%) patients. Only one of these patients was discharged on flecainide; this patient remains ongoing.

Table 24 shows a listing of total daily doses received by all patients at discharge, and by ongoing patients at discharge and at their most recent visit.

A summary of the reasons for patient discontinuations is listed by frequency in Table 25A and the reasons for discontinuation for each patient are shown in Table 25B. Most patients who discontinued did so early in the study. Of the 49 discontinued patients, 27 (55%) discontinued flecainide prior to hospital discharge. These included eight patients whose arrhythmias worsened during initial hospitalization from one to 17 days after initiation (two increased frequency of VPCs and non-sustained VT; two had

VT that was more difficult to convert; one had more easily induced sustained VT, one had more easily induced non-sustained VT; one had inducible VT on PES that recurred the next day; and one developed new spontaneous VT different from baseline. Two later pro-arrhythmia episodes also occurred, one increased VPCs and non-sustained VT's and one arrhythmia that was more difficult to convert. In marked contrast to studies 028 and 057 (see below), however, there were no early deaths. Serious conduction disturbances including 3° A-V block were also seen in four patients after two, five, six and 100 days of therapy. All nine deaths and all five discontinuations due to noncardiac adverse experiences occurred after discharge.

Of the nine patients on flecainide who died in this study, three patients died in association with a documented acute MI; six died from sudden death experiences outside of the hospital, or en route to the hospital. Three of these patients had a previous history of sustained VT, three had non-sustained VT. No patients died of congestive heart failure, conduction disturbance, or in association with a documented proarrhythmic event.

The overall mean trough plasma levels for 31 discharged patients with analyzable samples, (mean daily dose, 260 mg) was 532 ng/ml. The overall mean plasma levels at discharge for sustained VT patients (556 ng/ml) and nonsustained VT patients (526 ng/ml) were not significantly different. The first 8 patients with pro-arrhythmic responses had mean daily doses of 325 mg and plasma levels of 622 ng/ml, only slightly higher than the mean dose and plasma levels for all discharged patients. Daily doses in seven patients with conduction disturbances were low, mean 271 mg. The one patient stopping therapy with worsened CHF was on 400 mg, with a plasma level of 620 ng/ml. Patients who died had a mean dose of 289 mg/day (9/9 patients) and a plasma level of 600 ng/ml (4/9 patients).

TABLE 22

Demographic Results

Total No. patients	96
No. males	68 (71%)
females	28 (29%)
Mean age (yrs)	61 (16-82)
Mean weight (kg)	74 (40-106)

Cardiac Diagnoses[a]	% of patients N = 96
Atherosclerotic heart disease	74%
Previous MI	57%
Cardiomyopathy	17%
Valvular disease	20%
Hypertensive heart disease	28%
Primary rhythm disorder	5%
History of CHF	45%
History of VT	98%
History of sustained VT	51%
History of nonsustained VT	47%
Mean number of previous antiarrhythmic agents	4.4

[a] Patients may have more than one cardiac diagnosis.

TABLE 23
Efficacy Results

	All Patients	Sustained VT	Nonsustained VT	PVCs only
Enrolled	96	49	45	2
Discharged from the hospital on flecainide	70 (73%)	29 (59%)	39 (87%)	2 (100%)
Ongoing	47 (49%)*	22 (45%)	23 (51%)	2 (100%)
Free of symptomatic VT	46 (48%)	22 (45%)	22 (49%)	2 (100%)
All deaths	9 (9%)	5 (10%)	4 (9%)	0
Sudden Death	6 (6%)	3 (6%)	3 (7%)	0

*Mean duration of therapy 8.0 months (244 days)

TABLE 24

Flecainide Doses for Discharged and Ongoing Patients

Total daily doses (mg)	Dose at discharge for all pts (N=70)	Dose at discharge for ongoing pts (N=47)[a]	All patients (N=47)[a]	Dose for Ongoing Patients at Most Recent Visit[b] Patients sus. VT (N=22)	Patients nonsust.VT (N=23)
100	0	0	2 (4%)	1 (4%)	1 (4%)
150	2 (3%)	2 (4%)	3 (6%)	2 (9%)	1 (4%)
200	29 (42%)	21 (45%)	14 (30%)	5 (23%)	8 (35%)
250	1 (1%)	1 (2%)	0	0	0
300	31 (44%)	19 (40%)	20 (43%)	11 (50%)	8 (35%)
400	7 (10%)	4 (9%)	8 (17%)	3 (14%)	5 (22%)
Median dose		250 mg	300 mg	300 mg	300 mg
Mean dose		255 mg	269 mg	268 mg	272 mg

[a] Two patients had PVCs only.

[b] Mean duration of therapy for the 47 ongoing patients was 8.0 months.

TABLE 25A
Patient Discontinuations

Reason	No. of Patients N = 96		Discontinued in hospital	out
Inadequate response	12	(12.5%)	11	1
Worsened arrhythmia	10	(10.4%)	7	3
Death	9	(9.4%)	--	9
Non-cardiac adverse experiences	5	(5.2%)	--	5
Personal reason*	5	(5.2%)	2	3
Conduction disturbance	4	(4.2%)	3	1
Non-compliance	2	(2.1%)	--	2
Intercurrent disease	1	(1.0%)	--	1
Signs of CHF	1	(1.0%)	1	--
TOTAL	49	(51%)	24	25

*One patient moved to another city; the patient discontinued this study but enrolled in another flecainide study at the new location.

Table 25B

Patient Discontinuations (DC)

Center	Pt. No.	No. Days on Oral Flecainide	Total Daily Dose (mg) at DC	Reason for Discontinuation
-01	101	77	400	Death
	102	13	300	Inadequate response-worsened arrhythmia
	103	14	300	Inadequate response
	105	1	200	Inadequate response - worsened arrhythmia
-02	301	3	200	Inadequate response
-06	101	86	350	Adverse experience - palpitations, malaise, blurred vision, anorexia
	104	15	300	Worsened arrhythmia
-07	101	69	300	Death
	103	12	200	Death
	104	6	300	Conduction disturbance - sinus pause
-10	101	7	300	Inadequate response
	102	201	400	Worsened arrhythmia
-11	10'	3	200	Worsened arrhythmia
-12	101	2	100 oral + 80 IV	Inadequate response
	103	44	300	Inadequate response
	104	98	200	Adverse experience vertigo associated with blurred vision
	106	1	200	Personal reason - patient withdrew consent
	108	4	200	Inadequate response
	109	13	400	Inadequate response
	110	21	200	Death
	112	14	400	Signs of congestive heart failure
	113	5	200	Conduction disturbance - complete AV block
	115	2	200	Conduction disturbance - complete heart (AV) block
	119	100	200	Conduction disturbance - 2° AV block
-26	102	8	300	Inadequate response - worsened arrhythmia
	107	16	400	Inadequate response worsened arrhythmia

Table 25B - continued

Patient Discontinuations (DC)

Center	Pt. No.	No. Days on Oral Flecainide	Total Daily Dose (mg) at DC	Reason for Discontinuation
-26	108	4	200	Inadequate response
	110	3	200	Inadequate response - other reason - wanted to increase dose before protocol would allow
	113	17	400	Inadequate response worsened arrhythmia
-31	102	83	300	Death
	103	41	200	Patient felt weak, short of breath
-34	104	12	300	Inadequate response
-63	101	16	500	Inadequate response - worsened arrhythmia
	102	10	600	Worsened arrhythmia
-65	101	5	200	Inadequate response
-72	101	14	200	Inadequate response
	105	58	150	Personal reason - discharged to nursing home

CONCLUSION: In patients with VT, a baseline-controlled trial is the best that can be done, because prolonged outpatient placebo therapy is unacceptable and only an effective therapy can be maintained. This study demonstrated that administration of flecainide in lower initial doses (100 mg bid) with upward titration of dose to 200 mg bid as necessary (but most patients received 300 mg/day or less) to optimize efficacy and tolerance can result in effective treatment of refractory ventricular arrhythmias with marked reduction of VPBs. Symptomatic VT also seems to have been eliminated in many, although without a concurrent control this conclusion is not wholly secure. The frequency and severity of adverse experiences were more favorable than in trials with larger doses of drug (see report of study 057 and Safety section), supporting the recommendation of an initial dose of 100 mg bid with careful upward titration in patients with severe heart disease and associated ventricular tachycardia.

d) Flecainide-Disopyramide Trial (Study 060), Norway

STUDY DESIGN: Four Norwegian investigators participated in this multicenter study to evaluate and compare the efficacy and safety of flecainide acetate and disopyramide phosphate when given orally in the treatment of premature ventricular contractions (PVCs).

This was a randomized, double-blind, crossover comparison study of seven weeks duration. Following an initial seven-day placebo period, patients were randomly assigned to receive either flecainide 200 mg bid or disopyramide 150 mg qid for a period of 14 days. A second seven-day placebo washout period followed, after which patients were crossed over to alternative active treatment for a further 14 days. A third and final seven-day placebo period terminated the study. Following enrollment, each patient returned to the hospital for weekly safety and efficacy evaluations at days 7, 14, 21, 28, 35, 42, and 49.

Patients who met inclusion/exclusion criteria had various baseline evaluations performed including 24-hour Holter analysis. Patients qualified for treatment if they had more than 1,000 PVCs per 24 hours present during baseline monitoring plus 1) five or more isolated PVCs in any one minute of analysis, and/or 2) two or more consecutive PVCs recorded in any one minute of analysis. Patients were excluded if they 1) were not between 16 years and 75 years of age; 2) had NYHA Class III or IV CHF; 3) had digitalis intoxication arrhythmias; 4) had second degree or greater A-V block; 5) had bifascicular block or bundle branch block plus any A-V block; 6) had a history of myocardial infarction within six months; 7) had a history of ventricular tachycardia with syncope; or 8) required beta-blockers or other negative inotropic therapy.

RESULTS: A total of 32 patients with PVCs enrolled at four study centers. Twenty-six patients were male and six were female, with a mean age of 55.3 years. Cardiac diagnoses included ischemic heart disease, 16 patients; previous myocardial infarction(s), 14 patients; cardiomyopathy, eight patients; unknown etiology, six patients; and valvular heart disease, two patients. Baseline arrhythmia profiles (complexes per hour) are shown in Table 26.

Table 26
Baseline Arrhythmia Profile
Flecainide-Disopyramide Trial (060)

	Mean ± SD
Total aberrant beats[a] (n = 25)	552.4 ± 835.7
Premature aberrant[b] beats (n = 25)	325.5 ± 609.8

[a]Total aberrant includes all forms of beats which differ from "normal" configuration as defined by the analyst on the Pathfinder System (Hertford Research).

[b]Premature aberrant beats most closely approximate PVCs counted on Cardiodata Systems which was utilized in U.S. studies.

Twenty-six of the 32 (81%) patients enrolled completed the study. Six patients discontinued during the study including two who died. One of the six dropped out on day one (placebo) for personal reasons; he also was not within the age requirement. Two patients discontinued while receiving disopyramide: one suffered acute pulmonary edema and severe, bloodstained diarrhea during the second day of drug, and the other patient presented with deep vein thrombosis and pulmonary embolism following one week of drug administration. One patient discontinued after one week of flecainide administration due to a possible myocardial infarction and ventricular fibrillation during the flecainide period.

Two patients died during the study. One died of cerebral thrombosis after the first week of disopyramide treatment; the second patient died suddenly while dancing following nearly two weeks of flecainide treatment.

Evaluation of the suppression of aberrant beats was performed in 25 of the 26 patients who completed the study; one patient was excluded due to an insufficient aberrant count throughout the placebo period. Disopyramide showed a median suppression of baseline total aberrant beats of 44% while flecainide showed a median suppression of 86%; the comparative difference was statistically significant ($p = 0.007$) using the paired t-test. For premature aberrant beats, disopyramide showed a 39% median suppression of baseline counts, and flecainide demonstrated a 92% median suppression; this difference was also statistically significant ($p = 0.002$).

The percentage of patients responding with greater than 50% suppression of total aberrant beats and 80% suppression of premature aberrant beats while on flecainide was significantly greater than on disopyramide. Flecainide showed a statistically significant greater suppression of multiform extrasystoles ($p = 0.005$) and couplets ($p = 0.048$). There was also some suggestion that flecainide was more effective in reducing episodes of salvos ($p = 0.079$) and bigeminy ($p = 0.155$), although these did not reach the level of statistical significance ($p = 0.05$).

Twenty-four of the 26 patients attained adequate therapeutic plasma levels of both study drugs. These were considered to be greater than 300 ng/ml flecainide and greater than 2.0 ug/ml disopyramide. One patient did not achieve a therapeutic plasma level of disopyramide which may account for the lack of efficacy observed. Another patient did not attain a therapeutic level of flecainide and tended toward the lower range during disopyramide administration; his compliance was questionable.

CONCLUSION: At a dose of 400 mg/day, flecainide was more effective than disopyramide 600 mg/day in the suppression of simple ventricular ectopic contractions and more complex arrhythmic events. Tolerance was generally good and no differences emerged between the two drugs in the incidence or severity of reported adverse effects. Two possible pro-arrhythmic events occurred during treatment with flecainide; one sudden death while dancing after two weeks of treatment; and one episode of VF following a possible AMI.

2. Chronic Safety and Efficacy Trials

a. Chronic Follow-up of Dose-Ranging Trial (Study 031)

OBJECTIVE: The purpose of this open-label study was to evaluate the long-term safety and continuing efficacy of flecainide in patients who successfully completed the 030 dose-ranging studies. The same three centers participated in this study.

RESULTS: A total of 30 patients were eligible for this study. Each had achieved greater than or equal to 80% suppression of baseline PVC frequency in the dose-ranging study. Patients returned to the study sites for interval visits at least every three months. The investigator determined the dosage regimen for each patient and made necessary changes to control or eliminate side effects, maintain efficacy, or determine the lowest effective maintenance dose. The maximum total daily dose allowed was 600 mg.

Twenty-nine patients elected to continue taking flecainide long-term. Twenty-four of 29 patients (83%) who entered the long-term study completed 12 months of treatment and 23 completed a second year of therapy (24 months). Five patients dropped out during the first year of the study. Only one patient discontinued because of adverse experiences; this patient wished to discontinue following month two because of blurred vision, dizziness, lightheadedness, and nervousness. A second patient withdrew from the study, without explanation, following month one and was lost to followup. The three remaining dropouts were judged to be therapeutic failures.

By the end of 24 months, 23 patients remained ongoing with one patient discontinuing during the second year due to loss of therapeutic effect (at month 21).

The following table shows the number of patients taking each of the various total daily doses at month 12 and month 24; 400 mg total daily dose remained the most common dose regimen in these patients.

Table 27
Summary of Total Daily Flecainide Dosing

Total Daily Dose of flecainide	Number of Patients at Month 12	Total Daily Dose Month 24
600 mg	2	2
500 mg	1	3
450 mg	0	1
400 mg	10	8
350 mg	0	2
300 mg	7	3
200 mg	4	4
Total Patients	24	23
Mean Daily Dose	358 mg	380 mg
Median Daily Dose	400 mg	400 mg

Sixteen patients were on a bid dose schedule at month 24, 4 patients were on a tid schedule, and 3 patients received flecainide in divided (unequal) doses either at 2 times per day (2 patients), or 3 times per day (1 patient).

The last Holter data available for 23 of the 24 patients who completed the first 12 months of therapy showed an average PVC suppression of 94% (range, 53% to 100%; median, 99%) and an average multiple PVC suppression of 98% (range, 86% to 100%; median, 100%). These results are comparable to the short-term dose-ranging study (030) results. Holter monitoring was infrequently performed during the second year of treatment and analysis of these Holter data was not done.

CONCLUSION: Flecainide efficacy data during the first year in ongoing patients was comparable to results in the earlier short-term study (030). Flecainide continued to be well-tolerated in this population through 24 months of therapy.

b. Chronic Followup of Flecainide-Quinidine Comparison Trial (033)

OBJECTIVE: Patients who participated in the short-term Flecainide-Quinidine Comparison Study (032) entered this long-term, chronic dosing study to receive either flecainide or quinidine therapy. Investigators and study sites were the same as those for Study 032.

RESULTS: A total of 211 patients entered the study. Those who received flecainide in the short-term study continued to take flecainide in this study. Patients who received quinidine in the short-term study could receive either quinidine or flecainide in the long-term study. Patients were permitted to cross over from quinidine to flecainide during the long-term study but not vice-versa (with one exception). Of the 211 patients, 194 received flecainide from the beginning of the long-term study while 17 started the study on quinidine. During the course of therapy, four patients crossed over from quinidine to flecainide while one switched from flecainide to quinidine. Therefore, a total of 198 patients have received flecainide, 103 having first received it as part of study 032, and 95 being switched from quinidine; 18 have taken quinidine. Because of the difference between the number of patients on each drug, only the data from those taking flecainide were analyzed.

The mean duration of therapy for ongoing flecainide patients was 12 months (6 to 24 months reported).

Eighty-one of 198 (41%) flecainide patients discontinued the study after a mean exposure of 3 months; 117 (59%) were still ongoing. Adverse experiences or adverse experiences accompanied by ECG changes, were the reason for the discontinuation of 23 patients (11.6%); 16 patients (8.1%) discontinued due to noncompliance or loss to followup; 12 patients (6.1%) died; 10 patients (5.1%) discontinued for personal reasons; 13 patients (6.6%) discontinued due to loss of therapeutic effect; and the remainder discontinued due to other reasons.

Adverse experiences were generally similar to those seen in study 032, perhaps surprising as doses were somewhat lower and half the patients had already completed their first exposure to the drug in the previous study. The main adverse experiences in the studies are shown below.

Adverse Experiences

	Study 032	Study 033
Dizziness	43/141 (30%)	49/194 (25%)
Abnormal vision	40/141 (28%)	63/194 (32%)
Nausea	13/141 (9%)	15/194 (8%)
Headache	12/141 (9%)	11/194 (6%)
Asthenia	7/141 (5%)	13/194 (7%)
Fatigue	7/141 (5%)	11/194 (6%)

There were 8 (4%) patients identified as having pro-arrhythmic responses to flecainide. Three patients, without a history of sustained VT, developed sustained VT on flecainide, in one case fatal (but that patient had recently begun another drug, aprindine) and in the other two cases sustained VT developed fairly shortly (7, 22 days) after starting flecainide. Three patients developed new supraventricular arrhythmias on flecainide, one new SVT, and the others sinus pause or arrest with symptomatic bradycardia and junctional escape rhythms. Two patients had increased rate of VPCs on flecainide, in one case with salvos of VT.

Six patients left the study early because of ECG changes, including 1° A-V block (four cases, with bundle branch block in two cases and sinus pauses in one), 2° block of Wenckebach type, and SVT. Eleven patients experienced new or worsened CHF on flecainide; one died of a cardiac arrest; six left the study (four because of CHF) and four remained in the study.

Up to 24 months of therapy, 12 patients died. The causes of death include autopsy-proven acute myocardial infarction (one patient), CHF (one patient), in-hospital arrhythmic death (three patients), and out-of-hospital sudden death (seven patients). Of the in-hospital deaths, one was 5 days after flecainide was stopped; one occurred after 8 1/2 months of treatment during worsening CHF, and one involved the pro-arrhythmic event described above. Of the 7 out-of-hospital deaths, 4 were unobserved deaths after 2, 6, 15 1/2 and 16 months of therapy, and one was a "collapse" (10 months) not medically observed. One, however, occurred after just 4 days of treatment, with no prior history of VT and the VT seen in the ambulance was resistant to conversion. In the last case, asystole developed after 21 days of treatment.

Efficacy evaluations were based on 24-hour Holter monitoring (required every six months). For the 90 patients with Holter results at month 12, 72/90 (80%) patients achieved at least 80% suppression of their total baseline PVCs, and 61/90 (68%) achieved at least 95% suppression, with a median suppression o 98.9%.

An analysis of baseline multiple PVCs, which included premature paired beats (couplets) and V-tach beats (three or more consecutive beats) also showed excellent suppression. For 78 patients who had couplets at baseline analyzed at month 12, 65 (83%) had greater than 95% suppression and 57 (73%) showed total (100%) suppression. For 50 patients with V-tach beats at baseline, 47 (94%) had total suppression during the month 12 Holter analysis, another patient had greater than 80% suppression, and the two remaining patients showed less than 50% suppression at that visit.

Most flecainide dosage adjustments were made early in the patients' treatment program. Although the recommended starting dose was 200 mg bid (400 mg total daily dose), adjustments were made to achieve the lowest effective maintenance dose, to reduce side effects, or to increase the level of efficacy.

At month 12, the most common daily dose was 400 mg, followed by 300 mg and 200 mg, respectively, with a mean daily dose of 335 mg (median, 300 mg). Only 7 of 102 patients were on more than 400 mg.

CONCLUSION: Of the 198 flecainide patients who were enrolled, 117 (59%) remained on therapy after completing 6 to 24 months of long-term therapy with a mean treatment period exceeding one year. Flecainide continued to be effective in suppressing ventricular arrhythmias without limiting side effects in these ongoing patients. The effectiveness was not without cost, however, as there were serious side effects, including pro-arrhythmic events. During the study there were eight patients with possible pro-arrhythmic responses, including two with new VT. In addition, there were seven out-of-hospital sudden deaths, two of which occurred soon after the start of flecainide and may have represented pro-arrhythmic responses.

c. Chronic Controlled Trial/Ventricular Ectopy (Study 035), Netherlands

STUDY DESIGN: Investigators at four study centers in the Netherlands evaluated the long-term safety and efficacy of flecainide when administered to patients who successfully responded with at least 85% suppression of PVCs without intolerable side effects during short-term testing.

This open-label study included two treatment periods: stage 1 was an eight-day inpatient period followed by stage 2, a long-term outpatient period.

Patients were excluded from the study if they had 1) uncompensated heart failure; 2) digitalis intoxication arrhythmias; 3) atrial flutter or fibrillation; 4) grade 2 or greater atrio-ventricular (A-V) block; 5) a history of myocardial infarction within three months prior to study entrance; 6) bundle branch block combined with first degree A-V block; 7) unstable angina; 8) presence of a cardiac pacemaker; and/or 9) an enlarged heart. During stage 1, qualifying patients received four days of placebo treatment during which baseline evaluations, including 24-hour Holter monitoring, were performed. Patients qualified for flecainide treatment (days five through eight) if they had at least 500 PVCs during the 24-hour monitoring period plus five or more isolated PVCs in any one minute and/or two or more consecutive PVCs recorded at any time during monitoring. Qualifying patients received flecainide 200 mg bid beginning on day five. On day eight of stage 1, baseline procedures were repeated. If the patient experienced no toxicity during the three to four days of flecainide administration, and if the repeat Holter analysis showed at least 85% suppression of baseline PVCs, the patient entered the long-term phase (stage 2) of the study.

In stage 2 (outpatient therapy), the investigators could adjust a patient's dose and/or frequency of administration of flecainide based on monthly safety and efficacy evaluations. The maximum daily dose allowed was 500 mg. During stage 2, each patient returned to the hospital once for a flecainide withdrawal period after 3, 6, 9 or 12 months of therapy to determine the need for continued flecainide therapy. A return to flecainide treatment was appropriate if the off-drug Holter analysis showed that 1) the total number of PVCs exceeded the pre-withdrawal number by a factor of two or more; 2) the number of repetitive PVCs exceeded the number of pre-withdrawal episodes; and/or 3) the number of episodes of more than five isolated PVCs in any one minute of recording exceeded the pre-withdrawal numbers.

Safety evaluations were performed at each visit; ophthalmologic examinations were performed at yearly intervals, and each patient underwent Holter monitoring every two months to evaluate efficacy.

Each patient could continue to receive flecainide as long as it remained safe and effective for a minimum of one year. The investigator determined the dosage regimen for each patient and made necessary changes to control or eliminate side effects, maintain efficacy, or determine the lowest effective maintenance dose.

RESULTS: A total of 78 patients enrolled at four centers; 12 patients did not qualify because of insufficient PVCs at baseline. Sixty-six patients qualified for study participation, including 48 males and 18 females with a mean age at enrollment of 53.1 years (range, 21 to 69 years).

Although the protocol required that patients were to have greater than or equal to 85% suppression of PVCs in part 1 to continue into part 2, investigators usually entered patients into part 2 if PVC suppression was considered adequate in the investigator's opinion.

Thirty-seven (56%) patients completed 12 to 28 months of therapy.

Forty-nine of 66 patients completed the flecainide one week washout period. Of these patients eight did not have the required number of PVCs return in order to continue therapy. Only one patient, however, was discontinued for lack of return of arrhythmia. The remaining seven patients

continued in the study; three continued because PVCs returned after the first week of washout and four continued because the investigator felt these patients required therapy.

During this study, 29 (44%) qualifying patients discontinued flecainide therapy. The reasons for the 29 discontinuations in decreasing order of frequency were: inadequate PVC suppression during short-term treatment (nine patients); death (seven patients); adverse experiences (three patients); inadequate suppression during long-term treatment (three patients); personal reasons (two patients); end of one year study participation (two patients); non-compliance (one patient); acute myocardial infarction (one patient); and no return of arrhythmia during washout (one patient). Two discontinuations are of interest; one patient developed a junctional bradycardia (50 bpm); a second had sinus pauses up to 1.65 seconds and a syncopal episode.

The cause of death for the seven patients who died in this study were cancer (one patient), in-hospital arrhythmic death (three patients), and out-of-hospital sudden death (three patients two of whom probably had AMIs). Two of the three in hospital deaths occurred early in the course of treatment, at 1 day and 4 days after initiation. One patient had a history of MI, CHF and recurrent sustained VT, poorly controlled by other agents, but developed VF on flecainide. A large left ventricular aneurysm was found at autopsy. The other, with a prior history of sustained VT developed non-resuscitable VT/VF after three days of flecainide therapy.

Twenty-four-hour Holter monitoring was performed every other month during long-term treatment on all ongoing patients through month 12; after month 12, Holter analysis was performed at the discretion of each investigator. The month 6 results on data from 49 patients showed that 43/49 (88%) of the patients achieved at least 80% suppression of baseline PVCs, and 35/49 (71%) of the patients achieved at least 95% suppression, with a median suppression at month 6 of 99.5%. Similarly, for data from 43 patients analyzed a month 12, 38/43 (88%) of the patients achieved at least 80% suppression of baseline PVCs, 33/43 (77%) achieved at least 95% suppression, and the median suppression was 99.5%.

Although the recommended starting dose for flecainide was 200 mg bid (400 mg total daily dose), the investigators made dosage adjustments to achieve the lowest effective maintenance dose, to reduce side effects, or to increase the level of efficacy. For 45 patients reporting at month 12, the most common total daily dose of flecainide was 300 mg (16 patients), followed by 400 mg (14 patients) and 200 mg (nine patients); the mean total daily dose was 308 mg (median, 300 mg).

CONCLUSION: Of the 66 patients who participated in this study, 37 (56%) remained on flecainide therapy at the time of this analysis, having completed 12 to 28 months of long-term therapy with a mean treatment period of approximately 17 months (median, 15 months).

Flecainide continued to be effective in suppressing ventricular arrhythmias without limiting side effects in these ongoing patients.

3. Compassionate-Use Trials

Trials 028 and 057 were similar in that both were designed to evaluate seriously ill patients with either very frequent VPCs or ventricular tachycardia/ventricular fibrillation. In fact, most patients enrolled in both trials had a history of VT/VF, often needing resuscitation, and often accompanied by CHF, a history of acute infarction and a low ejection fraction. The patients were clearly sicker and more at risk of dying than patients in the chronic VPC trials (030, 031, 032, 033, 035) and an increase in the number of deaths on flecainide was expected once these trials were begun. By late 1982, however, examples of cardiac arrests began to accumulate. These occurred early after the start of flecainide therapy accompanied by arrhythmias that were different from those seen previously and that were unusually difficult or impossible to reverse despite prompt resuscitative attempts in sophisticated medical environments. Sixteen such cases were found, 12 of which represented cases where deaths were early in the course of flecainide treatment and no other explanation for lack of successful resuscitation was apparent. These were discussed at an investigators meeting in December 1982. Enrollment of patients was suspended pending evaluation. The meeting concluded that while the patients were high risk patients (15/16 prior AMI, 11/16 prior arrests, 15/16 history of VT) the difficulty of resuscitation was unusual, suggesting a drug relationship; it was also noted that blood levels seemed high in these patients. Based on the meeting, the lower dose, slower titration, plasma level monitoring approach of study 057 amended was developed and studies 028 and 057 ceased further enrollment. In addition, the sponsor surveyed all investigators in early 1983 to review the history of all treated patients for instances of worsened arrhythmia

a. Study 028

STUDY DESIGN: Investigators at 45 sites participated in this open-label study to assess the safety and efficacy of oral flecainide when provided on a compassionate-use basis to patients with ventricular arrhythmias who were intolerant of marketed antiarrhythmic agents or whose arrhythmias were refractory to marketed anti-arrhythmic agents.

Arrhythmias were characterized by greater than 30 premature ventricular contractions (PVCs) per hour, uncomfortable or intolerable symptoms associated with PVCs, or ventricular tachycardia or fibrillation (VT or VF).

Patients with any of the following cardiac abnormalities were excluded from the study: 1) digitalis intoxication arrhythmias; 2) atrial flutter or fibrillation without a ventricular arrhythmia; 3) second degree or greater atrioventricular (A-V) block; 4) complete bundle branch block associated with first degree A-V block; 5) QRS interval greater than 0.15 seconds, PR interval greater than 0.28 seconds; 6) a recent clinically unstable myocardial infarction; 7) unstable angina; 8) pacemaker dependent rhythm; 9) a need to continue verapamil or disopyramide (excluded because of their negative inotropic effects), and 10) severe or uncompensated heart failure.

Patients were required to discontinue other antiarrhythmic therapy a minimum of two half-lives before starting flecainide, though in some cases patients were maintained on lidocaine until after flecainide had been started.

Throughout most of this study, the usual recommended starting dose of flecainide was 200 mg bid. During the study, accumulating experience indicated that lower doses were effective in many patients and perhaps provided a greater margin of safety, particularly in patients with more severe disease. Thus, during the course of the study, 100 mg bid also became a frequent starting dose. The study allowed for upward and downward alterations in dose levels and dosing schedules up to a maximum of 600 mg a day. Unlike the acute and chronic study of VT (Study 057 amended) there were no restrictions to the time interval between dosage adjustments.

Quantitative efficacy determinations, such as those obtained through 24-hour Holter monitoring were not required in this study, but were left to the discretion of the investigator. Determination of effective response was generally based on one or more of the following: a patient's arrhythmia symptoms, arrhythmia monitoring (24-hour Holter, telemetry or rhythm strip), programmed electrical stimulation (PES) and exercise stress testing.

RESULTS: A total of 228 patients received flecainide through this compassionate-use protocol. Individual periods of treatment ranged from one dose to 20.5 months (mean 5.5 months). For the ongoing patients, the mean time on flecainide was 13.5 months (median 13.3 months; range 7.1 to 20.5 months). The mean time on drug for discontinued patients was 2.3 months (range, one dose to 18.4 months).

Of the 228 patients who received flecainide, 200 were refractory to or intolerant of marketed antiarrhythmic agents and 28 transferred from other Riker sponsored studies. Baseline demographic data were available for 227 patients: the most frequently occurring cardiac diagnoses were atherosclerotic heart disease (61%), previous MI (51%), congestive heart failure (48%), hypertension (19%), cardiomyopathy (18%), and valvular disease (17%); 198 patients had a history of VT; 82 patients had a history of sustained VT. Forty patients were survivors of sudden death. Eighty-three patients had evidence of underlying conduction disturbances on baseline ECGs. The mean number of previous antiarrhythmics was 3.7 with some patients having received as many as ten marketed or investigational agents before receiving flecainide.

Of the 228 patients who received flecainide, 89 (39%) were ongoing as of September 1, 1983. Of the 198 patients with a history of VT, 70 (35%) were ongoing. Of the 82 patients who had a history of sustained VT, 21 (26%) were ongoing.

Although Holter monitoring was not required in this study, 32 ongoing patients had baseline and followup Holter recordings available for analysis. Based on the last Holter tape obtained during flecainide therapy for these patients, the median percent suppression of PVCs was 95.1%. Twenty-four of these patients had VT on their baseline Holter recordings; of these, 23 (96%) showed complete suppression of VT on their last Holter recording.

Programmed electrical stimulation (PES) was used by some investigators to determine efficacy in some patients. It is not known how many patients underwent electrophysiological testing on flecainide because investigators did not always provide these data. Fifteen patients who are known to have been tested electrophysiologically remain in the study and 25 patients who continued to be inducible by PES while on flecainide were discontinued as therapeutic failures.

Of the 228 patients who received flecainide, 139 (61%) discontinued this study. The most common single reasons for discontinuation given by the investigator were lack of response (45 patients, 25 of whom failed PES), adverse experience (41 patients), and death (27 patients). Most patients who discontinued flecainide tended to do so early in therapy in this study. Forty percent (56/139) of the patients who discontinued did so during the first week of therapy; and 65% (90/139) discontinued during the first month of therapy.

Non-cardiac adverse experiences were given as reasons for discontinuation in 26 patients (some had more than one). Most frequently reported as reasons for discontinuation were dizziness (11 patients); visual disturbances (10 patients); ataxia and nausea (four patients each); hypoesthesia, fatigue and tremor (three patients each); and nervousness, dyspnea, rash or dermatitis, paresthesia and headache (two patients each).

Cardiac side effects were given as reasons for discontinuation in 25 patients. These included: VT with increase in ectopy (12 patients); CHF (four patients); sinus node dysfunction (three patients); complete heart block (two patients); VT and CHF, VT and bundle branch block, and bundle branch block (one patient each). An additional patient was discontinued for widened intervals. These increases, as measured from study initiation to discontinuation, were: PR 0.19 to 0.32, QRS 0.10 to 0.15, and QT 0.38 to 0.54. Further evaluation identified additional patients who had apparent proarrhythmic events; some of those initially listed merely had their usual arrhythmia. Pro-arrhythmic effects, conduction disturbances, and CHF will be discussed in the Safety section below in detail. Briefly, of the 228 patients, 24 were felt to have had pro-arrhythmic events; one had an increased frequency of PVCs with short runs of VT, another bradycardia, and 22 new or worsened significant ventricular tachyarrhythmias. Of the 22 cases of sustained VT/VF, all had a prior history of VT, 16 had a history of heart failure, 19 had a history of old myocardial infarction and 12 had a documented prior arrest. Eight of the 22 patients died. All had prior MI and a history of VF and CHF. Seven of the eight had a prior arrest and the mean ejection fraction was 23.6%. The kinds of events considered pro-arrhythmic are shown in Table 27A.

TABLE 27A

Proarrhythmic Events
Characterization of New or Worsened Ventricular Tachycarhythmias

Criteria	Patient ID	No. Patients Satisfying Primary Criterion
Occurrence of non-sustained VT[a] with no previous history.		0
Occurrence of sustained VT with no recent[b] history of same.	028-26-010 028-27-002 028-37-001	3
Occurrence of VT with a more "malignant" morphology or higher rate than recently observed.	028-13-001 028-26-011 028-44-105 028-87-101	4
Asymptomatic VT which becomes symptomatic	028-44-103 028-44-104	2
VT progresses to VF[a] where this has not occurred recently.	028-26-004 028-28-004	2
Cardioversion is required where it has not been required recently.	028-21-101	1
Resuscitation is more difficult (or impossible to accomplish) than previous resuscitations.	028-12-101[c] 028-14-132[c] 028-14-133[c] 028-33-103 028-34-101[c] 028-37-003 028-42-101[c] 028-43-003[c] 028-43-005[c] 028-72-103[c]	10
	Total	22

[a] VT = ventricular tachycardia.
VF = ventricular fibrillation.
[b] The definition of "recent" depends on the investigator's determination. "Recent" may be as short a period as a few weeks if there appeared to be a stable period prior to flecainide treatment.
[c] Patient died.

Thirty-two (15%) of the patients developed new or worsened CHF (not necessarily attributable to flecainide); 26 (29%) with pre-existing failure and six (5.1%) without prior CHF. Of the 32, 18 patients stayed on treatment, some with reduced dose, five discontinued treatment at least partly because of CHF, three discontinued for other reasons, and six patients died, four of those attributed to CHF/low output. A detailed discussion of CHF appears below in the Safety section.

ECG changes were seen in many patients, including episodes of 3° A-V block, bradycardia, sinus pauses, and bundle branch block. These too are discussed in the Safety section.

Twenty-seven (11.8%) patients who received flecainide died during the study, 12 in the first 10 days of treatment. These included: 11 cases of in hospital arrhythmic death (one of which occurred after just 5 days of treatment and could represent another pro-arrhythmic death), 5 cases of out of hospital sudden death, 5 cases of CHF/low cardiac output death, 3 cases of non-cardiac death, one case of acute myocardial infarction and two cases where the patients had incomplete information at the time of the report. Most patient deaths occurred early in therapy and most occurred in patients with severe pre-existing arrhythmias and underlying myocardial dysfunction. Deaths are discussed in more detail below. As noted earlier, some of the deaths were considered possibly or probably flecainide related.

The median total daily starting dose was 400 mg; in ongoing patients the median daily dose was 300 mg. This reduction in median total daily dose after a length of time on therapy has been observed in other studies where the recommended daily starting dose was 400 mg (Study 033).

Adverse experiences will be discussed in the Safety section below, but it is of interest that reports in this study were similar to those in other chronic studies despite the expected lesser rigor of a many - investigator "compassionate" protocol.

Adverse Experiences

ADR	% of patients long-term studies chronic ventricular arrhythmias n=280 (%)	% of patient 028 n=197 (%)
Dizziness	32	26
Abnormal vision	30	25
Headache	10	6
Nausea	10	6
Tremor	4	6
Asthenia	6	3
Palpitations	6	3
Fatigue	6	3
Dyspnea	5	4
Nervousness	5	2
Chest pa	4	2

CONCLUSIONS: Flecainide at a mean dose of 334 mg/day was an effective antiarrhythmic agent for some patients in this refractory population, providing successful therapy (evidenced by continued use by the physician) for 7 to 20 months (mean, 13.5 months) in 39% of patients enrolled. The drug did not appear to be associated with clinically significant physical, opthalmologic or laboratory abnormalities. Flecainide was, however, associated with some potentially serious cardiac side effects, notably worsening of arrhythmia, congestive heart failure, and to a lesser extent, conduction disturbances. The early pro-arrhythmic events led to the development of a more controlled protocol, the Acute and Chronic Study of Ventricular Tachycardia (057 amended), which investigated the safety and efficacy of lower doses of flecainide in a similar population of patients.

b. Study 057

STUDY DESIGN: Thirteen investigators participated in this open-label study to assess the safety and efficacy of chronic oral flecainide in treating patients with ventricular arrhythmias associated with significant cardiac disease.

The minimum criteria for entry into this study were greater than 10 PVCs per hour refractory to marketed antiarrhythmic therapy. (38/39 patients had significant VT; only one patient was treated for ...tifocal PVCs.) Investigators were encouraged to enr... ...tients with significant VT (greater than or equal ... beats in a row at a rate of greater than 100 beats/min), a conduction abnormality (BBB or IVCD), or Class III or Class IV CHF (New York Heart Association Classification). Patients were excluded from the study if they had digitalis intoxication arrhythmias, second or third degree A-V block, recent unstabilized MI, QRS greater than or equal to 0.15 or PR greater than 0.28 sec, or a pacemaker dependent rhythm. Other Class I antiarrhythmic agents, investigational drugs known to cause significant organ toxicity, calcium channel blocking drugs and any other medications that would affect myocardial contractility, with the exception of cardiac glycosides, were not permitted as concomitant medications. Beta-blocking agents and beta-stimulants were allowed for patients who required these because of conditions other than arrhythmia control.

Chest radiograph, a 12-lead electrocardiogram (ECG), laboratory studies, and a 24-hour Holter recording were required within one week prior to starting flecainide. All patients with Class III or IV CHF, or a CT ratio greater than 0.50 on their prestudy chest x-ray were required to undergo radionuclide ejection fraction (RNEF) testing. The recommended starting dose of flecainide was 200 mg every 12 hours (bid). For patients with a history of either CHF or conduction abnormalities, an initial dose of 100 to 150 mg bid was suggested.

At approximately one week, one month, and three months after initiation of therapy, and at quarterly intervals thereafter, patients were required to return for follow-up evaluations.

Investigators were allowed to determine effective response to flecainide based on a patient's arrhythmia symptoms, arrhythmia monitoring (24-hour Holter and ECG rhythm strip) and occasionally by exercise stress testing or programmed electrical stimulation (PES).

Although not initially required, plasma flecainide samples were obtained in the majority of the patients.

RESULTS: Of the 39 patients who entered the study, 31 were male and eight were female. The majority of the patients had significant cardiac disease. Of the 39 patients, 29 (74%) had a history of atherosclerotic heart disease, 25 (66%) a history of congestive heart failure (CHF), and 12 (31%) a history of electrocardiographic conduction abnormalities. Thirty-eight (97%) of the 39 patients had a history of refractory ventricular tachycardia (VT) prior to starting flecainide, and one patient had multifocal premature ventricular contractions (PVCs). Although investigators were not required to characterize a patient's VT, 16 patients were reported by the investigators to have a history of sustained VT. Of the 16 patients with sustained VT, at least six were known to have a previous history of sudden death (ventricular fibrillation/cardiac arrest).

Thirty-nine patients enrolled in this study; 14 of 39 patients were ongoing for a mean length of time of 11.6 months (range ten to 12 months). Among the 25 patients who discontinued, nine were from one center where flecainide was evaluated with other investigational antiarrhythmics prior to choosing the most appropriate drug for chronic therapy and flecainide was discontinued due to side effects or "patient convenience." All nine patients enrolled at this site were discontinued after three or four days of flecainide therapy.

Efficacy in the ongoing patients was well maintained as evidenced by the frequency distributions of percent suppression of PVCs, paired beats, and VT beats. The median percent suppression of PVCs at the week one visit was 94.8% (18 patients); at all followup visits the median percent suppression was greater than 85%. The median percent suppression of paired beats was greater than 96% at all visits and the median percent suppression of VT beats was 100% (complete suppression). Overall, as of May 1, 1983, 7/17 ongoing study patients (41%) had not had any recurrence of their VT (mean length of flecainide therapy 4.8 months). In the other 10/17 ongoing patients, the investigators have considered the patients to be responders in that they have shown overall improvement of their VT.

Seven patients died. Of these seven patients, six were associated with unresuscitable ventricular arrhythmias. Four of the seven patients had a previous history of sustained VT, of which two had experienced at least one episode of "sudden death." According to the investigators, three of the deaths were possibly flecainide related, two were probably not related, one was definitely not related, and one was unknown. Four of the cases were among

"pro-arrhythmic" deaths considered at the December 1982 meeting of investigators. They occurred 10, 13, 24 and 60 days after flecainide was started.

Eight patients were discontinued as nonresponders. Seven patients discontinued because of adverse experiences, two because of adverse experiences and nonresponse, and one patient was discontinued because of personal reasons. One of the adverse experiences was a patient who developed difficult-to-convert VT/VF on exercise testing.

CONCLUSION: Flecainide was considered effective in 14 of 39 high risk patients with refractory ventricular arrhythmias for 10 to 12 months, but seven patients died, six with unresuscitable ventricular arrhythmias and several under conditions suggesting drug-relatedness.

C. Safety

Apart from its cardiac effects, flecainide had few serious side effects, although there was a high rate of dizziness and visual disturbances.

Table 28 provides an overall summary of the incidence of adverse experiences listed by study and patient population. It is notable that the rates in chronic and short term studies are similar. The adverse effects of flecainide, both cardiac and non-cardiac were generally manifested early.

Table 28
Incidence of Adverse Experiences[a] Which Occurred in Greater than 3% of Patients in Any of the Studies Presented Below

Median Starting Dose Adverse Experiences	% Patients in Short-term V-Ectopy Study (032) 400 mg/day (N = 162)	% Patients in Chronic Studies (031,033,035) 400 mg/day (N = 290)	% Patients in Compassionate-Use Study (028) 400 mg/day (N = 197)	% Patients in VT Study (057 Amended) 200 mg/day (N = 92)
Non-Cardiac				
Dizziness	32%	34%	26%	9%
Visual Disturbances	28%	31%	25%	7%
Headache	8%	12%	6%	2%
Nausea	8%	11%	6%	2%
Dyspnea	6%	5%	4%	7%
Chest Pain	6%	6%	2%	1%
Asthenia	5%	6%	3%	4%
Fatigue	4%	8%	3%	3%
Nervousness	4%	5%	2%	1%
Palpitations	4%	8%	3%	3%
Tremor	4%	5%	6%	2%
Hypoesthesia	3%	3%	3%	1%
Paresthesia	3%	1%	0%	0%
Constipation	1%	3%	3%	0%
Syncope	1%	3%	3%	2%
Rash	0%	4%	3%	2%
Cardiac				
Pro-arrhythmic events[a]	2%	4%[b]	13%	8%
CHF[a]	4%	5%	15%	10%
Serious Conduction Defects	1%	2%	4%	2%

[a]Incidence of pro-arrhythmic events and CHF were assessed by direct questioning of investigators. All other adverse experiences were assessed by indirect questioning of patients.

[b]Study 035 was not surveyed for pro-arrhythmic events.

The discussion of safety will focus on eight major areas.

1. Non-cardiac Adverse Experiences - Dizziness and visual disturbances were the most frequent non-cardiac adverse experiences reported by patients taking flecainide. Non-cardiac adverse experiences lead to discontinuation of therapy in 5% to 12% of patients. These effects appear to be dose-related.

2. Proarrhythmic Events - Approximately 6.8% of patients developed a worsening of arrhythmia while on flecainide. The risk of such a response is greatest in patients with serious arrhythmias but present in patients who have arrhythmias of lesser severity such as frequent VPCs. In the compassionate use studies about a dozen patients died from unresuscitable ventricular arrhythmias that may have been drug-related. All such patients had pre-existing congestive heart failure and were treated for ventricular tachycardia. Most had undergone previous resuscitations. While it is often difficult to distinguish an adverse drug effect from a failure of effectiveness as a cause of death, review of deaths indicate that flecainide poses life-threatening potential problems in such patients and requires close monitoring during early use.

3. Congestive Heart Failure (CHF) - Five percent of patients developed new or worsened CHF while taking flecainide. Patients with congestive heart failure prior to taking flecainide are at greatest risk of responding adversely to the drug. CHF developed rarely (1%) in patients who had no history of CHF.

4. Effects of Flecainide on the Scaler ECG and Conduction Disturbances - The majority of patients show significant increases in the PR interval and QRS intervals (each increase about 25%). These increases appear to be dose-related. First degree A-V block occurs in as many as 40% of patients. Other A-V conduction defects or effects on SA node function are less common but potentially serious. About 1% of patients have developed second or third degree A-V block and about 1.5% of patients developed evidence of sinus node dysfunction such as bradycardia or sinus pause. Occasional patients develop a time prolonged QT and one patient developed a torsade de pointes VT.

5. Effects of Flecainide on Vital Signs - Small increases in mean systolic and diastolic pressures have been seen in various patient populations studied with flecainide. Clinically significant changes, however, have rarely occurred (less than 1%). Drug related sinus bradycardia was reported in less than 1% of patients.

6. Effects of Flecainide on Routine Laboratory Measurements - Isolated elevation of alkaline phosphatase occurred in five patients studied at one center and isolated sustained SGPT elevations occurred in one patient in U.S. studies. In West German marketing experience, a small number of patients were found to have liver-related abnormalities while on flecainide. There is insufficient evidence at this time to determine whether flecainide can cause hepatic toxicity.

7. Safety Experience with the Use of Flecainide with Other Antiarrhythmic Drugs and with Beta Blockers - The experience to date does not suggest an adverse interaction between flecainide and other antiarrhythmic drugs or other beta blockers.

8. Post Marketing Experience in United Kingdom and West Germany.

Safety Section Database: The database for this discussion includes the following trials:

Dose-Ranging Study (030) n=37; Flecainide/Quinidine Comparison Study (032) n=162; Chronic Studies/Ventricular Ectopy (031, 033, 035) n=290; Compassionate Use Studies (028, 057) n=266; Acute and Chronic Study/Ventricular Tachycardia (057 amended) n=96.

The Chronic Studies/Ventricular Ectopy group included patients followed long-term who had previously been in the Dose-Ranging Study and in the Flecainide/Quinidine Comparison Study, as well as a multicenter study of 66 patients in the Netherlands which was monitored by the U.S.-based sponsor.

Spontaneous adverse reaction reports from physicians treating patients in West Germany and the United Kingdom, where flecainide is presently marketed, are included. It is estimated that over 50,000 patients have been treated in these two countries.

The NDA contains safety information on an additional 201 patients who were treated in clinical studies overseas (United Kingdom, Germany, France and Norway). Sixty-nine of these patients were followed for one year or more. The adverse reactions reported in these studies were consistent with those reported in the U.S. studies and are not part of the database for these analyses.

1. Non-cardiac Adverse Experiences (NCAEs)

The incidence of non-cardiac adverse effects which occurred in at least 3% of patients taking either flecainide or quinidine in the pivotal Flecainide/Quinidine Comparison Study is presented in Table 29. The most frequent adverse experiences in patients taking flecainide were dizziness and visual disturbances. Dizziness included reports of lightheadedness and giddiness. Visual disturbances included reports of blurred vision, difficulty focusing, spots before eyes, etc. These visual disturbances were typically most apparent on lateral gaze and were usually transient.

TABLE 29

Flecainide-Quinidine Trial

Median Daily Dose (mg) Adverse Effect	Percent of Patients Reporting Flecainide 400 (N=162)	 Quinidine 1200 (N=152)
Dizziness*	32	11
Visual Disturbances†	28	7
Headache	8	13
Nausea	8	18
Dyspnea	6	3
Chest Pain	6	1
Asthenia	5	4
Fatigue	4	5
Nervousness	4	<1
Palpitation	4	3
Tremor	4	1
Hypoesthesia	3	0
Paresthesia	3	0
Diarrhea	<1	39
Fever	0	5
Myalgia	1	4
Rash	0	5
Abdominal Pain	0	3
Vomiting	1	3

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

Animal studies have shown that flecainide possesses CNS effects which, at larger doses, are predominantly stimulant in nature. Effects of flecainide in mice and rats included ataxia and convulsions (by oral, intraperitoneal and intravenous routes) and in dogs included tremors, ataxia, emesis (by oral and intravenous routes), and clonic convulsions (by intravenous route only). Although flecainide was selected from a large series of closely related compounds primarily on the basis of reduced CNS effects, these stimulant signs, other than tremor, were prominent in animal toxicity studies when large doses were used.

Flecainide administration to humans also provokes CNS effects and the wide variety of neurological adverse experiences (dizziness, visual disturbances, tremor, hypoesthesia, parethesia, nervousness, ataxia and nystagmus) suggests effects on the central nervous system. These side effects, particularly dizziness and visual disturbances, commonly occur in the same patient, suggesting a central mechanism.

The incidence of noncardiac adverse experiences in the Flecainide-Quinidine Comparative Study (032) compared to that found in the Chronic Studies/Ventricular Ectopy (031, 033, 035), the Compassionate-Use Study (028), and the Acute and Chronic Study of Ventricular Tachycardia (057 amended) showed that experiences were quite similar in the different patient populations except that patients treated in 057 amended, the Acute and Chronic Study of Ventricular Tachycardia, had much lower incidences of adverse experiences, particularly dizziness and visual disturbances (see Table 28). These lower incidences appear to be associated with lower doses of flecainide (usually 200 to 300 mg/day) than those most commonly used in the other studies (400 to 600 mg/day).

Further evidence that noncardiac adverse experiences are dose-related is provided by intrapatient comparisons in the Dose Ranging Study (030) and the Flecainide-Quinidine Comparison Study (032). The following figure (Figure 13) shows the incidence of common noncardiac adverse experiences in patients who had the opportunity to receive two or more dosing regimens of flecainide. Lower daily doses were associated with fewer reports of noncardiac adverse experiences.

FIGURE 13

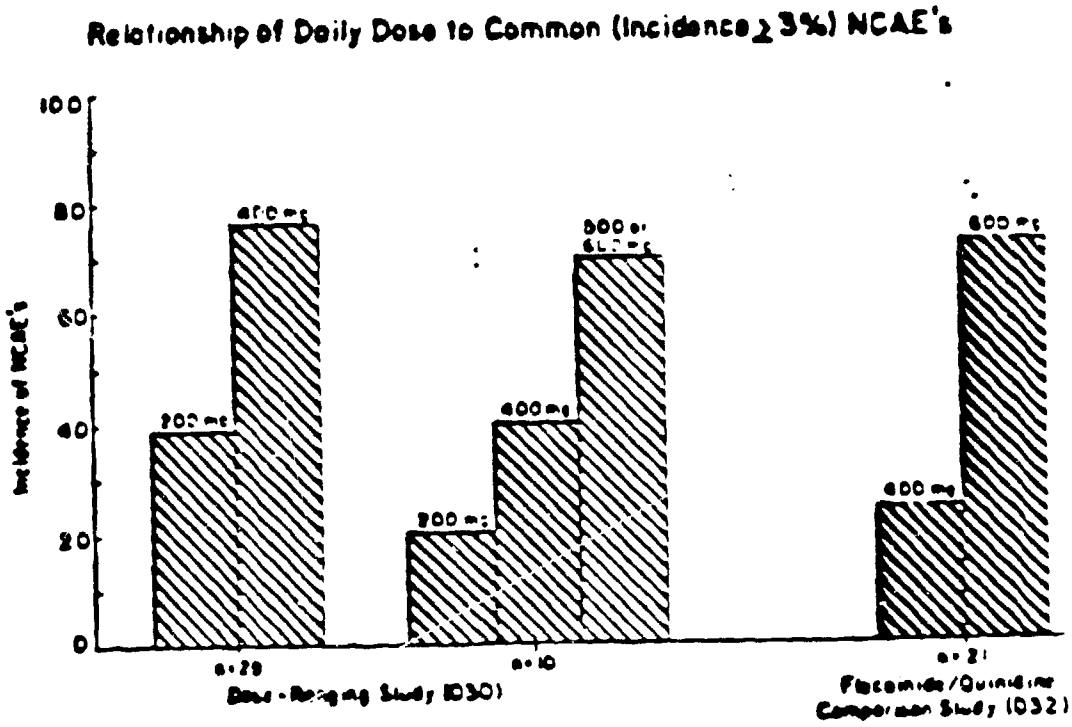


Table 30 shows the significant adverse experiences associated with flecainide therapy reported by 1% to 3% and by less than 1% of patients in all the major efficacy trials.

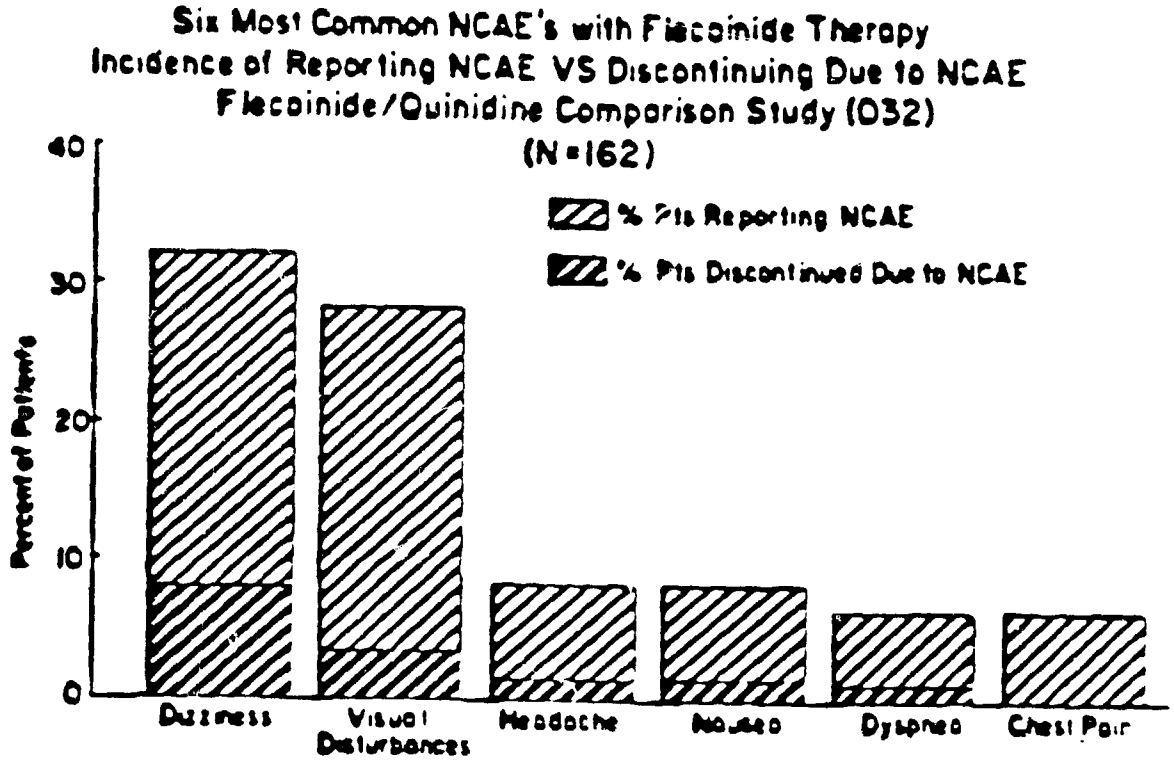
TABLE 30

Significant Adverse Experiences
Occurring in 1-3% and Less Than 1% of Patients
In All Major Efficacy Trials

	1% to 3%	Less Than 1%
Body as a Whole:	edema, malaise, fever	arthralgia, bronchospasm, myalgia, swollen lips, tongue and mouth
Cardiovascular:	tachycardia, sinus pause or arrest	angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension
Gastrointestinal:	vomiting, dyspepsia, anorexia, diarrhea	flatulence
Hepatic:		jaundice, elevation of transaminase levels and alkaline phosphatase levels,
Renal:		polyuria, urinary retention
Skin	rash	exfoliative dermatitis, urticaria pruritis
Visual	diplopia	eye pain or irritation, photophobia, nystagmus
Nervous system:	hypoesthesia paresthesia, paresis, ataxia, flushing, increased sweating, syncope, somnolence, tinnitus, vertigo	weakness, change in taste, twitching, dry mouth, convulsions, impotence, speech disorder, stupor
Psychiatric:	anxiety, insomnia, depression	amnesia, confusion, morbid dreams, apathy, decreased libido, depersonalization, euphoria

Noncardiac adverse experiences usually did not require discontinuation of flecainide. In the Flecainide-Quinidine Comparative study (032), 12% of patients discontinued because of noncardiac adverse experiences. It is possible, of course, that patients tolerated two weeks of symptoms that would not have proved acceptable in a longer-term study. Figure 14 below compares the incidence of reporting the six most common adverse experiences with the incidence of discontinuing flecainide because of each adverse experience in this trial. All patients treated in this study received doses of 400 to 600 mg/day and downward dosage adjustments to decrease side effects were not allowed in this protocol. In the Acute and Chronic Study of Ventricular Tachycardia (057 amended) which used lower doses (usually 200 to 300 mg/day), 3% of patients discontinued because of noncardiac adverse experiences.

FIGURE 14



In summary, dizziness and visual disturbances were the most frequent noncardiac adverse experiences. Noncardiac adverse experiences were usually well tolerated but led to discontinuation in 5% to 12% of patients. It appears that the incidence of noncardiac adverse experiences is dose-related, and the use of daily doses in the range of 200 to 300 mg/day is associated with a lower incidence of adverse experiences resulting in a much lower rate of discontinuation.

2. Proarrhythmic Events and Arrhythmic/Sudden Deaths

a. Early observation of pro-arrhythmic events - survey

As described previously, early experience in the 028 and 057 protocols showed that flecainide could have important pro-arrhythmic effects. An initial review was carried out because investigators were reporting examples of patients who sustained cardiac arrest in which resuscitation was unexpectedly difficult or impossible, even in good clinical circumstances. Sixteen patients with in-hospital deaths after an arrest, 12 within the first two weeks of flecainide therapy, were examined (four arrested outside the hospital, received CPR outside before reaching the hospital, but care may have been less than optimal). It was clear that they were members of a very sick population, six with mean EF of 25%, prior AMI in 15/16, a history of CHF in 15/16, prior cardiac arrest in 11/16, but some of the episodes seemed to represent drug-related worsening. No particular ECG or other lab finding marked these patients particularly, but plasma levels were higher than expected in the eight patients measured with 7/8 above 1000 ng/ml and 5/8 above 1900 ng/ml, compared with less than 1000 ng/ml in most patients in chronic studies. The possibility thus arose that the doses used were too high, at least for this population. Of the 12 who died within two weeks, 10/12 were receiving at least 400 mg/day.

The review of the 16 deaths led to a change in the protocol used for seriously ill patients (057 amended) and to a more detailed look at possible pro-arrhythmic events (fatal and nonfatal) in all treated patients. Because there had been no prospective definition of, or search for, pro-arrhythmic events the best available mechanism for receiving data up to that point was felt to be a survey of investigators, relying on their judgement to determine whether worsening of arrhythmia had occurred. While this is reasonable, it should be appreciated that this approach has numerous problems, some of them inherent in any open study of patients with serious arrhythmias, some in the survey methodology. The approach will, in general, not capture one class of pro-arrhythmic events at all, those being sudden deaths. These could represent pro-arrhythmic events but there is no way to know this in the absence of a control group. There is also a distinct possibility of overreporting in any study of this kind, as it is often impossible strictly to distinguish lack of effectiveness from a pro-arrhythmic event.

Fifty-five of 57 investigators responded to a questionnaire regarding proarrhythmic events and provided information on 588 of 592 patients surveyed. This survey included all patients studied in the major efficacy trials conducted in the U.S. with the exception of the Acute and Chronic Study of VT (057 amended). (In that study, designed after the pro-arrhythmia question had arisen, specific questions regarding proarrhythmic events were included in the case report forms.) Investigators were each allowed to use their own criteria to determine whether drug related worsening of arrhythmia had occurred. With three exceptions, two cases of QRS widening and one of second degree heart block (not an arrhythmia), the investigator's criteria were accepted.

b. Results of survey

Proarrhythmic events were reported in 47 (8%) patients; less the three doubtful cases, there were 44 such events in 588 patients (7.5%). Thirty of the events occurred among the 254 relatively ill patients from studies 028 and 057 (11.8%) while the remaining 14 took place in 334 other patients (4.2%). The rate in study 057 amended was 10/96 (10.4%).

Not all pro-arrhythmic events were equally worrisome. The sponsor classified them in three broad categories:

Category I - Increased PVC's compared to baseline (6 patients, no fatalities)

- One patient showed a tenfold increase compared to baseline Holter.

- Two patients showed a 3-4 fold increase compared to baseline Holter, one with new salvos of VT (that case should perhaps have been placed in category III).

- One patient showed a 50% increase compared to baseline Holter.

- Two patients showed more frequent VPCs on rhythm strip than had been seen on baseline Holter.

(Of these, only the 10-fold increase is really a persuasive pro-arrhythmic event, as spontaneous 50% to 3-4 fold changes are not uncommon.)

Category II - New supraventricular arrhythmias (5 patients, two fatalities)

- One patient developed severe sinus bradycardia and could not be resuscitated

- One patient developed AF with a bizarre wide QRS complex and could not be resuscitated

- One patient developed new SVT

- Two patients developed sinus pauses with junctional escape rhythms

(The patient with AF was thought at post-mortem to have an evolving AMI.)

Category III - New or Worsened Ventricular Tachyarrhythmia (33 patients, 12 fatalities)

- 1 New non-sustained VT

- 8 Sustained VT without recent history of this,

- 4 Increased rate or more"malignant" morphology of VT

- 2 Asymptomatic VT became symptomatic,

- 3 VT progressed to VF with no recent history of this,

- 1 Cardioversion required with no recent history of this,

- 14 Resuscitation more difficult or impossible (12 died).

In three of these cases (one hypotensive VT needing rep ated cardioversion, one new morphology VT requiring cardioversion and one sustained VT/VF with difficult resuscitation) the pro-arrhythmic event was observed during PES.

Among the 44 patients with pro-arrhythmic events, 18 had resuscitations that were prolonged, required unusual measures, or were unsuccessful, and 14 of these patients died. The clinical background for these patients is shown in Table 30A.

All of the patients who died, except one, were from studies 057 and 028. The only exception was a patient from study 033 that had a history of sustained VT on quinidine and procainamide and was always PES-inducible; death occurred after aprindine was begun. The patients were all clearly very ill, all 14 having histories of cardiac failure and

Table 30A
Patient Deaths

Study/Ptno	AGE	SEX	ASHD	OLD MI	HISTORY OF CHF	VT	CHF AND VT	DOCUMENTED PRIOR ARREST	LEFT VENTRICULAR EJECTION FRACTION (%)	CONCOMITANT MEDICATIONS	FLECAINIDE TOTAL DAILY DOSE (MG)	WEIGHT (KG)	PLASMA FLECAINIDE LEVELS (NG/ML)	DATE OF DEATH
028-12-101	44	M	+	+	+	+	+	+	17	Digoxin, Lasix, Coumadin, prednisone	600	64.4	6/10/82 553 ng/ml	6/12/82
028-14-112	75	M	+	+	+	+	+	+	30	Prazosin, Lasix, Isordil	200	64.4	none	6/06/82
028-14-132	61	M	+	+	+	+	+	+	25	Digoxin, Lasix, Minipress	400	89.4	none	10/22/82
028-14-133	55	M	+	+	+	+	+	+	12	Digoxin, Lasix, Isordil, hydralazine Coumadin	400	62.6	none	11/02/82
028-34-103	66	M	+	+	+	+	+	+	28	Digoxin, Lasix	400	69.4	10/30/82 471 ng/ml (4-1/2 hrs postdose)	10/30/82
028-42-101	61	M	+	+	+	+	+	-	15-18	Prednisone, Albuterol inhaler	500	67.1	none	9/24/82
028-43-003	55	M	+	+	+	+	+	+	30	Digoxin, Lasix, Isordil, allopurinol	400	90.7	6/28/82 1296 ng/ml	6/30/82
028-43-005	72	M	+	+	+	+	+	+	20	Digoxin, Lasix, Isordil	400*	81.7	none	7/14/82
028-72-103	73	M	+	+	+	+	+	+	35	Digoxin, Lasix	200	61.2	11/9/82 2238 ng/ml	11/09/82
033-14-006	22	M	-	-	+	+	+	+	16	Lasix, Isosorbide, Coumadin, aprindine	300	79.8	10/12/81 1468 ng/ml 1/8/82 2594 ng/ml	1/11/82
057-02-204	80	M	+	+	+	+	+	-	46	Lanoxin, Lasix, nifedipine	400	84.8	10/7/82 595 ng/ml 10/11/82 2050 ng/ml	10/11/82
057-02-205	55	F	+	+	+	+	+	-	24	Digoxin, Lasix, Aldactone, nifedipine prazosin	250	68.0	11/3/82 1303 ng/ml 11/7/82 2401 ng/ml	11/07/82
057-03-003	66	M	+	+	+	+	+	+	28	Digoxin, Lasix, Coumadin	400	71.2	9/3/82 418 ng/ml	9/13/82
057-06-007	72	M	+	+	+	+	+	+	24	Digoxin, Isosorbide, HCTZ, mexiletine	200	71.7	11/2/82 566 ng/ml	11/29/82

* Dose of flecainide had been increased from 200 BID to 300 BID, patient received one 300 mg dose.

prior VT, 13/14 having a history of AMI, and 11/14 having been previously resuscitated; the mean EF was 24%. Nine of the 14 had plasma levels of flecainide within a few days of death, and, of these, five were outside the therapeutic range (upper limit 1000 ng/ml).

Proarrhythmic events were most likely to occur early in flecainide therapy; 43% in the survey occurred within the first four days of therapy and 57% within the first seven days. These events are also more likely to occur soon after a dosage change: 29% of proarrhythmic events in this survey occurred within four days of a dosage change. (It is possible, of course, that earliness of therapy or a recent dosage change were what led the investigator to identify an arrhythmic event as "pro-arrhythmic").

c. Comparison of pro-arrhythmia patients and other patients

The patients in whom pro-arrhythmia events developed were not distinct from the rest of the patients except with respect to the seriousness of their underlying disease. The mean daily dose was only slightly higher in the pro-arrhythmic patients (369 mg/day vs an average of 339 mg/day in all patients in chronic studies), not a likely source of the difference and perhaps simply a reflection of the initial dose in all studies being 400 mg and the early nature of most pro-arrhythmic events.

ECG interval changes were not helpful in predicting a pro-arrhythmic response. Interval changes were compared for 4 subsets of patients with pro-arrhythmic events (deaths, non-deaths, category I, II of arrhythmias, category III of arrhythmias) and two control groups, patients in studies 031 after one year of therapy and in 033 after six months of therapy. Data were available for 36 of the 44 pro-arrhythmia patients; in all cases the dose at the time of ECG was the same as that at the time of the pro-arrhythmic event. Results are shown for absolute interval change and percent change in Tables 30B and 30C. It can be seen that, in general, there are not major differences. QRS was significantly prolonged in the all pro-arrhythmia events, fatal PA events and Category III groups compared to study 033 but not study 031. There is perhaps a suggestion of a greater effect on JTc in the fatal and category III subgroups but it is a minimal difference at best. Patients with large interval changes (at least 50%) in PR, QRS, or QTc were no more common among the total or fatal pro-arrhythmia groups than in the patients in study 032 who experienced no pro-arrhythmic events.

The pro-arrhythmia patients did differ from the others in cardiovascular diagnoses and histories.

	Percentage of Patients with Diagnosis/History of:				
	ASHD	MI	VT	CHF	VT and CHF
Patients with PA-events	73	68	80	57	52
Other Patients	50	38	44	28	19
Ratio PA/Other	1.5	1.8	1.8	2.0	2.7

Proarrhythmic Events Associated With Flecainide Therapy

TABLE 30B

Mean Absolute Increase from Baseline ± 1 Standard Error (Seconds)

ECG Interval	Patients with PA[a] Events (n=36)	PA Deaths (n=12)	PA Non-Deaths (n=24)	PA Patients Categories I & II (n=11)	PA Patients Category III (n=25)	Chronic Patients on Flecainide 031-Month 12 (n=23)	Chronic Patients on Flecainide 033-Month 6 (n=95)
PR	0.040 ± 0.008	0.044 ± 0.013	0.038 ± 0.009	0.030 ± 0.014	0.045 ± 0.009	0.042 ± 0.006	0.032 ± 0.002
QRS	0.023 ± 0.004	0.030 ± 0.009	0.020 ± 0.005	0.015 ± 0.006	0.026 ± 0.006	0.025 ± 0.003	0.015 ± 0.002
QTc	0.029 ± 0.011	0.056 ± 0.023	0.015 ± 0.010	0.010 ± 0.012	0.037 ± 0.014	0.020 ± 0.010	0.023 ± 0.005
JTc	0.006 ± 0.010	0.018 ± 0.019	0.000 ± 0.011	-0.003 ± 0.015	0.010 ± 0.012	-0.004 ± 0.009	0.005 ± 0.008

TABLE 30C

Mean Percent Increase from Baseline ± 1 Standard Error (Seconds)

ECG Interval	Patients with PA Events (n=36)	PA Deaths (n=12)	PA Non-Deaths (n=24)	PA Patients Categories I & II (n=11)	PA Patients Category III (n=23)	Chronic Patients on Flecainide 031-Month 12 (n=23)	Chronic Patients on Flecainide 033-Month 6 (n=95)
PR	23 ± 4	23 ± 7	23 ± 5	20 ± 7	25 ± 4	26 ± 4	20 ± 2
QRS	24 ± 5	29 ± 10	22 ± 6	15 ± 6	28 ± 7	32 ± 5	18 ± 2
QTc	7 ± 3	14 ± 6	4 ± 2	3 ± 3	9 ± 4	5 ± 3	6 ± 1
JTc	0.0 ± 0.03	0.1 ± 0.05	0.0 ± 0.03	0.0 ± 0.05	0.0 ± 0.04	-0.4 ± 3	3 ± 2

[a] PA = Proarrhythmic.

Although the risk of a pro-arrhythmic event is clearly greater in the patients with a prior history of ASHD, AMI, CHF and post VT, and was greater in the studies of patients with serious arrhythmias and a higher likelihood of such risk factors, patients with lesser degrees of illness and, in particular, no prior history of sustained VT, are also at risk for a serious arrhythmic event as the following cases illustrate:

Category I

1. 033-05-16

2. 033-17-025

Category III

3. 032-08-006

4. 032-17-017

5. 033-13-015

6. 033-14-006

7. 033-17-012

8. 057-02-204

9. 028-WD-101

Cases 033-05-16 and 032-17-017 represent apparent induction of new non-sustained VT; cases 028-WD-101, 032-08-006, 033-13-015, 033-17-012, and 057-02-204 represent new sustained VT in patients without prior history of more than short non-sustained VT. Because these cases emerged in open studies, it is not possible to say whether these event rates were more, less or just as frequent as they would have been with other, or no, antiarrhythmic therapy, but they were considered by investigators to represent possible flecainide-caused events and the case histories support this possibility.

818-033-05-16

This 53-year-old male had a history of ASHD and hypertension treated with nadolol. A month prior to flecainide therapy a Holter showed 158 PVCs/hour. Flecainide was started on 10/22/81 at 200 mg BID. This was stopped due to complaints of dizziness, fatigue, weakness and staggering on 10/24 and restarted three days later at 150 mg BID. Two weeks later a Holter showed 709 PVCs/hour and salvos of VT. Flecainide was discontinued on 11/12. There were no significant changes in PR, QRS or QT intervals.

818-033-17-025

This 66-year-old male had a history of old anterior myocardial infarction with angina and class I congestive heart failure. A mitral insufficiency murmur and an S3 gallop were heard prior to therapy with flecainide. At baseline patient had an average of 133 PVCs/hour with bigeminy and R on T phenomenon. Prior antiarrhythmic therapy included quinidine, Pronestyl and tocainide. On 11/5/81 flecainide 200 mg BID was started and his PVCs increased to 178 per hour. The dose was increased to 300 mg BID which caused dizziness, blurred vision and headache. On 11/25 he entered the 033 study on flecainide 50 mg BID which reduced PVCs to 25 per hour. On 1/7/82 the dose was increased to 50 mg TID. In February, the patient had approximately 60 PVCs per hour. This increased to 575 PVCs per hour in June. On 8/9 flecainide was increased to 100 mg TID, the Holter on 8/19 showed 1651 PVCs per hour. Flecainide was discontinued on 9/8. PR interval prior to flecainide therapy was 0.28, QRS was 0.10, QT was 0.46. On therapy in August 1982, PR interval was 0.20, QRS was 0.09 and QT was 0.52.

818-032-08-006

This 55-year-old male had a history of old inferior myocardial infarction and coronary bypass surgery. He was being treated with Isordil for angina and Coumadin for recurrent deep vein thrombophlebitis. Prior antiarrhythmic therapy, for frequent PVCs, included quinidine, disopyramide and acebutolol. The patient was started on flecainide at 200 mg BID on 6/19/81 for an average of 128 PVCs/hour. The dose was increased to 300 mg BID on 6/26 because he had achieved only 52% suppression of PVCs. "On 6/28 the patient reported to the ER with palpitations and lightheadedness, the evaluation revealed wide complex tachycardia which did not respond to usual conservative meas[illegible] such as Valsalva and Tensilon. He did respond to a 50 [illegible] sec. cardioversion and converted to relatively

regular rhythm. He was admitted to CCU and continued on flecainide 300 mg BID. Approximately 1-1/2 hours after the next dose, he again developed wide complex arrhythmia. All further medications were held, except the nitrates, and over the next 12 hours, he converted back to his normal ECG. A prophylactic pacemaker was inserted at the time he had the wide complex tachycardia because of possible periods of complete heart block. The patient did well and was subsequently discharged on alternate antiarrhythmic therapy. The PR interval prior to flecainide was 0.16, QRS 0.08 and QT 0.44. On the 25th of June at 200 mg BID the PR interval was 0.17, QRS 0.07 and QT 0.37. Within hours after cardioversion, the PR was 0.22, QRS was 0.18 and QT was 0.48.

818-032-17-017

This 63-year-old male had a history of hypertensive cardiovascular disease treated with Catapres. Holter monitor showed 70 PVCs per hour with couplets. Flecainide therapy was started at 200 mg BID on 10/8/81. A week after starting flecainide, his Holter showed 245 PVCs per hour and non-sustained ventricular tachycardia which had not occurred before. The PR interval prior to flecainide was 0.19, QRS 0.09 and QT 0.36. On flecainide the PR interval was 0.23, QRS 0.13 and QT 0.44.

818-033-13-015

This 64-year-old diabetic male had a history of an old inferior MI and multifocal PVCs with couplets. Previous therapy included procainamide, tocainide and quinidine. He completed the 032 study on quinidine. The patient entered the 033 study and started flecainide on 8/17/81 at 200 mg BID. This was stopped on 8/24 due to malaise. "Holter on 8/24 demonstrated ventricular tachycardia starting at 18:46 and continuing to end of tape at 21:12. Ventricular tachycardia was still present at exam on 8/26. He was admitted to the hospital and cardioverted. Patient had stopped taking flecainide himself and prior to this was taking flecainide irregularly. He was in CHF at this time (probably percipitated by VT). Patient had sino-atrial conduction time abnormality at EP study after cardioversion." PR interval prior to therapy was 0.14, QRS was 0.13, QT was 0.42. On 8/24 the PR interval was 0.20, QRS was 0.14, QT was 0.40.

818-033-14-006

This 22-year-old male had a history of severe congestive cardiomyopathy felt likely secondary to excessive alcohol intake. He had easy fatigability, extertional dyspnea, orthopnea and PND. He was found to have cardiomegaly, hepatomegaly and a pleural effusion with an ejection fraction of 16%. He was treated with digoxin, Lasix and isosorbide dinitrate. Holter monitoring showed 7,500 PVCs over a two-day period, with episodes of nonsustained ventricular tachycardia. He was placed on quinidine; six days later he had an episode of ventricular tachycardia and fibrillation from which he was successfully resuscitated. Following successful EP study on 10/5/71, he was started that day on flecainide, 200 mg BID, however he developed syncope on 12/31/81. He later underwent repeat EP study which showed nonsustained ventricular tachycardia could be readily induced. The decision was made to discontinue flecainide. On 1/9/82 the dose was reduced from 250 mg BID, to 150 mg BID at which time aprindine was begun. Two days later he abruptly went into sustained ventricular tachycardia, which degenerated into ventricular fibrillation. Cardioversion resulted in asystole and he could not be resuscitated. According to the investigator, "while flecainide initially proved 95% suppression of his ventricular ectopy, and completely controlled his ventricular tachycardia, the episode on 12/31/81 (syncope), in retrospect, was likely ventricular tachycardia. A subsequent electrophysiology was 'different' from the one done on 10/31/81, and indicated that yet another antiarrhythmic medication should be tried. His death was an arrhythmic death." Prior to therapy the PR interval was 0.18, QRS 0.14 and QT 0.44. On flecainide, the PR interval was 0.20, QRS 0.12 and QT 0.52.

818-033-17-012

This 68-year-old male had a history of cardiomyopathy and hypertension treated with captopril. A S3 gallop was heard prior to therapy with flecainide. On 8/20/81, flecainide therapy at 200 mg BID was instituted for PVCs with couplets, bigeminy and ventricular tachycardia "3 beats in a row." Patient achieved 99% suppression of baseline PVCs (1,200 PVCs/hour) in the 032 study. On 9/10 he entered the 033 study on the same dose of flecainide, 200 mg BID. Two days later he entered the hospital with ventricular tachycardia requiring CPR, bretylium, magnesium sulfate, lidocaine, dopamine, propranolol and IV digoxin being given before he maintained normal sinus rhythm. The investigator noted that the patient had had a similar event while on

therapy with Pronestyl. Prior to therapy his PR interval was 0.18, QRS was 0.09, QT was 0.42. On therapy the PR interval was 0.24, QRS was 0.12, QT was 0.54.

818-057-02-204

This 80-year-old male had a history of recurrent subendocardial myocardial infarctions, and class III congestive heart failure with an ejection fraction of 46% (higher than expected because of mitral regurgitation). He had symptoms of dyspnea, orthopnea, PND, edema, fatigue and palpitations. He had chronic atrial fibrillation and was treated with Lanoxin, nifedipine, Lasix and hydralazine. Previous antiarrhythmic therapy for multifocal PVCs included quinidine and procainamide, which were discontinued due to side effects, and disopyramide, discontinued because of increasing heart failure. The patient was begun on 100 mg flecainide BID on 10/2/82. Over the next 10 days he was gradually increased to 200 mg BID because of lack of therapeutic effect. On 10/11 "patient came to ER complaining of increased shortness of breath and fatigue." ECG showed wide, irregular QRS complex tachycardia without P waves. This rhythm was unresponsive to cardioversion and continued until death. This patient had no prior history of sustained ventricular tachyarrhythmias before beginning flecainide. The patient had severe left ventricular dysfunction. Post mortem exam showed recent posterior infarction. QRS prior to flecainide therapy was 0.116, QT was 0.329. Four days before his death, the QRS was 0.132, QT was 0.379.

818-028-WD-101

This 58-year-old male had a history of cardiomyopathy and cerebral embolus secondary to atrial fibrillation. He was being treated with flecainide for chronic atrial fibrillation by an investigator (W.D.) using a separate IND application for this purpose. Concomitant medications included digitoxin and Coumadin. On 10/23/82 flecainide 100 mg BID was started and increased on 11/1 to 200 mg TID with conversion to normal sinus rhythm. On 12/18 the dosage was changed to 300 mg q12 hours. The patient went in and out of atrial fibrillation, and on January 25, 1983, the Holter showed recurrent ventricular tachycardia alternating with sinus rhythm. The patient was hospitalized and flecainide was withdrawn. Atrial fibrillation returned with only occasional PVCs thereafter noted. Patient's digitoxin level was normal at the time of his ventricular tachycardia. The ECG intervals on 10/19/82, prior to flecainide were QRS 0.12, QT 0.40, on 1/3/83 the PR was 0.24, QRS 0.12 and QT 0.46.

d. Arrhythmic Deaths and Sudden Death

Through October 15, 1983, 65 of 770 patients receiving oral flecainide had died. Six of these were non-cardiac deaths; 3 were deaths associated with an autopsy-proven acute myocardial infarction; 8 were deaths attributed to congestive heart failure and low-output states (see discussion of CHF below). The remaining 44 deaths were caused by documented arrhythmias or were sudden deaths; these are summarized in two tables, 30D and 30E, showing in-hospital documented arrhythmic deaths (21 of the 44) and out-of-hospital sudden or unobserved deaths (23 of the 44), respectively. The tables include the investigator's opinion of the relation to flecainide; but note that this changed in some cases when a "no-relation" case was included as a possible pro-arrhythmic event in the survey. Of course, sudden death experiences, some undoubtedly resulting from an undocumented AMI, in this population are to be expected and cannot, in most cases, be attributed to flecainide. As discussed earlier, however, some did seem to represent pro-arrhythmic events and have been included in the survey, and a number of others, not in the survey, but ocrurring early after therapy could potentially represent pro-arrhythmic events. With respect to the latter, the following cases are of interest because there was no prior history of sustained VT and because they occurred relatively soon after starting flecainide.

1. 033-02-007

2. 033-17-005

3. 028-59-101

R-818-033-02-007

This 63-year-old male with ASHD received flecainide for three weeks with good suppression of his chronic ectopy until he suddenly collapsed at home after breakfast. Upon arrival of the paramedics, he was found to be in asystole. During treatment he developed a supraventricular rhythm which degenerated into VT and VF, and he could not be resuscitated in the ambulance or emergency room. Cause of death was listed as "either ventricular tachyarrhythmias or ventricular asystole." The investigator felt that the patient's death was possibly related to flecainide. Although this patient's data was presented at the Flecainide Investigators' Meeting in December 1982, the investigator chose later not to consider this patient's death as a proarrhythmic event in that survey.

R-818-033-17-005

This 50-year-old male with ASHD, a previous MI and congestive failure received flecainide for four days for ventricular ectopy when he collapsed while attending a picnic. Monitoring by paramedics demonstrated ventricular tachycardia which was extremely resistant to therapy in the ambulance and the hospital room. The patient could not be resuscitated. The cause of death was listed by the investigator as "ventricular fibrillation, with severe atherosclerotic heart disease, severe CHF." The investigator felt that the patient's death was probably not related to flecainide.

R-818-028-59-101

This 64-year-old male received flecainide for frequent PVCs unresponsive to conventional drugs. After three days of monitoring, his arrhythmia appeared to be well controlled, but while playing tennis the following day he collapsed, and cardiopulmonary resuscitation was unsuccessful. He was dead on arrival at the local hospital. The cause of death was listed as "ventricular fibrillation." The investigator felt a relationship of the death to flecainide was possible.

SUMMARY OF I .IENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

TABLE 30D

Patients Who Developed Arrhythmias In-Hospital Leading to Death

R-818 Study No.- Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
●*028-12-101	44	M	+	+	+	VT	+	+	600	6 days	VT	No
●*028-14-112	75	M	+	+		VT	+	+	200	5 days	Cardiac arrest	No
028-14-114	76	F	+	+	+	VT	+	+	250	6 mos	VT/VF as a result of ischemic heart disease and E-M dissassociation	No
028-14-123	61	M	+	+		VT	+	+	500	5 days	VT	No
●*028-14-132	63	M	+	+	+	VT	+	No CHF EF 13%	400	3 days	Cardiac arrest as consequence of VT	Probably
●*028-14-133	55	M	+	+	+	VT/VF	+	+	400	2 days	VT/VF	Probably
●*028-34-103	66	M	+	+		VT/VF	+	+	400	11 days	Incessant VT	Probably
*028-42-101	61	M	+	+	+	VT		+	500	2 days	Acute coronary insufficiency with subsequent exacer-bation of ventric-ular dysrhythmias	Probably not
●*028-43-003	55	M	+	+		VT/VF	+	+	400	5 days	Ref.V-arrhythmia, low cardiac out-put → acidosis	Possible
●*028-43-005	71	M	+	+		VT	+	+	600	4 days	Refractory VT	Unknown
●*028-72-103	73	M	+	+		VT	+	+	300	5 days	Cardiac arrest	Possible

* Patients discussed at Investigator's Meeting, December 10, 1982.
● Deaths related to proarrhythmic events in survey, February, 1983.

SUMMARY OF PATIENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

TABLE 30D (Concluded)

Patients Who Developed Arrhythmias In-Hospital Leading to Death

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Investi-gator's Opinion: Death Related to Flecainide?
033-06-005	74	M	+			PVCs		+	400 (off F 5 days)	30 days	Terminal VF	No
033-06-016	75	M	+	+		PVCs			400	9-1/2 mos	Cardiac arrest (VT/VF)	Probably not
@*033-14-006	22	M			+	VT/VF	+	+	300	3-1/2 mos	VT/VF asystole	No
@*057-02-204	80	M	+	+		PVCs		+	400	9 days	VF resulting in cardiogenic shock & death	Possible
*057-03-003	66	M	+		+	VT/VF	+	+	200	3 days	Incessant VT	Possible
*057-06-007	72	M	+	+		VT	+	+	200	2 mos	Recurrent VT	Probably not
057-08-005	54	M			+	VT	+	+	500	12 days	Intractable VF	Probably not
(035)-EM-03-203	39	M			+	VT		+	400	4 days	VF	Probably not
(035)-EM-03-016	53	M	+	+		VT		+	400	1 day	VF	Possible
(035)-EM-03-006	31	M				VT			400	8 mos	VT - asystole	Probably not

* Patients discussed at Investigator's Meeting, December 10, 1982
@* Deaths related to proarrhythmic events in survey February, 1983.

SUMMARY PATIENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

TABLE 30E

Patients Who Died Following Out-of-Hospital Sudden Death Experiences
or Unobserved Deaths

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
028-02-104	76	M	+	+		VT/VF	+	+	200	13 1/2 mos	Probable cardiac arrest due to ischemic heart disease	Probably not
028-07-105	62	M	+	+		PVCs			300	7 mos	Possible CVA	Probably not
028-14-120	61	M	+		+	VT			200	2 mos	Probable cardiac arrest and sudden death	Probably not
028-55-001	71	M	+	+		VT		+	400	1 1/2 mos	Cardiac arrhythmia	Unknown
028-59-101	64	M	+	+		PVCs		+	400	4 days	V-fib	Possible
028-74-102	52	M	+			VT			350	5 mos	AMI, Cardiac arrest?	No
*031-03-009	63	M	+	+		VT			400	25 mos	VF	Possible
032-06-004	71	M	+	+		PVCs		+	600	14 days	Possible acute arrhythmia	Probably not
033-02-001	66	M				PVCs			400	16 mos	Probable arrhyth-mia either with or without MI	Probably not
*033-02-007	63	M	+	+		PVCs		+	200	21 days	Either VT or V-asystole	Possible
033-06-007	76	M	+	+		PVCs		+	400	6 mos	Cardiac arrest & arrhythmia. ? 2° to AMI	No

* Patients discussed at Investigator's Meeting, December 10, 1982.

SUMMARY OF PATIENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

TABLE 30E

Patients Who Died Following Out-of-Hospital Sudden Death Experiences
or Unobserved Deaths

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
033-11-002	49	M	+		+	VT		+	200	15 1/2 mos	Cardiac arrhyth-mia probable VF	No
033-13-008	71	M	+			VT			400	2 mos	Sudden death ? MI ? arrhythmia	No
033-14-14	61	M	+	+		VT			400	10 mos	Probable MI, cardiac arrest	Probably not
*033-17-005	50	M	+	+		PVCs		+	400	4 days	VF with severe ASHD, severe CHF	Probably not
057-01-101	51	M	+	+		VT	+		400	2 1/2 mos	VT/VF sudden death	Possible
@*057-02-205	55	F	+	+		VT		+	250	24 days	Arrhythmia ?type ? cause	Possible
057-02-206	75	M			+	VT/VF	+	+	200	7 mos	Sudden death, either AMI or arrhythmia	Unknown
057-07-101	71	M	+	+	+	VT/VF	+	+	300	70 days	Arrhythmia-either primary or secon-dary to ischemic event	Probably not
057-07-103	67	M	+	+	+	VT		+	200	13 days	Ischemia causing pulmonary edema (inferred)	Probably not

* Patient discussed at Investigator's Meeting, December 10 1982.
@ Deaths related to proarrhythmic events in survey February, 1981.

SUMMARY O IENTS WHO DIED WHILE
RECEIVING FLECAINIDE THERAPY

TABLE 30E (Concluded)

Patients Who Died Following Out-of-Hospital Sudden Death Experiences or Unobserved Deaths

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
(035)-BM-03-209	55	M	+	+		PVCs			300	14 mos	Cardiac arrest	No
(035)-BM-03-105	66	M	+	+		PVCs			400	1 mo	Sudden death, Probable VF	No
(035)-BM-03-024	67	F	+	+		VT		+	400	6 days	Myocardial infarction	Probably not

Of the 44 patients, 38 (86%) had ASHD, 32 (73%) had a prior AMI, 14 (32%) had cardiomyopathy, 18 (41%) had a prior cardiac arrest requiring resuscitation, 32 (73%) had histories of VT and/or VF while 12 (27%) were being treated for chronic VPCs, and 31 (70%) had prior histories of CHF.

Sixteen of the 44 (36%) died within the first 10 days of flecainide therapy; 24 (55%), within the first month. The mean dose was 365 mg/day.

The following tables summarize all of the cardiac deaths in flecainide-treated patients by study through October 15, 1983, including four with incomplete information.

Study	n	Proven AMI	CHF	In-Hospital Arrhythmia	Out-Hospital Arrhythmia or SD
030	35				
031	29				1
032	141				1
033	198	1	1	4	7
035	66			3	3
037	10	1	1		
057	39		1	4	6
028	228	1	1	11	8
060	31				1

e. Study 057 amended

The use of the lower dosing regimen in the 057 amended study only slightly lowered the incidence of proarrhythmic events. However, the severity of these experiences was decreased compared to studies of similar patients treated with higher doses in the compassionate-use studies. Although nine deaths occurred in the 057 amended study (six out-of-hospital sudden deaths, three MIs) no deaths were thought by the investigator to be related to proarrhythmic events. Table 30F lists these nine patients and includes cardiac history and total daily dose at time of event.

Table 30F

Patient Deaths

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
057-01-101	51	M	+	+		VT_s	+		400	77 Days	VT/VF sudden death.	Probably not
057-06-110	30	M	+	+		VT_{ns}		+	400	107 Days	Cardiac arrest secondary to acute MI - suspected. No autopsy.	No
057-06-113	70	M	+	+		VT_s		+	200	163 Days	Acute ischemic episode - MI on autopsy.	No
057-07-101	71	M	+	+		VT_s	+	+	300	70 Days	Arrhythmia-either primary or secondary to ischemic event.	Probably not
057-07-103	67	M	+	+		VT_{ns}		+	200	12 Days	Ischemia causing pulmonary edema (inferred).	Probably not
057-12-110	69	M			+	VT_{ns}		+	200	21 Days	Cardiac arrest. Precipitating factors unknown.	Unknown
057-26-105	57	M	+	+		VT_{ns}			400	242 Days	Cardiac arrhythmia. Sudden collapse while dancing.	Probably Not
057-31-102	74	M	+	+		VT_s	+	+	300	83 Days	Hospitalized for MI. No autopsy.	No
057-12-110	72	F	+	+		VT_s		+	200	153 Days	Cardiac arrhythmia. Collapsed in hallway.	No

Table 30F

Patient Deaths

R-818 Study No. Patient No.	Age	Sex	ASHD	MI	Cardio-myopathy	Prior Arrhyth-mia	Previous Resusci-tation	CHF	Last Daily Dose (mg/day)	Therapy Duration	Cause of Death	Invest Opinion: Death Related to Flecainide?
057-01-101	51	M	+	+		VT_s	+		400	77 Days	VT/VF sudden death.	Probably not
057-06-110	30	M	+	+		VT_{ns}		+	400	107 Days	Cardiac arrest secondary to acute MI - suspect-ed. No autopsy.	No
057-06-113	70	M	+	+		VT_s		+	200	163 Days	Acute ischemic episode - MI on autopsy.	No
057-07-101	71	M	+	+		VT_s	+	+	300	70 Days	Arrhythmia-either primary or secon-dary to ischemic event.	Probably not
057-07-103	67	M	+	+		VT_{ns}		+	200	12 Days	Ischemia causing pulmonary edema (inferred).	Probably not
057-12-110	69	M			+	VT_{ns}		+	200	21 Days	Cardiac arrest. Precipitating factors unknown.	Unknown
057-26-105	57	M	+	+		VT_{ns}			400	242 Days	Cardiac arrhymth-mia. Sudden collapse while dancing.	Probably Not
057-31-102	74	M	+	+		VT_s	+	+	300	83 Days	Hospitalized for MI. No autopsy.	No
057-12-110	72	F	+	+		VT_s		+	200	153 Days	Cardiac arrhythmia. Collapsed in hallway.	No

f. Conclusion

Like other antiarrhythmic drugs, flecainide can worsen pre-existing arrhythmias or create new ones. As most long term data on flecainide comes from open studies it is not possible to compare its pro-arrhythmic potential with other drugs. Podrid, Lown, and co-workers had described pro-arrhythmia frequencies of 10% or greater for a variety of drugs, indeed, for virtually all artiarrhythmic drugs, [Velebit, et al: Circulation 65:886-894, 1982] but those authors' vigorous exercise testing and repeated Holter measurements may have represented a more vigorous search than occurred in flecainide patients. Winkle, Mason and co-workers [Am Heart J 102:857-864, 1981] have described dramatic worsening of arrhythmias in 11% of 90 patients with prior VT/VF given encainide, a close relative of flecainide, and of the development of VT needing resuscitation in one of 47 patients with frequent VPCs and non-sustained salvos. Other studies have shown worsening of arrhythmias in some patients receiving amiodarone.

For the patients with serious prior arrhythmias, the pro-arrhythmic potential of flecainide seems within a range that is similar to other drugs. What is less clear, on the basis of short-term controlled data and longer term open, uncontrolled studies, is what the risk of flecainide is in patients with relatively benign arrhythmias such as frequent VPCs. That flecainide can induce life-threatening arrhythmias in these patients, at least on occasion, seems clear. Complete assessment of this risk will require further data in these populations, preferably longer term controlled data. Part of the difficulty in evaluating this risk, of course, is the absence of evidence that antiarrhythmic agents are of life-prolonging value in patients with less serious arrhythmias.

It is important to note that most pro-arrhythmic events have occurred early during treatment, both in the older studies and in 057 amended. In the latter study, slower dose-titration and close observation have been associated with an outcome of no fatal pro-arrhythmic events although non-fatal events have continued to occur. Starting flecainide in-hospital with close observation is clearly prudent for patients with sustained ventricular tachycardia, symptomatic congestive heart failure, sinus node dysfunction, or ejection fractions less than 30%.

3. Congestive Heart Failure

Animal and human clinical pharmacologic data show a negative inotropic effect of flecainide. In all of the major studies cases of CHF were identified on the basis of the physician's diagnosis or the presence of symptoms, e.g., shortness of breath, that suggested CHF. This initial screen was then referred by further review to eliminate cases in which the diagnosis of CHF or of a relationship to flecainide was unlikely.

Table 31A shows the incidence of new or worsened CHF in three groups of patients: those patients treated primarily for chronic ventricular ectopy (030, 031, 032, 033, 035); those patients treated in the Compassionate-Use Studies (028, 057); and those patients in the Acute and Chronic Study of Ventricular Tachycardia (057, amended); both the initial screen and reviewed values are given. Tables 31B and 31C show the clinical characteristics of the patients and the sponsors view of drug-relatedness. Many of the episodes, especially those considered drug-related occurred early in treatment with flecainide.

The overall incidence of developing possibly flecainide-related new CHF in patients without a previous history of CHF is thus low, about 1%, regardless of the population studied. The incidence of developing worsened CHF in patients with pre-existing heart failure was 9% in the ventricular ectopy studies and 19% in the compassionate use experience in which patients with more severe heart disease were treated. In the Acute and Chronic Study of VT which used lower initial doses to treat patients with severe cardiac disease, the incidence was the same as that in the ventricular ectopy studies, 9%. In this last study, five of the six patients who developed new or worsened CHF continued on flecainide in spite of developing CHF. All six were successfully treated by adjusting diuretics.

TABLE 31A

Incidence of Flecainide-Associated CHF

	New CHF		Worsened CHF	
	Initial Screen	Reviewed	Initial Screen	Reviewed
Acute & Chronic Studies/ Ventricular Ectopy (030, 031, 032, 033, 035)	2% (6/306)	0.7% (2/306)	15% (10/67)	9% (6/67)
Compassionate Use Studies (028, 057)	5% (6/131)	0.8% (1/131)	2% (32/115)	19% (22/115)
Acute and Chronic Study/VT 9% (4/43) (057 Amended)		6% (3/53)	4% (2/53)	12% (5/43)
All Studies	3.1% (15/490)	1% (5/490)	20.9% (47/225)	14% (32/225)

New and Worsened CHF

	Initial Screen	Reviewed
All Studies	8.7% (62/715)	5% (37/715)

TABLE 31B

Summary of Patients Who Developed CHF While on Flecainide Therapy

Patient No.	Age	Sex	History of CHF	Cardiomegaly	On Dig/Diuretics at Study Start	Symptoms at Study Start	Coronary Artery Disease	Old MI	Cardiomyopathy	Valvular Heart Disease	Hypertensive Heart Disease	Exposure to Flecainide at Time of CHF (Months)	Dose at Time of CHF (mg bid)	Flecainide Discontinued?	Flecainide Restarted (mg bid)	In Biker's Opinion, Was This a Patient with Flecainide-Related CHF?
035-02 (8101)	57	M	+	+	+	+	+	+	-	-	-	2	200	Yes	200	Yes
												11	100 tid	No	---	---
030/031-03 (8002)	43	F	+	-	Dc'd	+	-	-	+	-	-	3-4	100 tid	No	---	No
032/033-02 (8006)	62	M	-	-	-	-	+	+	-	-	-	1 1/2	200	Yes	No	Yes
032/033-02 (8007)	63	M	+	+	+	-	+	+	-	-	+	8 days	200	Yes	100	Yes
032/033-05 (8008)	72	F	+	+	+	+	-	-	-	+	-	1 day	200	Yes	No	No
032/033-06 (8013)	73	M	-	-	-	-	+	+	-	-	+	1 dose	100	Yes	No	No
032/033-07 (8003)	70	M	+	+	+	+	+	+	-	-	-	2 1/2	200	No	---	Yes
032/033-07 (8020)	65	M	-	+	-	-	+	+	-	-	+	7 days	200	Yes	No	Yes
032-10 (8003)	63	F	+	+	+	+	+	+	-	-	+	1 day	200	Yes	No	Yes
032/033-11 (8002)	48	M	+	+	+	+	-	-	+	-	+	9	100	Yes	100	No
032/033-11 (8008)	47	M	+	+	+	+	-	-	+	-	-	1 1/2	100	No	---	Yes
												6	100	Yes	50	---
032/033-12 (8012)	62	M	+	+	+	+	+	-	-	-	+	7	150	Yes	No	Yes
033/033-13 (8007)	67	M	-	+	-	+	+	+	-	-	-	3	200	No	---	No
032/033-13 (8015)	64	M	-	+	-	-	+	+	-	-	-	7 days	200	Yes	No	No
032/033-17 (8014)	77	M	-	+/-	-	+	+	+	-	+	+	15	300 QD	No	---	No
032/033-17 (8026)	72	F	+	+	+	+	+	-	+	+	-	5	50 tid	No	---	No

TABLE 31C

Congestive Heart Failure - Summary of
Patients who Developed New Or Worsened CHF During Flecainide Therapy

Patient I.D	BNP (1)	Age	Sex	History CHF	Cardiomegaly	Cm Hg at Baseline	Symptoms/Findings at Baseline	Coronary Artery Disease	Old MI	Valvular Heart Disease	Hypertensive Heart Disease	Exposure to Flecainide at time of CHF	Dose at time of CHF	Outcome (d/c = flecainide discontinued)	In Biker's opinion was this a Patient with flecainide-related CHF?
018-01-102		51	M	-	-	-	-	+	+	-	-	46 Days	200 BID	ongoing, dose ↓ to 150 BID	No
-103		69	M	-	-	-	-	+	+	-	-	13 Days	200 BID	d/c, restart 100 BID	No
-07-101		76	M	+	+	+	+	+	+	+	+	3 Days	100 BID	died (CHF related death)	No
-107		58	M	+	+	+	+	+	+	-	-	14 Days	150 BID	d/c	No
-08-112		67	M	+	-	-	+	+	+	-	-	1 Day	200 BID	ongoing, dose ↓ to 100 BID	No
-11-104		61	M	+	-	+	+	+	+	-	-	23 Days	100 TID	pt. trans. to another flec. study, dose ↓ to 100 BID	No
-14-101		53	M	-	-	-	-	+	+	-	-	180 Days	150 BID	ongoing	No
-115		35	F	+	-	-	-	+	+	-	-	36 Days	100 BID	ongoing	No
-131		64	M	+	+	+	+	+	+	-	-	10 Days	300 BID	died (CHF related death)	No
-133		55	M	+	+	+	+	+	+	-	-	2 Days	200 BID	died (arrhythmic death)	No
-19-101		75	F	+	-	+	+	+	+	-	-	6 Days	200 BID	d/c	No
-26-003		72	M	+	-	+	+	+	+	-	-	37 Days	150 QAM	ongoing ↓ 100 BID	No
-003		67	M	+	+	+	+	+	+	-	-	75 Days	300 BID	ongoing, dose ↑ 200 BID	No
-27-011		74	M	+	-	-	+	+	+	-	-	75 Days	150 BID	continued fo 6 more weeks then d/c for other reasons	No
-28-002		76	F	+	+	+	+	+	+	-	-	65 Days	100 QAM	continued for 1 more month then d/c for other reasons	No
-006		67	M	+	+	+	+	-	-	-	-	1 Days	100 TID	d/c	No
-007		59	M	+	-	+	-	+	+	-	-	78 Days	200 QAM	ongoing	No
-012		61	M	-	+	-	-	-	-	-	+	71 Days	200 QAM	ongoing	No
-34-101		55	M	+	+	+	+	-	-	-	-	10 Days	150 QAM	died (CHF related death)	Yes.
-102		56	M	+	+	+	+	+	+	-	-	24 Days	200 BID	continued for 4 more months, then d/c for other reasons	Yes
-008		84	M	+	+	+	-	+	+	-	-	1 Years	100 BID	ongoing	No
-37-003	30	59	M	-	-	-	-	+	+	-	-	9 Days	200 BID	d/c	No
-51-102		64	M	+	+	+	-	+	+	-	+	12 Days	200 BID	d/c	Yes
-103		69	M	-	-	-	-	-	-	-	+	80 Days	200 BID	ongoing	Yes
-60-101	26	75	M	+	+	+	+	-	-	-	-	101 Days	100 BID	ongoing	No
-61-101		57	M	+	+	+	+	+	+	-	+	11 Days	250 BID	died (acute MI)	No
-103	26	63	M	+	-	+	+	+	+	-	+	95 Days	200 BID	died (CHF related death)	Yes
-65-101		60	F	+	+	-	+	+	+	-	+	11 Days	200 BID	ongoing	No
-68-102	119	63	M	+	+	-	+	+	+	-	-	2 Days	200 BID	d/c	Yes
-70-101		64	M	+	+	-	-	+	+	+	-	10 Days	200 BID	ongoing	Yes
-87-101		29	F	+	-	+	+	+	-	-	+	1 Day	200 BID	d/c	Yes
-98-101		84	M	+	-	+	+	+	+	-	-	30 Days	100 BID	dose ↓, then pt. d/c due to intercurrent disease	Yes
053-02-201*	25	79	M	+	+	+	+	+	+	-	+	180 Days	300 BID	ongoing	Yes
-06-003	31	62	M	+	+	-	+	+	+	-	+	14 Days	150 BID	ongoing	No
-06-006	31	68	M	+	+	+	-	-	+	-	-	60 Days	300 BID	ongoing, changed schedule to 200 TID	Yes
-06-007	84	72	M	+	+	+	+	+	+	-	+	30 Days	150 TID	died (cardiac arrest)	Yes
-10-007	20	71	M	+	+	+	+	-	-	-	-	2 Days	300 BID	d/c	Yes
-11-003	80	668		+	+	-	+	-	-	+	-	1 Day	150 BID	ongoing, dose ↓ to 100 BID	No

* Baseline value of 668 spuriously high because patient's CHF status was worse at this time than several months earlier when BNP was 245

Figure 15 shows the outcome of the 37 patients who developed new or worsened CHF likely to have been related to flecainide. One-half of these patients continued on flecainide despite the occurrence of new or worsened CHF. Most of these continued flecainide at the same dose, with the investigator adjusting digitalis, diuretics, or both. The others continued flecainide at a reduced dose. One-half of the 37 patients (2.5% of patients taking flecainide) discontinued flecainide because of CHF. Four of these patients died of CHF related deaths; three of these four were receiving flecainide at the time of death and one died two days after discontinuing flecainide. All four were in the Compassionate-Use studies. Seven (22%) of the 37 patients who developed new or worsened CHF did so during the first four days of therapy; two-thirds during the first month of therapy. There were four other patients who died of low output states or CHF not likely to have been related to flecainide.

FIGURE 15

37
Patients Developed CHF
on Flecainide
(All Studies)

51% (19/37) Continued on Flecainide		49% (18/37) Discontinued Flecainide
35% (13/37) Continued at the SAME Dose	16% (6/37) Continued at a REDUCED DOSE	11% (4/37) Died

In summary, the risk of a patient developing new congestive heart failure while on flecainide therapy was small (about 1%) when the patient had no history of congestive heart failure. In patients with pre-existing heart failure 9% to 19% of patients develop worsening of CHF at some time during the studies. In the majority of these cases, congestive failure was easily treated following adjustments in digitalis and/or diuretics, reducing the dose of flecainide, or discontinuing flecainide, but a few patients died at least partly due to worsened failure. Most patients who developed new or worsened CHF did so during the first month of therapy.

4. Effects of Flecainide on the Scaler ECG/Conduction Disturbances

Changes in ECG intervals are an expected pharmacological effect of flecainide. There is a positive relationship between dose and degree of interval lengthening during the initial flecainide titration period (Table 31D) and the ECG interval changes seen after initial therapy tend to remain stable with chronic therapy. Table 31E shows this for studies 032 (acute) and 033 (chronic) and other acute/chronic comparisons.

PR intervals increase commonly by 25% (0.04 seconds) and as much as 118% in some patients. First degree A-V block (PR greater than 0.20 seconds) occurred in up to 40% of patients. To date, four patients have developed third degree A-V block and two patients have developed second degree A-V block (Wenckebach type) while on flecainide.

QRS intervals increase commonly by 25% and as much as 150% in some patients usually without producing detrimental clinical effects. Many patients with unifascicular bundle branch block and five patients with bifascicular block have received flecainide; some of these patients progressed to higher degrees of block. In the C mpassionate-Use study 4% of patients developed new bundle branch block. There were two occurrences in all studies of new bifascicular block.

QT interval changes are usually minimal (8%) with most of the change due to increases in the QRS interval rather than the JT interval (QT minus QRS). This is expected from the known preferential electrophysiologic effects of flecainide on depolarization rather than repolarization. There have, however, been occasional patients with true QT prolongation. This effect predisposes to a Torsade de Pointe type VT and one such event has occurred in a patient with QT prolongation.

In all studies 11 patients showed signs of sinus node dysfunction while receiving flecainide, resulting in sinus bradycardia, sinus pause or sinus arrest with junctional escape rhythms.

ECG changes led to a total of 28 discontinuations, sometimes because the investigator became uncomfortable with the large changes seen but more often because they were dangerous or symptomatic. Table 31F shows these discontinuations.

TABLE 31D

Absolute and Percent Changes for ECG Intervals
after Three Days of Therapy in R-818-030 Dose-Ranging Study

	Mean Percent Increase From Baseline			Mean Absolute Increase From Baseline (sec)		
	Dose (mg Bid)			Dose (mg Bid)		
	100	200	250/300	100	200	250/300
PR	9.0%	18.9%	24.1%	0.015	0.031	0.038
QRS	11.7%	20.7%	26.5%	0.009	0.016	0.021
QT	6.2%	7.5%	6.3%	0.022	0.027	0.023
JT*	4.8%	3.9%	0.7%	0.013	0.011	0.002

*JT = QT minus QRS

TABLE 31E

Acute Dose and Chronic Therapy Comparison:
Absolute Increase in ECG Intervals

	Patients from Studies 030 and 031		Patients from Studies 032 and 033			Patients from Study 035	
	030 Day 14	031 Mo. 12	032 Wk 2	032 Wk 3	033 Mo. 6	035 Stage 1 Day 8	035 Stage 2 Mo. 12
PR	0.036	0.042	0.042	0.039	0.032	0.024	0.026
QRS	0.022	0.025	0.020	0.017	0.015	0.008	0.010
QT	0.033	0.032	0.024	0.028	0.026	0.009	0.014
JT	0.013	0.008	0.004	0.011	0.012	0.001	0.004

Table 31F

Discontinued Patients - ECG Changes

Study	Center	Pt No.	Flecainide Dose (mg bid)	Duration	Reasons	Interval Changes (seconds)
032	04	005	200	10 days	1° AV block, worsened, blurred vision, dizziness	PR: 0.24 to 0.32
		015	200	7 days	1° AV block, bradycardia	PR: 0.18 to 0.23
		020	200	7 days	1° AV block, dizziness	PR: 0.16 to 0.28
	11	002	200	8 days	Widening of PR and QRS	PR: 0.21 to 0.26 QRS: 0.08 to 0.12
		007	200	4 days	Widened QRS non-qualifying patient	QRS: 0.10 to 0.16
	17	021	200	2 days	Widened PR non-qualifying patient	PR: 0.17 to 0.22
033	01	002	200	3 months	Sick sinus syndrome 1° AV block	PR: 0.28 to atrial fibrillation
	03	003	200	6 days	1° AV block, complete RBBB with marked right axis deviation	PR: 0.18 to 0.22 QRS: 0.09 to 0.14
		008	200	6 days	1° AV block LBBB, severe dizziness	PR: 0.16 to 0.24
	04	009	150	3 days	NSR with sinus pauses, junctional escape beats, 1° AV block, PACs	PR: 0.16 to 0.22
	12	024	300	31 days	Lack of therapeutic response, 2° AV block (Wenckebach), blurred vision, light-headedness, constipation	PR: 0.20 to 0.26

Table 31F - continued

Discontinued Patients - ECG Changes

Study	Center	Pt No.	Flecainide Dose (mg/) at DC	Duration	Reasons	Interval Changes (seconds)
028	04	101	50 TID		Widened QRS	QRS: 0.14 to 0.24
	11	102	200 BID	3 days	Sinus pause	PR: 0.19 to 0.20
			100 TID	3 days	resolved with decreased dose; D/C due to lack of efficacy.	QRS: 0.08 to 0.10 QT: 0.36 to 0.42
	13	001	200 BID	3 months	Widened intervals Proarrhythmic events.	PR: 0.19 to 0.32 QRS: 0.10 to 0.15
	14	102	200 BID	3 days	Bradycardia Sinus exit block	Baseline: PR: 0.24 QRS: 0.12 QT: 0.38 Followup: Not available
	14	112	100 BID	5 days	Severe bradycardia Hypotension Died	Baseline: PR: 0.18 QRS: 0.10 QT: 0.52
	14	129	200 BID	1 day	3° AV Block Bradycardia Dizziness, Nausea	Baseline: PR: 0.12 QRS: 0.08 QT: 0.34 Followup: Not available
	14	130	200 BID	4 days	Bundle branch block Widened intervals. Increased VT on holter	PR: Not avail. QRS: 0.10 to 0.20 QT: 0.40 to 0.43

Table 31F - continued

Discontinued Patients - ECG Changes

Study	Center	Pt No.	Flecainide Dose (mg/) at DC	Duration	Reasons	Interval Changes (seconds)
028	20	102	200 BID	1 dose	Widened PR, QRS, QT	Baseline: PR: 0.26 QRS: 0.12 QT: 0.40 Followup: Not available
	20	103	200 BID	1 day	Sinus pauses LBBB	PR: 0.20 to 0.20 QRS: 0.08 to 0.14 QT: 0.44 to 0.48
	26	010	200 BID	14 days	Widened intervals proarrhythmic event	PR: 0.16 to 0.18 QRS: 0.08 to 0.16 (ADV. EXP.) QT: 0.42 to 0.52
	28	014	200 BID 100 BID	1 day 2 days	Sinus pause	Baseline: PR: 0.14 QRS: 0.08 QT: 0.44 Followup: Not available
	44	104	200 BID	2 days	Widened intervals Proarrhythmic event	PR: 0.18 to 0.22 QRS: 0.08 to 0.10 QT: 0.44 to 0.46
	54	102	200 BID	2 days	3° AV block, Hypotension, Polyuria	Baseline: PR: 0.176 QRS: 0.101 QT: 0.341
057	10	002	100/150	2 days	2° AV Block	Baseline: PR: 0.18 QRS: 0.12 QT: 0.34 Followup: Not available
		008	300	4 days	IVCD Blurred vision	Baseline: PR: Not avail.

Table 31F - continued

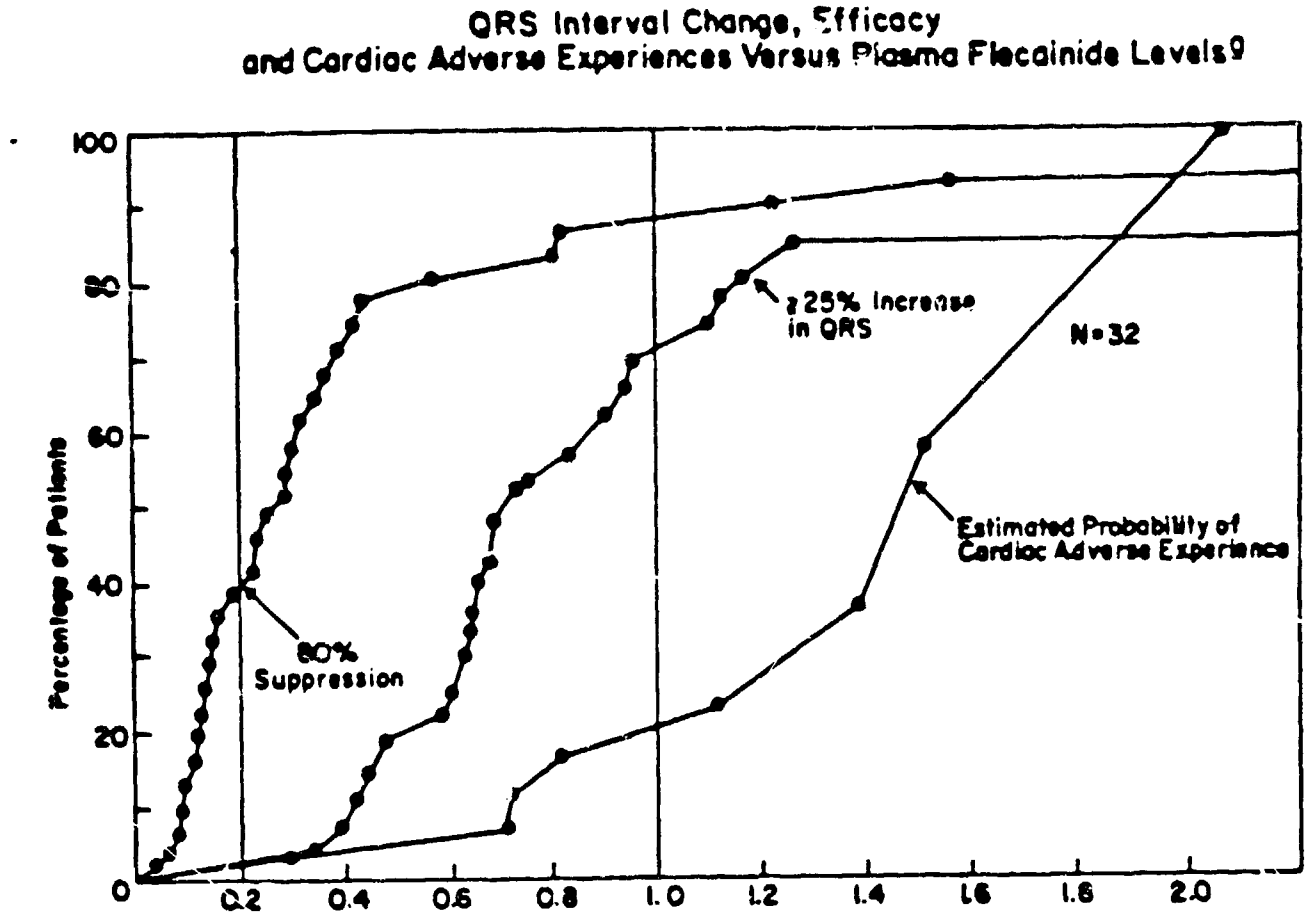
Discontinued Patients - ECG Changes

Study	Center	Pt No.	Flecainide Dose (mg/) at DC	Duration	Reasons	Interval Changes (seconds)
057, amended	12	113	100 BID	5 days	3° AV block	Baseline: PR: 0.20 QRS: 0.08 QT 0.48
	12	115	100 BID	2 days	3° AV block	Baseline: PR: 0.24 QRS: 0.12 QT: 0.40

The incidence of sudden deaths, proarrhythmic events or second or third degree AV block was not higher in 352 patients who developed 25% or more increases in PR or QRS intervals while receiving flecainide than in 95 patients who did not develop such increases (studies 030, 031, 032, 035, 057 and 057 amended).

Figure 15(A) shows an estimate of the probability for QRS changes greater than or equal to a 25% increase over baseline as a function of plasma level in 32 patients studied by Hodges in the 030, 031, 032 and 033 studies. The figure also shows estimates of the probability of achieving 80% suppression of PVCs and the probability of developing cardiac adverse experiences ("Therapeutic Window" analysis to be discussed further in Safety Section 6.) While the probability of all three events (80% suppression of PVCs, developing 25% increase in QRS, and cardiac adverse effects) appear to be related to plasma level, there does not appear to be a direct relationship between widening of QRS and either 80% suppression of PVCs or development of cardiac adverse experiences. The cardiac adverse experiences in these studies, it should be noted, include principally bundle branch block and bradycardia, not pro-arrhythmic events.

Figure 15A



[9] Hodges - Dose Ranging Study (030), Chronic Followup (031)
Quinidine Comparison Study (032), Chronic Followup (033)

5. Vital Signs

The sponsor reviewed mean changes in blood pressure, heart rate, and respiratory rate taken at each visit in patients treated in the Acute and Chronic Ventricular Ectopy Studies (033, 031, 032. 033, 035). In addition, all reports of adverse reactions related to vital sign changes were reviewed from all trials.

Blood pressure showed an average increase of about 5mm in systolic pressure and about 3mm in diastolic pressure compared to baseline. The changes did not increase with time. Two patients were reported as developing hypertension while receiving flecainide.

Mean heart rate showed no consistent trend; there were six reports of sinus bradycardia. In five of these six patients, however, bradycardia was either present to the same degree prior to flecainide, or the bradycardia was noted only once and did not recur with continued flecainide therapy.

Mean respiratory rate usually fell in these studies. These changes, however, were insignificant (about 1 breath per minute), and no patient was found to have clinically significant changes in respiratory rate.

6. Routine Laboratory Measurements

In U.S. monitored studies two questions were raised regarding possible effects of flecainide on routine laboratory measurements.

a. In the Dose-Ranging Trial (030) five patients developed new persistent elevations of alkaline phosphatase. All patients showing this abnormality were studied at one center. The elevations were less than twice the normal range and were not associated with elevations of bilirubin, SGOT. SGPT, leucine aminopeptidase (LAP), 5' nucleotidase, calcium, phosphorus, or urinary hydroxyproline. Four of the five patients continue to receive flecainide for over two years with elevations persisting but not increasing. One patient discontinued at three months for unrelated reasons; moved away and no follow-up data is available.

   No persistent alkaline phosphatase elevations were found in 198 patients taking flecainide in the chronic followup of patients in the Flecainide-Quinidine Comparative study and there were no reports of persistent elevations in other studies.

b. In the chronic followup of patients studied in the Flecainide-Quinidine Comparative study, one patient developed small (2 x normal) rises in SGPT after 15 months of flecainide therapy. These changes persisted during six additional months of flecainide therapy. Flecainide was discontinued and within two months SGPT had returned to normal. The investigator refused to rechallenge the patient.

In West Germany flecainide has been marketed since August 1982. In December 1983, after 15 months of marketing experience, the sponsor estimated that at least 30,000 patients had received flecainide in West Germany. Reports of adverse experiences have been consistent with the results of U.S. studies with one addition: 18 patients have been reported who developed liver-related abnormalities including increased hepatic enzymes and "cholestatic jaundice." Of these patients:

- Two patients' abnormalities resolved while remaining on flecainide. (One patient developed acute "typical" hepatitis, the second patient had a single elevated SGPT value.)

- Four patients had either pre-existing liver disease or elevated hepatic enzymes prior to initiating flecainide.

- Three patients had elevations which were less than twice the normal range.

- Five patients had significant elevations in bilirubin and/or transaminases though no consistent pattern was present. The only biopsy in this group was read as "viral hepatitis."

- Four patients had virtually no information provided despite attempts by the sponsor to obtain further details.

Several of these 18 patients were on multiple drugs while taking flecainide. Where information is available, all abnormalities in these patients were either improving or had resolved as of the most recent information.

The reports to date are not sufficient to conclude whether flecainide can cause hepatic toxicity. No patient was rechallenged, which would provide the truest test of drug effect. The incidence may be low enough to reflect the spontaneous occurrence of such abnormalities in a presumed population of 30,000. Although no cause and effect relationship has been established, it is advisable to discontinue flecainide in patients who develop unexplained jaundice or signs of hepatic dysfunction in order to eliminate flecainide as the possible causative agent. The package insert states that reports of elevated transaminase levels and jaundice have occurred in patients taking flecainide.

7. Safety Experience With the Use of Flecainide with Other Antiarrhythmic Drugs and With Beta Blockers

Adverse experiences were reviewed in 226 patients taking other antiarrhythmic drugs either concomitantly with flecainide, or shortly before or after flecainide therapy.

In US studies, 81 patients received one or more of nine other antiarrhythmic drugs during treatment with flecainide. Five deaths were reported in these patients; four were arrhythmic deaths and one patient died of "pump failure." All five patients had pre-existing CHF and previous resuscitations. Other adverse experiences were consistent with known side effects of flecainide or the other antiarrhythmic drug. Thirty-one of these 81 patients received lidocaine, usually during the first few days of flecainide therapy. One of the five deaths occurred in these 31 patients. Other side effects in patients taking lidocaine with flecainide were: sinus pause (1), syncope (1), bundle branch block (1), chest pain (1) and loss of appetite (1). The other 4 deaths occurred in patients receiving amiodarone, procainamide, aprindine and bretylium.

Seventy-five patients received flecainide within one day after stopping another antiarrhythmic drug (during washout of the previous antiarrhythmic). Three of these patients developed 3° AV block. Otherwise adverse experiences which occurred during the subsequent two days of flecainide therapy were consistent with those reported for flecainide or the other antiarrhythmic drug.

Seventy patients received another antiarrhythmic drug within three days after discontinuing flecainide (during flecainide washout). The adverse experiences were consistent with those reported for flecainide or the other antiarrhythmic drugs.

Adverse experiences were reviewed for 94 patients who for periods up to 36 months received beta blockers while taking flecainide. The most commonly used beta-blockers included propranolol (42 patients), metoprolol (23 patients), nadolol (14 patients) and atenolol (11 patients). The incidences of both non-cardiac and cardiac adverse experiences in these patients were similar to those reported for all patients taking flecainide. The incidence of fatigue (an adverse experience common to both beta blockers and flecainide) was somewhat higher in patients taking beta blockers (8%) than in all patients taking flecainide (usually 3-4%). Forty-two percent of the 94 patients experienced no adverse experiences.

8. Post Marketing Experience

a. United Kingdom

Tambocor[R] (flecainide acetate) has been marketed in the United Kingdom (UK) since September 1983. By the end of January 1985, over 1.4 million tablets had been sold. Based on an average dose of 300 mg (3 tablets) per day, it is estimated that approximately 3,000 patients have been treated with 1,300 patient-year exposure. An additional 10,000 ampuls (150 mg/ampul) have been sold for intravenous use.

The Committee On Safety of Medicine (CSM) has received a total of 44 adverse reaction reports (yellow cards) during the 17 month period from September 1983 to February 1984, when the product was commercially available. Four of these were cases that resulted in death (two from "cardiac arrest," one from "arrhythmia" and one from "myocardial infarction"). Table 32(A) is the list of adverse reactions provided by the CSM in February 1985. All reported adverse effects are consistent with US data submitted in the NDA.

b. West Germany

Tambocor[R] (flecainide acetate) has been marketed in West Germany since September 1982. By the end of January 1985, 60 million tablets had been sold with an average of 2.4 million tablets sold per month during the most recent three months. Marketing surveys suggest an average dose of 250 mg/day (2.5 tablets). This suggests an exposure of 65,000 patient-years in 50,000 to 100,000 patients.

Adverse drug reactions are usually reported by physicians directly to the pharmaceutical company, and occasionally to the Drug Commission of the German Medical Association. Table 32(B) lists the adverse experiences reported in West Germany from September 1982 through November 1984. A total of 336 adverse reactions were reported.

TABLE 32A

Post Marketing Adverse Reactions Reported in the United Kingdom (9/83 through 1/85)

Reaction Name	Reports	Deaths
Skin and Appendages		
rash	1	0
rash maculo-papular	2	0
urticaria	1	0
Central Nervous System		
headache	1	0
migraine	1	0
myoclonus	1	0
neuropathy	1	0
paresthesia	1	0
tremor	1	0
Autonomic Nervous System		
accommodation abnormal	2	0
palpitation	1	0
Visual Disorders		
teichopsia	1	0
vision abnormal	1	0
Gastro-Intestinal Disorders		
dispepsia	1	0
flatulence	1	0
stomatitis ulcerative	1	0
vomiting	2	0
Hepatic Disorders		
hepatic function abnormal	1	0
hepatitis	1	0
Metabolic and Nutritional		
weight increase	1	0
Cardiovascular Disorders		
cardiac failure	1	0
cardiac failure left	2	0
ECG abnormal	1	0
Intra-Cardiac Disorders		
angina pectoris aggravated	1	0
myocardial infarction	1	1
Arrhythmias		
arrhythmia	1	1
AV block	2	0
cardiac arrest	3	2
fibrillation ventricular	1	0
Peripheral Vascular Disorders		
thrombophlebitis	3	0
thrombophlebitis arm superficial	1	0
Respiratory Disorders		
pulmonary edema	1	0
Application Site Disorders		
injection site reaction	3	0

TABLE 32B

Post Marketing Adverse Reactions Reported in West Germany (9/82 through 11/84)

Reaction Name	Reports
Skin and Appendages	
rash	4
alopecia	2
pruritis	1
sweating	1
photosensitivity reaction	1
allergic skin reactions	1
Muscle Skeletal Disorders	
pain in extremities	2
Collagen Disorders	
lupus erythematous (physician later determined not related to drug)	1
Central and Peripheral Nervous System	
headache	7
dizziness	6
hypoaesthesia	2
paresthesia	1
polyneuropathy	1
tremor	1
Hearing and Vestibular Disorders	
tinnitus	1
temporary loss of hearing	1
Visual Disorders	
vision abnormal	11
eye pain	2
photopsia	1
diplopia	1
conjunctivitis	1
Psychiatric Disorders	
confusion	6
impotence	3
sleep disorder	2
parancid reaction	1
paroniria	1
agitation	1
psychosis	1
hallucination	1
euphoria	1
loss of artistic activity	1
Gastro-Intestinal Disorders	
nausea	8
diarrhea	4
constipation	3
vomiting	2
dysphagia	1

TABLE 32B (continued)

Post Marketing Adverse Reactions Reported in West Germany (9/82 through 11/84)

Reaction Name	Reports
Liver and Biliary System (see Effects of Flecainide on Routine Laboratory Measurements page 96)	
increase in liver function tests	8
no information	4
cholestasis	2
(1 with pre-existing alcoholic cirrhosis)	
hepatitis	1
chronic aggressive hepatitis	1
viral hepatitis (non A, non B)	1
jaundice and increase in liver function tests	1
Metabolic and Nutritional Disorders	
hyperglycemia	1
hyperkalemia	1
hypokalemia	1
weight increase	1
Endocrine Disorders	
gynecomastia	4
breast enlargement	1
Blood Disorders (*these were reported in detail, Safety Update 10/84)	
*leukopenia	3
(1 later determined to be secondary to acute myelomonocytic leukemia)	
*thrombocytopenia	1
(later determined to be present prior to flecainide)	
*pancytopenia	1
(later determined secondary to "pre-leukemia")	
*agranulocytosis	1
(physician retracted report without explanation, no details)	
leukopenia	2
(physicians refuse to provide details)	
increased prothrombin time	2
Vascular Disorders	
thrombophlebitis	1
phlebitis	1
Respiratory System Disorders	
bronchospasm	1
hyperventilation	1
Urinary System Disorders	
urinary retention	1
Body as a Whole - General Disorders	
muscular weakness	2
(1 in arms and legs)	

TABLE 32B (continued)
Post Marketing Adverse Reactions Reported in West Germany (9/82 through 11/84)

Reaction Name	Reports
Cardiac Side Effects	
Cardiovascular Disorders General	
cardiac insufficiency	12
circulatory collapse	6
edema	5
pulmonary edema	4
negative inotropic effect	2
hypotension	1
cardiac asthma	1
cardiogenic shock	1
ECG changes	1
stroke	1
low output syndrome	1
Myocardial, Endocardial, Pericardial and Valve Disorder	
angina pectoris	4
myocardial infarct	1
Heart Rate and Rhythm Disorders	
QRS widening	22
bradycardia	19
BB block (with edema and QT prolongation, 1 case after exercise)	18
AV block	13
ventricular tachycardia	10
ventricular fibrillation	10
cardiac arrest or asystole or syncope (1 case after iv injection)	7
proarrhythmic effect	6
QT prolongation	5
AV block or bundle branch block (unspecified)	5
SA block	4
ventricular flutter	4
atrial fibrillation	2
Adams-Stokes	2
pacemaker exit block	1
extrasystoles	1
ventricular extrasystoles	1
QT widening	1
AV dissociation	1
reentry syndrome	1
repolarization disturbance	1
atrial flutter	1
sinus dysfunction	1
Deaths	
cardiac arrest	5
myocardial infarction (1 probable)	3
left cardiac insufficiency	3
ventricular tachycardia	1
cause unspecified	19

D. Dosing Rationale and Plasma Level Monitoring

The recommended starting dose of flecainide is 100 mg every 12 hours. This should be increased in increments of 50 mg bid every four days until efficacy is achieved. The maximum recommended dose is 200 mg every 12 hours for patients with sustained ventricular tachycardia. For patients with nonsustained ventricular tachycardia and PVCs, if the symptoms are not controlled at 400 mg/day and plasma level is below 0.6 µg/mL, the dosage may be cautiously increased to 600 mg/day. The four day interval allows for the attainment of steady-state plasma levels. For patients with congestive heart failure, myocardial dysfunction, or renal impairment the dose should be kept as low as possible but again the maximum dose should not exceed 200 mg every 12 hours. This section will address the following topics:

1. Starting Dose
2. Maximum Dose
3. Dose Interval
4. No Loading Dose
5. Evidence to Support a Low Starting Dose with Upward Titration
6. Therapeutic Range
7. "Therapeutic Window" (plasma level vs. effect/adverse effects)

1. Starting Dose

The initial dose of 100 mg every 12 hours was tested in the Dose-Ranging Study (030). Twenty-six percent of patients achieved greater than 80% suppression of PVCs at that dose. In the Acute and Chronic Study of Ventricular Tachycardia (057 amended), 30% of patients who entered the trial were effectively treated with 100 mg bid and discharged from the hospital on that dose.

2. Maximum Dose

Studies of VPC suppression suggested some added response to doses as high as 600 mg per day. In the Dose-Ranging Study (030) 14% of the patients required 300 mg twice-a-day in order to achieve efficacy of 80% suppression. In the Flecainide-Quinidine Comparison Study (032), 18% of patients required 300 mg twice a day, the highest dosage studied. Of the patients in the chronic studies of ventricular ectopy, after one year of therapy, 4% of patients were taking 600 mg/day, and 21% were taking 200 mg/day or less. During this year patients could be titrated upward or downward to optimize efficacy and tolerance. Therefore, it appears unlikely that higher doses would be required by a significant percentage of patients. In study

057 amended the dose was limited to 400 mg per day and most patients received 300 mg or less with favorable effects compared to studies using larger doses. There is no documented reason to use doses above 400 mg in patients with serious arrhythmias.

3. Dose Interval

Hour-by-hour Holter monitoring data were available for 31 patients in the Dose-Ranging Study (030). During the third day of dosing, at the dose determined to be efficacious for each patient, the median percent suppression of PVCs, at each hour, remained greater than 90%; that is, there was no evidence of decreased suppression at the end of each 12-hour dosing period.

In the Dose-Ranging Study (030) after three days of receiving an efficacious dose, patients underwent a placebo washout of flecainide. Holter monitoring during the first 24 hours of washout showed that patients who were treated successfully with 100 mg bid or 200 mg bid did not show less than 80% suppression of PVCs at any hour during the 24-hour washout. Patients requiring the higher dose, 300 mg bid, began to show breakthrough of arrhythmia at about 13 hours after the last dose. These data support the use of a bid-dosing regimen.

4. Loading Dose Not Recommended

In the Package Insert the sponsor notes that a loading dose is not recommended because of the increased likelihood of adverse effects. The bases for this conclusion are:

a. Single dose Study (024) which shows that the most pronounced negative inotropic effects of flecainide occurred when plasma levels were rising most rapidly rather than when levels were highest.

b. Three of eight patients developed CHF after one to six doses of flecainide in Study 056 which used a loading dose of 200 mg every eight hours.

c. A higher incidence of cardiac adverse effects or death occurred during the first four days of therapy in patients who received an initial dose of 200 mg bid (approximately a loading dose regimen) in the Compassionate-Use Studies compared to a similar patient population in the 057 amended study who received an initial dose of 100 mg bid (10.8% versus 1%).

d. The nonloading regimen, with hospitalization and careful upward titration, proved to be practical and effective as shown by the safety and efficacy data presented for the Acute and Chronic Study of Ventricular Tachycardia (057 amended). In this study over half the patients were treated for refractory sustained ventricular tachycardia; the group of patients who might be expected to benefit most from a loading dose regimen.

5. Evidence to Support a Low Starting Dose with Upward Titration

Two study populations, the compassionate-use studies (028,057) and the Acute and Chronic Study of VT (057 amended), had similar demographic characteristics. The only discernible difference in the treatment of these two populations was the recommended flecainide dosing schedule.

In the compassionate-use studies, the recommended starting dose was 400 mg/day (200 mg bid), with upward and downward adjustments allowed at the discretion of each investigator with no time restrictions for adjustments; the maximum allowable dose was 300 mg bid.

In the Acute and Chronic Study of VT, the recommended starting dose was 200 mg/day (100 mg bid), with upward and downward adjustments allowed, but upward adjustments were made no more frequently than every 4 days; the maximum allowable dose was 400 mg/day (200 mg bid).

There is evidence that adverse experiences were more frequent when the higher dosage regimen was used. In the compassionate-use studies, the incidence of new or worsened CHF was 19%, compared with 9% in the Acute and Chronic Study of VT. Patient discontinuations due to cardiac adverse effects or sudden death within the first four days of treatment were 10.8% in the compassionate-use studies compared with 1% in the Acute and Chronic Study of VT. The incidences of the most common non-cardiac adverse experiences, dizziness and visual disturbances, were also higher in the compassionate-use studies, 23% and 25%, respectively, compared with 9% and 7% in the Acute and Chronic VT study (p less than 0.05).

6. Therapeutic Range

During the washout phase of the Dose-Ranging trial (030) the plasma level associated with the return of PVCs (to less than 80% suppression) was determined for each patient. Figure 16 displays the data from that trial showing that plasma levels ranged from a low of 0.12 ug/ml to a high of just over 1.0 ug/ml at the time that PVCs returned.

FIGURE 16

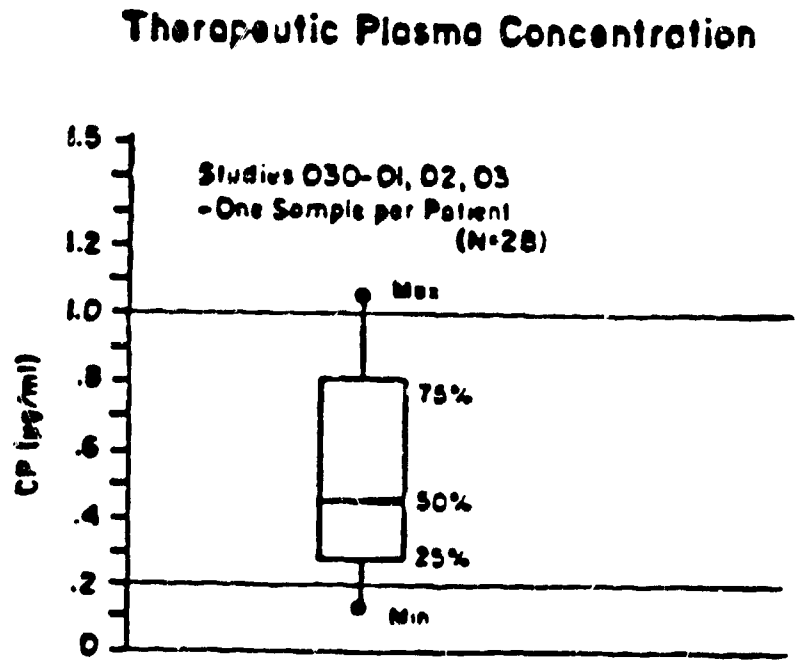
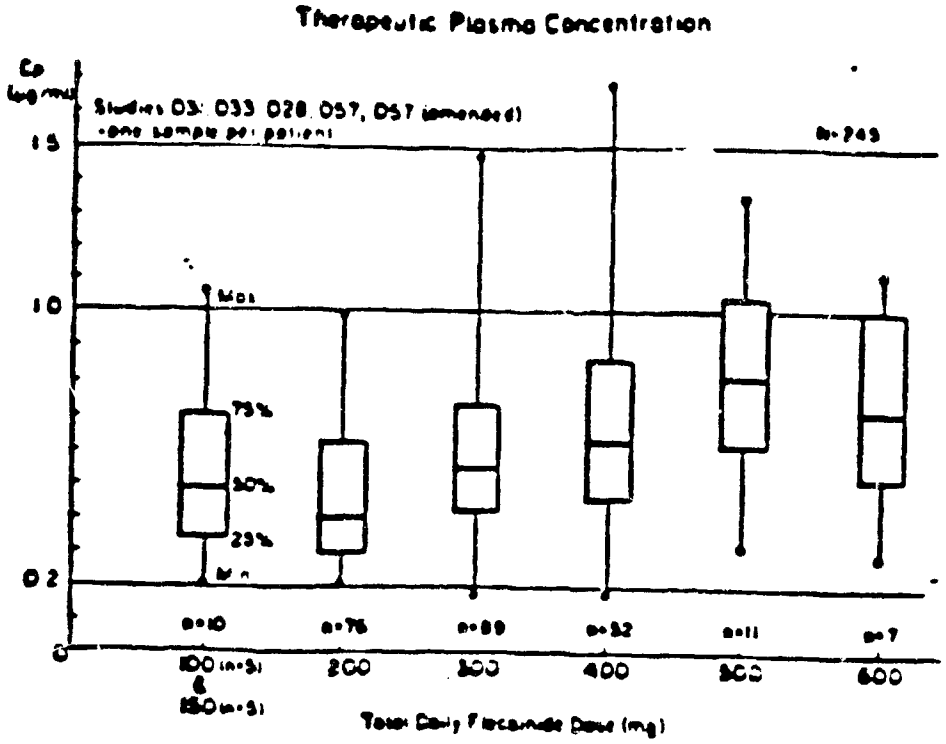


Figure 17 shows the most recent trough plasma levels obtained in 245 patients in chronic followup studies including patients with chronic stable PVCs and those with more serious heart disease and ventricular tachycardia. At each dosage level are displayed the maximum and minimum plasma levels for that group of patients. The boxes represent the 25th, 50th, and 75th percentile. Ninety percent of samples fall within the range of plasma levels of 0.2 to 1.0 ug/ml, the proposed therapeutic range. A few patients were doing well with plasma levels higher than the therapeutic range.

FIGURE 17



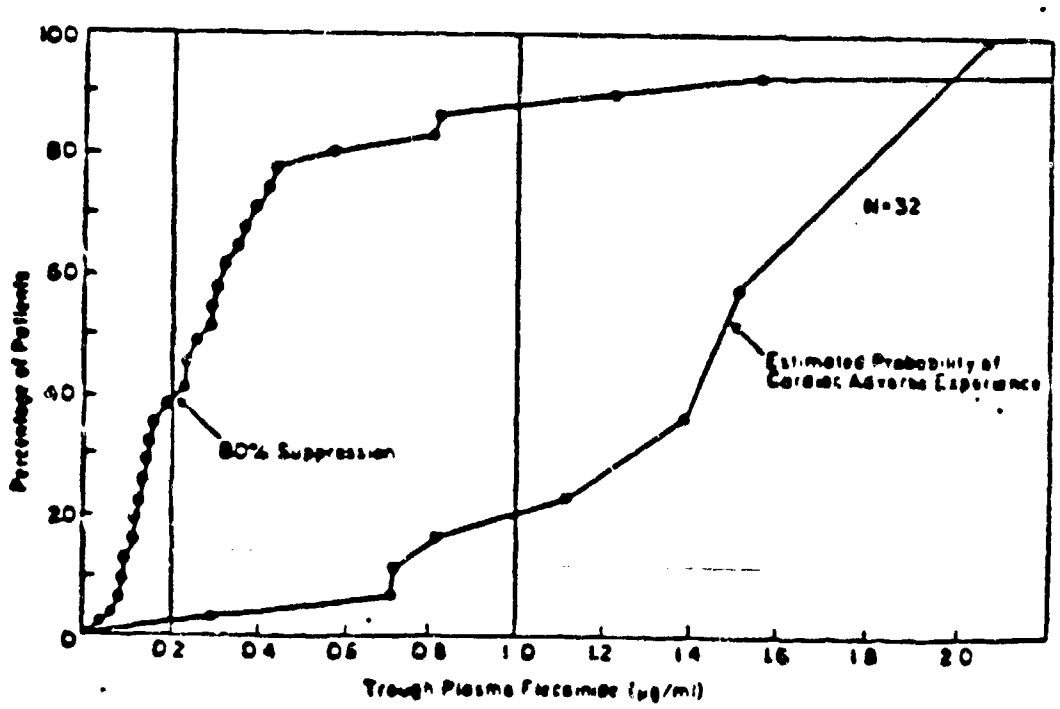
7. "Therapeutic Window" (plasma level versus effect/adverse effects)

In one institution an attempt was made to correlate plasma levels with effectiveness at suppression of PVCs and cardiac adverse experiences. Figure 18 shows data from 32 patients at one center from a variety of flecainide studies who had plasma level data available to evaluate the levels associated with suppression of PVCs and the levels associated with cardiac adverse experiences. The two lines represent the probability of achieving 80% suppression of PVCs and the probability of developing cardiac adverse experiences, respectively, as a function of plasma level. The probability of achieving 80% suppression of PVCs rises rapidly with plasma levels in the therapeutic range, but after 1.0 ug/ml there is little increased efficacy. The probability of developing cardiac adverse experiences is low until one reaches the upper end of the therapeutic range. Above 1.0 ug/ml the probability of cardiac adverse experiences increases sharply. Therefore, it is recommended that a therapeutic plasma concentration for flecainide be considered to be between 0.2 and 1.0 ug/ml. The relevance

of this analysis to the recurrent VT/VF population is uncertain. It is clear, however, that the lower doses used in 057 amended were often effective; mean trough plasma levels in 31 discharged patients was 532 ng/ml suggesting that the plasma level response curve of these arrhythmias may not be greatly different from VPCs.

FIGURE 18

Efficacy and Cardiac Adverse Experiences Versus Plasma Flecainide Levels[9]



[9] Hodges - Dose Ranging Study (030), Chronic Follow-up (031)
Exercise Comparison Study (032), Chronic Follow-up (033)

VI. Pertinent Advisory Committee Minutes

On June 21, 1984, the Cardiovascular and Renal Drugs Advisory Committee reviewed flecainide and recommended approval. The committee agreed that there was sufficient evidence that flecainide was effective in suppressing PVCs, nonsustained and sustained VT.

The Committee felt that the cautionary statement regarding hepatic dysfunction related to flecainide treatment in the proposed package insert was adequate. The sponsor and FDA should monitor reports of such occurrence post-marketing and change the labeling if necessary.

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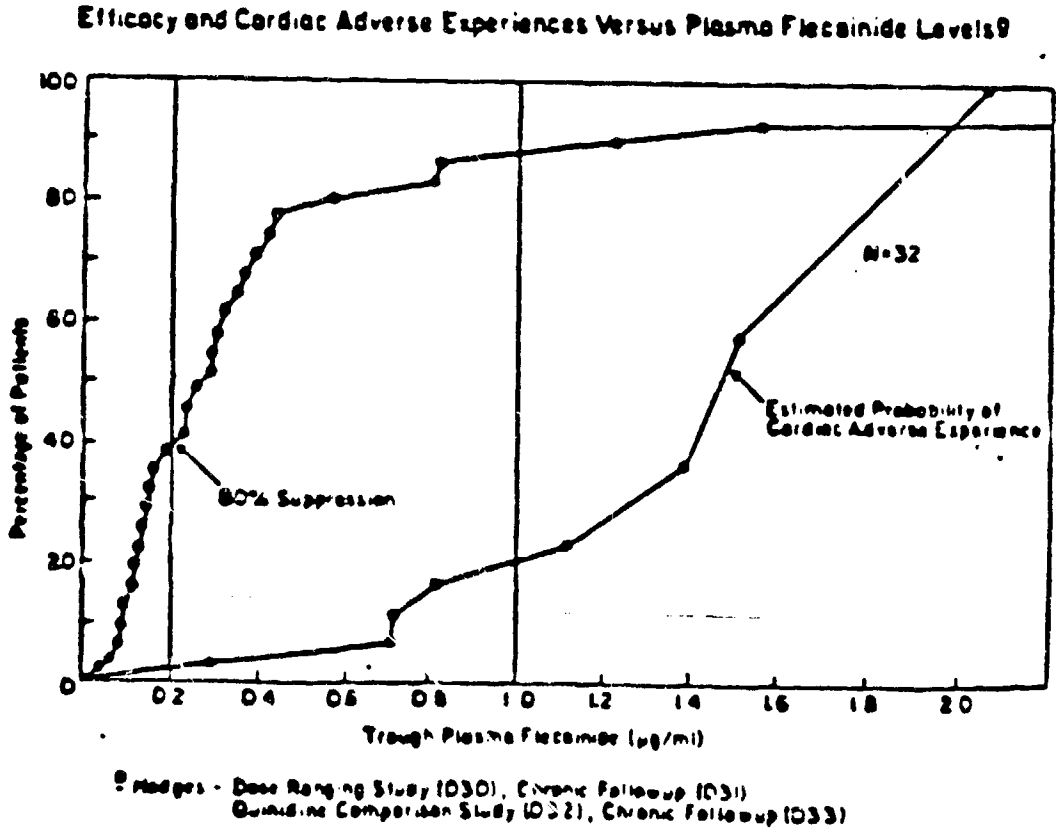

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The Committee felt that the cautionary statement regarding hepatic dysfunction related to flecainide treatment in the proposed package insert was adequate. The sponsor and FDA should monitor reports of such occurrence post-marketing and change the labeling if necessary.

The committee unanimously agreed that there was sufficient evidence regarding the hemodynamic effects of flecainide such that reasonable labeling could be written now, but requested that additional data be collected after approval in a patient population (to be defined by the FDA and sponsor) to better define the hemodynamic effects.

Since the sponsor had time to only briefly summarize concomitant medication data that were in the NDA, the committee suggested that the FDA and sponsor work out the labeling according to data available.

The committee urged the FDA to revise the indication for all antiarrhythmic drugs suggesting that they should be used only in symptomatic arrhythmias until the benefit of treating asymptomatic arrhythmias was proven.

VII. Safety Update

A. Cardiac Adverse Events

In September of 1985, the sponsor performed a cross-study analysis of several key safety issues.

A total of 1,330 patients was examined. This number includes 746 patients enrolled in studies previously discussed in the NDA, including the dose ranging study and chronic followup (030 and 031); the flecainide/quinidine comparative study and followup (032 and 033); the Rotterdam chronic efficacy and safety study (035); the compassionate use studies (028 and 057); and the acute and chronic study of ventricular tachycardia (057 amended). An additional 584 patients were enrolled in a postmyocardial infarction study (037, 10 patients); an open-label safety and efficacy study (067, 86 patients); a post marketing surveillance study (UK, 155 patients); and 333 additional patients enrolled in the 057 amended study.

Mean $\pm$ S.D. followup on all 1,330 patients was 292 $\pm$ 393 days (range, 1-1843 days; median 104 days). Mean $\pm$ SD followup on 573 ongoing patients was 506 days $\pm$ 464 days (range, 1-1843 days; median, 365 days). Followup was greater than six months for 580 patients, greater than one year for 369 patients, greater than two years for 188 patients and greater than three years for 118 patients.

Patients were first classified according to the severity of their underlying arrhythmia including 1) premature ventricular complexes only, 2) non-sustained ventricular tachycardia, and 3) sustained ventricular tachycadia. They were then further categorized by the presence or absence of structural heart disease, exposure to various dosage levels of flecainide, and in/out patient initiation of therapy. Patients were then analyzed for 1) possible or probable proarrhythmic events, 2) new or worsened congestive heart failure resulting in death or discontinuation, 3) serious conduction disturbances and 4) deaths due to cardiac and non-cardiac causes.

Table 33 shows the number of patients in each of the various categories and subgroups. Of the 1,330 patients, 470 had premature ventricular complexes only, 469 had nonsustained ventricular tachycardia and 391 patients had sustained ventricular tachycardia.

TABLE 33

PATIENTS IN DATABASE STRATIFIED FOR VARIOUS BASELINE CHARACTERISTICS AND DOSE(S) RECEIVED

	PVC ONLY	NONSUSTAINED VT	SUSTAINED VT	TOTAL
STRUCTURAL HEART DISEASE				
NO	132	64	28	224
YES	338	405	363	1,106
TOTAL	470	469	391	1,330
TOTAL DAILY DOSE[a]				
200	260	347	301	908
300	142	250	195	587
400	324	218	160	702
600	44	50	25	119
STUDY				
028/057	59	118	100	277
057, AMENDED	27	204	198	429
OUTPATIENT INITIATION OF THERAPY	273	88	15	376

[a] Patients were included more than once if exposed to multiple flecainide dosages.

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057, AMENDED	27	204	198	429
OUTPATIENT INITIATION OF THERAPY	273	88	15	376

[a] Patients were included more than once if exposed to multiple flecainide dosages.

Proarrhythmic events were classified into one of three categories:

1. Those arrhythmic events that resulted in death.

2. Those events that were considered serious but nonlethal, defined as worsened ventricular arrhythmias that required immediate termination with drugs, overdrive pacing or cardioversion. If the proarrhythmic event was associated with hypotensive symptoms, it was also considered serious but nonlethal.

3. Other proarrhythmic events as judged by the investigator included those with an increase in premature ventricular complexes (using previously published criteria), new or increased frequency of nonsustained ventricular tachycardia or new ventricular arrhythmias characterized by a change in configuration or rate (of ventricular tachycardia) but which did not result in worsening of symptoms as compared with baseline.

Proarrhythmic events occurred in 6.8% of the 1,330 patients in the database. These events were serious in 2.3% of patients and lethal in 1.0%. Serious nonlethal events occurred in 6.6% of patients with sustained ventricular tachycardia, in 0.9% with nonsustained ventricular tachycardia and 0% in those with premature ventricular complexes only. Proarrhythmic death occurred in 3.1% of patients with sustained ventricular tachycardia, in 0.2% with nonsustained ventricular tachycardia, and 0% with premature ventricular complexes. Serious nonlethal proarrhythmia occurred in 2.6% of patients with underlying structural heart disease as compared to 0.4% in patients in whom this finding was absent, and death occurred in 1.2% versus 0%, respectively.

New or worsened congestive heart failure leading to study discontinuation occurred in 1.4% of the 1,330 patients, and all had underlying organic heart disease. Six (0.5%) patients died of congestive failure; all had significant myocardial dysfunction prior to flecainide initiation. Although heart failure was related to underlying organic heart disease, there was no clear relationship to dose or type of arrhythmia.

Symptomatic conduction disturbances occurred in 29 (2.2%) of the 1,330 patients. Nineteen of these 29 patients had pre-existing conduction disturbances, 20 discontinued flecainide and nine continued taking the drug, eight of whom received permanent pacemakers. The incidence of significant conduction disturbances was not related to the presence or absence of structural heart disease, severity of underlying arrhythmia, or dose of flecainide.

As previously discussed, evidence from this analysis indicated that the incidence of proarrhythmic events is related to both the presence of underlying structural heart disease and type of ventricular arrhythmia. Further, patients with sustained ventricular tachycardia in the high initial dose compassionate studies (028, 057) had twice the incidence of proarrhythmic events (26%) compared with the patients in the low initial dose study (057 amended) of ventricular tachycardia (13.1%)

Another significant finding from this analysis concerns length of time on flecainide prior to the event. It is notable that 12 of the 13 proarrhythmic deaths occurred within 14 days of flecainide initiation. Also, 23 of 30 patients (77%) who had serious nonlethal proarrhythmic events, three of six deaths due to congestive heart failure, and three of four who developed syncope due to a conduction disturbance had these events within 14 days of starting flecainide treatment.

The fact that these adverse reactions usually occur early in treatment supports the recommendation that flecainide therapy be initiated in-hospital for patients with sustained ventricular tachycardia, serious compromised left ventricular function (particularly with symptomatic congestive heart failure), sick sinus syndrome and other unstable cardiac status, such as unstable ischemia and electrolyte imbalance (particularly hypokalemia). This analysis also supports the recommendation that patients start flecainide therapy at a low dose (100 mg BID) with careful upward titration (50 mg BID) at intervals no more frequent than every four days with appropriate monitoring of efficacy and flecainide plasma levels.

B. Non-cardiac Adverse Experiences

By July 1, 1985, 429 patients had enrolled in the 057 amended study (enrollment was initiated January 1983). The incidence of reported noncardiac adverse experiences was evaluated for all 429 patients, regardless of dose, and further evaluated by dose received during upward titration (Table 34). The pattern of these adverse experiences is consistent with that previously reported.

Table 34
Most Common Adverse Effects in Patients Treated With TAMBOCOR
in the Acute and Chronic Study of Ventricular Tachycardia

Adverse Effect	Incidence in All 429 Patients at Any Dose	Incidence by Dose During Upward Titration 200 mg/Day (N=426)	300 mg/Day (N=293	400 mg/Day (N=100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance+	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fa gue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

* Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.

\+ Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

VIII. Flecainide is an effective anti-arrhythmic agent. In studies of VPC suppression it was superior to quinidine and disopyramide, achieving 95% suppression of VPCs in 3/4 of patients in the largest study (flecainide vs quinidine, 032) and 100% suppression of paired beats and VTach beats in 70% and 79% respectively. In patients with documented VT, about half with sustained VT, who had been refractory to 3-4 other antiarrhythmic agents, flecainide was effective enough to allow hospital discharge in 73% including 59% of patients with sustained VT, with 48% free of symptomatic VT and still on drug after a mean follow-up of eight months. In 30-40% of patients with PES-inducible VT, flecainide provided complete suppression of inducibility.

Non cardiac side effects are reasonably well tolerated with dizziness and visual disturbances being the main problems each occurring in about 1/6 to 1/3 of patients. Flecainide has a negative inotropic effect, and about 14% of patients with CHF developed worse CHF; only 1% of patients developed new CHF. Flecainide caused 2^{o} or 3^{o} AV block in 10 patients (about 1%) and sinus node dysfunction/ bradycardia in 19 patients (about 1.5%). Both problems occur early in treatment, in general, and can be monitored. The pro-arrhythmic effects of flecainide, described above, are well-documented and serious and are present for patients with severe heart disease and serious arrhythmias (16.4%) and those with only PVCs (1.7%) and nonsustained VT (2.8%). While lower doses in study 057 amended seem to have reduced fatalities, an 8-10% rate for pro-arrhythmic events was still present.

Despite its pro-arrhythmic, negative inotropic and conduction-inhibiting effects, flecainide has a role in the treatment of patients with life threatening arrhythmias. With the recommended slow titration and hospital monitoring, it can be used to manage some patients not treatable with other agents with risks probably no worse than the other agents.

Although flecainide is very effective in VPC suppression, it can be recommended for this use at present only if the benefit of symptomatic relief outweighs the risks of proarrhythmia and other adverse effects, since there is no evidence that treatment of these lesser arrhythmias has a favorable effect on mortality or sudden death.

IX. Approved Package Insert:

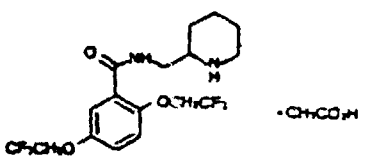
A copy of the package insert is attached.

TAMBOCOR®
(flecainide acetate)
Tablets

DESCRIPTION:

TAMBOCOR® (flecainide acetate) is an antiarrhythmic drug available in tablets of 100 or 200 mg for oral administration.

Flecainide acetate is benzamide,N-(2-piperidinylmethyl)-2,5-bis (2,2,2-trifluoroethoxy)-, monoacetate. The structural formula is given below:



Flecainide acetate is a white crystalline substance with a pK, of 9.3. It has an aqueous solubility of 48.1 mg/ml at 37°C.

CLINICAL PHARMACOLOGY:

TAMBOCOR has local anesthetic activity and belongs to the membrane stabilizing (Class I) group of antiarrhythmic agents; it has electrophysiologic effects characteristic of the IC class of antiarrhythmics.

Electrophysiology. In man, TAMBOCOR produces a dose-related decrease in intracardiac conduction in all parts of the heart with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods were observed only in the ventricle. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction (see Warnings).

TAMBOCOR causes a dose-related and plasma-level related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful 30-40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 μg/ml may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 μg/ml. Plasma levels above 0.7-1.0 μg/ml are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally.

In animals and isolated myocardium, a negative inotropic effect of flecainide has been demonstrated. Decreases in ejection fraction consistent with a negative inotropic effect have been observed after single administration of 200 to 250 mg of the drug in man; both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses (see Warnings).

Metabolism in Humans. Following oral administration, the absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range, 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life with steady-state levels approached in 3 to 5 days; once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% (of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one-fifth as potent) and the meta-O-dealkylated lactam of flecainide (non-active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found. In urine only 5% of an oral dose is excreted in free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 μg/ml).

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. (See Dosage and Administration.)

In patients with congestive heart failure (NYHA class III), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 14 hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar. (See Dosage and Administration.)

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 μg/ml. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs (see Precautions, Drug Interactions).

INDICATIONS AND USAGE:

TAMBOCOR is indicated for the treatment of documented life-threatening ventricular arrhythmias such as sustained ventricular tachycardia.

TAMBOCOR is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of TAMBOCOR, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, TAMBOCOR, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients depending on their cardiac status and underlying cardiac disease (see Dosage and Administration).

The effects of TAMBOCOR in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including TAMBOCOR, has been shown to have a favorable effect on mortality or sudden death.

CONTRAINDICATIONS:

TAMBOCOR is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Proarrhythmic Effects.

TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachyarrhythmia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias.

In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. Their frequency appears to be related to dose and to the underlying cardiac disease.

Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 25%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 6.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule (see Dosage and Administration).

Patients with less serious arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal.

The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).

Heart Failure.

TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of preexisting CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg bid (see Dosage and Administration) and patients should be monitored carefully. Close attention must be given to maintenance of cardiac function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics, others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/ml.

Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose related increases in PR, QRS and QT intervals. PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one-third of patients may develop new first-degree AV heart block (PR interval ≥0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythmia associated with flecainide induced QT prolongation and bradycardia.

Clinically significant conduction changes have been observed at these rates, sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block or right bundle branch block associated with a left hemiblock occur, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing threshold and may suppress ventricular escape rhythms. The effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration, and at regular intervals thereafter. Generally threshold changes are within the range of multiprogrammable pacemakers and, when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture.

Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmics. Preexisting hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

PRECAUTIONS:

Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin a 13% ±19% increase in plasma digoxin levels occurred at six hours postdose in a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently. Plasma flecainide levels were increased about 20% and propranolol levels were increased about 30% compared to control values in this formal interaction study. TAMBOCOR and propranolol were each found to have negative inotropic effects; when the drugs were administered together the effects were additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive in TAMBOCOR clinical trials. Patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.

Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction.

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgment of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with milrinone or dilitiazem to recommend concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

Pregnancy. Pregnancy Category C. Flecainide has been shown to have teratogenic effects (cleft palate, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day, respectively. However, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. It is not known whether flecainide is excreted in human milk. Because many drugs are excreted in human milk and because of the drug's potential for serious adverse effects in infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 16 years of age have not been established.

Use in Patients with Hepatic Impairment. Studies to determine the effect of hepatic impairment upon the elimination of TAMBOCOR have not yet been completed. Because the drug undergoes extensive biotransformation (most likely in the liver), patients with significant hepatic impairment should not receive TAMBOCOR unless the potential benefits clearly outweigh the risks.

ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR (described in detail in Warnings section) were new or exacerbated ventricular arrhythmias which occurred in 7% of patients and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest about 2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 µg/ml.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign post-marketing surveillance studies there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained surface of signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects are based on a multicenter efficacy study utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table I

Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 429 Patients at Any Dose	Incidence by Dose During Upward Titration 200 mg/Day (N=428)	300 mg/Day (N=293)	400 mg/Day (N=190)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance†	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400–600 mg/day, the incidence of these adverse experiences was similar except for dizziness (32%) and visual disturbances (28%).

The following additional adverse experiences possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies: *Body as a Whole* – malaise, fever; *Cardiovascular* – tachycardia, sinus pause or arrest; *Gastrointestinal* – vomiting, diarrhea, dysgeusia, anorexia; *Skin* – rash; *Visual* – diplopia; *Nervous System* – hypesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus; *Psychiatric* – anxiety, insomnia, depression.

The following additional adverse experiences possibly related to TAMBOCOR have been reported in less than 1% of patients: *Body as a Whole* – swollen lips, tongue and mouth, arthralgia, bronchospasm, laryngitis; *Cardiovascular* – angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension; *Gastrointestinal* – flatulence; *Urinary System* – polyuria, urinary retention; *Hematologic* – leukopenia, thrombocytopenia; *Skin* – urticaria, exfoliative dermatitis, pruritis; *Visual* – eye pain or irritation, photophobia, nystagmus; *Nervous System* – hemiplegia, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor; *Psychiatric* – amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the T-wave, a reduction in myocardial rate and contractility, conduction disturbances, hypotension; and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol, mechanically assisted respiration, circulatory assists such as intra-aortic balloon pumping, and transvenous pacing in the event of conduction block. Because of the long plasma half-life of flecainide (12 to 27 hours in patients receiving usual doses) and the possibility of markedly non-linear elimination kinetics at very high doses, these supportive treatments may need to be continued for extended periods of time. Hemodialysis is not an effective means of removing flecainide from the body.

DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels in patients with normal renal and hepatic function may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore **increases in dosage should be made no more frequently than once every four days** since during the first 2 to 3 days of therapy the maximal effect of a given dose may not be achieved.

For sustained ventricular tachycardia, patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most such patients do not require more than 150 mg every 12 hours (300 mg/day), and the maximum dose is 400 mg/day.

For patients with symptomatic nonsustained ventricular tachycardia, couplets or premature ventricular complexes, the recommended starting dose is also 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day and the plasma level is below 0.6 µg/ml, the dosage may be cautiously increased to a maximum of 500 mg/day.

Use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and congestive heart failure, particularly during the first few days of dosing (see Warnings). Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients, efficacy at the lower dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction (see Warnings). The initial dose should be no more than 100 mg every 12 hours if needed to achieve efficacy. The dosage may be increased cautiously in increments of 50 mg bid every four days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

In patients with renal impairment, the initial dosage should be 100 mg every 12 hours. Dosage increases should be made cautiously at intervals greater than 4 days, observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change. It is recommended that plasma level monitoring be used to guide dosage adjustments (see below).

Based on theoretical considerations, rather than experimental data, the following suggestion is made when transferring patients from another antiarrhythmic drug to TAMBOCOR: allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting TAMBOCOR at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalization of the patient.

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 µg/ml. The probability of adverse experiences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 µg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Because elimination of flecainide from plasma may be slower in patients with severe chronic renal failure or severe congestive heart failure, plasma level monitoring may be especially helpful in these patients.

HOW SUPPLIED:

TAMBOCOR is supplied as white, round, scored tablets containing either 100 or 200 mg of flecainide acetate and embossed with RIKER on one side and TR 100 or TR 200 on the other side.

Tambocor 100 mg/tablet is available in:
Bottles of 100 – NDC #0089-0307-10
Bottles of 500 – NDC #0089-0307-50 and
Bottles of 1000 – NDC #0089-0307-80

Tambocor 200 mg/tablet is available in:
Bottles of 100 – NDC #0089-0317-10
Bottles of 500 – NDC #0089-0317-50 and
Bottles of 1000 – NDC #0089-0317-80

Store at controlled room temperature 15°-30°C (59°-86°F) in a tight, light-resistant container.

TR-1 OCTOBER 1985

Manufactured by
Riker Laboratories, Inc./3M
St. Paul, Minnesota 55144

N 18830 Bio Portion of MOR -1

NDA 18830

B.10 portion

of mor

THESE PAGES ARE FROM
DR. SUGHOK CHUN'S MEDICAL REVIEW
DATED APRIL 20, 1984
FOR NDA 18-830

In experiments designed to measure changes in coronary arteriovenous oxygen differences and plasma potassium levels in normal pentobarbital anesthetized dogs and in conscious coronary ligated dogs (24 hours post ligation), a 5.0 or 7.5 mg/kg intravenous dose of flecainide did not alter either coronary arteriovenous blood gas or plasma potassium concentrations.

No apparent vasodilatory activity was observed for flecainide given intravenously in dose up to 1.2 mg in the dog perfused hind limb at constant blood flow. At an effective intravenous antiarrhythmic dose of 5.0 mg/kg, flecainide had no apparent effect on regional blood flow in carotid, femoral, renal and superior mesenteric vascular beds. Coronary blood flow in isolated perfused rabbit heart showed minimal variable changes at relatively high intracoronary doses of flecainide.

OTHER PHRAMACOLOGICAL STUDIES

In pentobarbital anesthetized male and female dogs with neuromuscular blockade by succinylcholine chloride and mechanical ventilation with room air, intravenous flecainide (5.0 or 10.0 mg/kg) did not block bronchoconstriction induced by intravenous histamine or methacholine.

Local anesthetic action similar to lidocaine was demonstrated for flecainide administered topically to the rabbit cornea. When given intramuscularly flecainide showed regional nerve block of equal intensity but of longer duration than lidocaine in the mouse sciatic nerve preparations.

In isolated smooth muscle tissues (trachea, ileum, uterus and seminal vesicle) taken from rats and guinea pigs, flecainide demonstrated a relatively weak nonspecific spasmolytic action.

Dose-related CNS depression was observed in rats administered flecainide intraperitoneally. Death was observed at 100 mg/kg. Orally administered flecainide to male and female mongrel dogs showed a mild CNS depressant activity and mild tachycardia at 10.0 and 20.0 mg/kg. Vomiting was the limting factor for the administration of higher oral doses of flecainide to dogs. A slight delayed weight loss was observed in dogs treated with flecainide at all oral doses.

R-818 did not block electrically induced arterial thrombosis in the pentobarbital anesthetized male rat at an intravenous dose of 5.0 mg/kg body weight.

a. Pharmacokinetics:

For all human plasma and urine samples from clinical studies, the concentrations of unchanged flecainide acetate (flecainide, R-818) were measured by the use of a sensitive and specific gas-liquid chromatographic (GLC) method.

A. Oral Absorption/Bioavailability

Follwoing single oral dose (60 to 240 mg) to healthy human subjects, flecainide absorption into the systemic circulation is reasonably prompt and nearly complete from both a capsule and a tablet formulation; flecainide does not appear to undergo any consequential presystemic biotransformation in humans. After single oral dose and multiple oral dosage regimens, plasma levels of flecainide are proportional to dose level (60 to 250 mg per dose); thus, the extent of absorption does not appear to be affected by dose level within the therapeutic range. Neither food nor an antacid affect the extent of flecainide absorption; any effect to slow the rate of absorption is small and of no clinical consequnce. In addition, oral absorption in patients with cardiac arrhythmias, renal disease, and congestive heart failure is also reasonably prompt and nearly complete. Efficacy data in patients confirm the effectiveness of oral flecainide dosage for the treatment of cardiac arrhythmias.

The capsule formulation has been used in many clinical trials, including pivotal therapeutic and long-term safety studies. The tablet formulation is the dosage form that will be marketed and it has been used in more recent clinical trials, includng long-term safety and comparative absorption studies.

B. Plasma Pharmacokinetics

Following single intravenous or oral doses to healthy human subjects, the terminal phase plasma half-life of unchanged flecainide is relatively long (mean, about 13 hours). After multiple oral dosage regimens to subjects, the plasma half-life is somewhat longer, on an average, than that after single doses. For patients with premature ventricular contractions (PVC's), the rate of flecainide elimination from plasma is slower (mean half-life, about 20 hours) than that for healthy subjects. In addition, the rate of flecainide elimination from plasma is somewhat slower in patients with moderate renal failure and in patients with congestive heart failure than that for healthy subjects and is markedly slower in some patients with end-stage renal disease. No sex-related difference in plasma half-life is apparent. Although not clearly evident, the rate of flecainide eliminiation from plasma may possibly be reduced in patients of more advanced age. Overall, the pharmacokinetics of flecainide eliminiation from plasma appear to be reasonably linear (not dose- or concentration-dependent). Efficacy data in patients with PVC's confirm the effectiveness of twice daily oral flecainide dosage.

C. Biotransformation

In human subjects, a substantial portion of a single oral dose is excreted in urine as unchanged flecainide. Also, the drug undergoes extensive biotransformation in humans and its metabolites are excreted mostly in urine.

In addition to unchanged drug, only two major metabolites of flecainide and several minor metabolites are found in human urine. The two major urinary metabolites are meta-O-dealkylated flecainide and the meta-O-dealkylated lactam of flecainide; each is found in the free and conjugated forms. In laboratory models, meta-O-dealkylated flecainide has some low but detectable antiarrhythmic activity. In addition, metabolites of flecainide are present in human plasma and the rate of elimination of total metabolites from plasma is only somewhat slower than that for unchanged drug.

D. Excretion

In healthy subjects, most (mean, 86%) of a single oral dose of carbon-14 labelled flecainide is excreted in urine as flecainide and its metabolites (radioactivity); only a small portion (mean, 5%) of the dose (carbon-14) is found in feces. Flecainide does not appear to undergo extensive biliary excretion in humans.

Overall, in human subjects, a substantial portion (mean, 27%) of a single oral dose is excreted in urine as unchanged flecainide; urinary excretion of the two major metabolites (each in its free and conjugated forms) accounts for most of the remaining portion of the dose in urine. In addition, renal clearance of unchanged flecainide (average, about 170 ml/min) accounts for about 25% of plasma (total body) clearance. The extent of urinary excretion and the renal clearance of unchanged flecainide are somewhat lower in patients with moderate renal failure and are markedly lower in patients with end-stage renal failure. Urinary excretion in patients with congestive heart failure is not altered. Hemodialysis does not appear to be an effective means for removal of unchanged flecainide from the body.

E. Plasma Flecainide Levels in Relation of Biological Effects

In patients with PVC's, minimum therapeutic plasma levels of flecainide (associated with greater than 90% suppression of PVC's) range from about 200 to 1000 ng/ml (mean, about 500 ng/ml). Trough plasma levels up to about 1500 ng/ml are well tolerated in most patients. During long-term drug administration to patients with PVC's, no evidence of consistent increasing or decreasing trends in plasma flecainide levels is apparent.

F. Drug-Drug Metabolic Interactions

Multiple oral dosage of flecainide to human subjects stabilized on a maintenance dose of digoxin was found to cause only a small (statistically significant at some times) increase in steady-state plasma digoxin levels. The magnitude of these changes in digoxin levels is small and should be of no clinical consequence for patients receiving chronic digoxin therapy. During coadministration of propranolol and flecainide to subjects, the magnitude of the higher plasma AUC values for propranolol (about 30%) and for flecainide (about 20%) is small and is probably of no clinical consequence.

G. Plasma Protein Binding

Flecainide is not extensively bound (about 40%) to human plasma proteins in vitro and binding is independent of plasma drug level over a wide range that markedly exceeds therapeutic levels. With ten other drugs that may be administered concomitantly, the extent of flecainide binding to human plasma proteins in vitro is either not changed or is only slightly less. Thus, consequential drug-drug interactions in vivo based on protein binding effects would not be expected. In addition, it is unlikely that changes in plasma proteins would alter binding to any clinically consequential extent.

b. Toxicology:

A. General Toxicology

Acute toxicity studies in four species (mouse, rat, dog and cat) by various routes of administration (iv, ip, po) indicated that large single doses of flecainide generally produced ataxia (prostration), dyspnea and convulsions. Emesis was also observed in dogs and cats. Death generally appeared to be due to respiratory depression and arrest. Surviving animals recovered rapidly (within several hours) with no observable residual drug effects.

The subchronic animal toxicity studies indicated adequate safety margins when compared to human projected dose levels - 10 to 20 times orally and 250 to 275 times intravenously.

Chronic toxicity studies were done in baboons for 6 months, in dogs for 18 months, in mice for 18 months and in rats for 24 months. The chronic administration of flecainide did not produce chronic toxic effects on the heart. The expected ECG changes occurred, but even after chronic administration the changes were generally completely reversible. One high dose baboon and one high dose dog died on the chronic toxicity studies, but the cause of death was not established as toxic signs were not observed preceeding death and tissue examinations did not reveal any toxic changes. Survival rates were not adversely affected in the long term rodent studies; in fact, the chronically treated rats had better survival than the controls.

The effect of high concentrations in pigmented eye tissues of flecainide and/or its metabolites as determined in drug metabolism studies was found to be of no toxicological consequence. Ophthalmologic examination, retinal photographs and gross or microscopic eye tissue examination demonstrated no changes in the pigmented portions or any other part of the eye that could be attributed to chronic flecainide administration.

Flecainide is also being studied for effectiveness in ventricular arrhythmias induced by exercise (R-818-034) and by programmed electrical stimulation (R-818-053 and R-818-056). All three studies are reported in an update to the NDA in December, 1983.

Special studies conducted with flecainide have included the assessment of its acute hemodynamic effects both intravenously (R-818-003, R-818-022 and R-818-054) and orally (R-818-024 and R-818-039) as well as an iv study of its effects on intracardiac conduction (R-818-015). Formal drug interaction studies, have been accomplished with propranolol (R-818-041) and digoxin (R-818-045) as probable agents which might be used concomitantly in the projected target use populations.

Metabolism and safety studies in healthy subjects (R-818-001, R-818-005 and R-818-018) provided information on tolerance by the intravenous and oral routes as well as yielding data on the pharmacokinetics of the drug in subjects. Pharmacokinetic data from other populations has been assembled from patients with PVCs (R-818-030), patients with renal insufficiency (R-818-038), and patients with congestive heart failure (R-818-039). Blood level-antiarrhythmic effect relationships have been investigated in Study R-818-030. In addition, the metabolic fate of flecainide has been elucidated using 14-C labelled compound in a suitable population of subjects (R-818-050-03). Documentation of the performance of formulations utilized in clinical studies and of the bioavailabilty of the dosage form to be marketed has been obtained in specific studies (R-818-005, R-818-026 and R-818-049).

5. Clincial Studies:

Table 1 is a list of sponsor's clincial reports NDA location and page of review.

The list and summary of SPECIAL STUDIES are shown in Table 2, PIVOTAL STUDIES in Table 3, OTHER CONTROLLED STUDIES in Table 4, and CHRONIC - DOSING STUDIES in Table 5.

A. Special Studies

(1) Pharmacokinetic Studies: Detail review refer to consultation review by HFN-525.

Safety studies in healthy volunteers established the feasibility of administering doses of flecainide up to 2.0 mg/kg, intravenously (R-818-001, and R-818-005) and 180 mg, bid, orally (R-818-018). These studies allowed use of the drug intravenously in hemodynamic and electrophysiologic studies and provided the basis for initial clinical studies for efficacy by the oral route.

(a) Clinical Study R-818-001-01; vol. 2.3: 1-13
vol. 2.8:95-184

Plasma Concentrations of R-818 in Man Following Single Intravenous Doses

Investigator: Donald B. Hunninghake, M.D.

Study Site: University of Minnesota Hospitals
Minneapolis, MN

Study Objective:

To assess the safety and tolerance of intravenous flecainide acetate and to obtain initial plasma pharmacokinetic data for flecainide in healthy human subjects.

Study Population:

Eight healthy, adult male subjects; one additional subject completed the study initially under a different dosage regimen.

Study Design:

Open label, safety and metabolic study with increasing intravenous doses.

Physical examinations, 12-lead electrocardiograms, standard exercise electrocardiograms, chest radiographs, clinical laboratory tests, and ophthalmologic examinations were obtained both prestudy and poststudy. During the eight hour study period, continuous electrocardiographic monitoring was conducted, and 12-lead electrocardiograms, one-minute electrocardiogram strips and vital signs were periodically obtained.

Blood samples were obtained predose, at 5, 15,, 30, 60 and 90 minutes, and at 2, 4, 6 and 8 hours following initiation of the intravenous dose to obtain plasma pharmacokinetic data.

Test Dosage:

Single, intravenous doses (0.5,, 1.0, 1.5, and 2.0 mg/kg) were administered over a five minute period; two subjects were completed at each dose level. One initial subject received escalating doses at two hour intervals to a total dose of 35 mg. (Formulation U-1a)

Results:

No drug-related changes occurred in any of the physical findings or clinical laboratory tests during the study. No clinically significant changes in vital signs or evidence of rhythm disturbances occurred during the eight hour observation period; small increases in PR interval (0.01 to 0.04 seconds) and QRS duration (0.01 to 0.03 seconds) were associated with drug administration.

The plasma concentrations of unchanged R-818 following I.V. single dosing widely varied during early phase of 5, 15 & 30 min samples but from 60 min and thereafter samples varied very little. There was some trend of dose response curve with increase dose, but not proportional.

The plasma half-life of flecainide during the terminal elimination phase was found to range from [redacted] hours (mean 11.0 hours) and is apparently independent of dose level. The relatively high plasma levels during the distribution phase at early times after dosage were associated with mild and transient side effects at the two highest doses.

Side Effects:

Only minor and transient side effects occurred and only with the higher doses; these included transient lightheadedness and blurred vision in one subject at 1.5 mg/kg, difficulty in focusing and dry mouth in another subject who received 2.0 mg/kg, and anesthesia of the buccal mucosa in a second subject at that same dose level. Venospasm occurred in one subject, and another subject reported tenderness at the site of injection.

Conclusions:

The single, intravenous doses (up to 2.0 mg/kg) were well tolerated by all subjects in the study.

The relatively long plasma half-life of flecainide indicates that plasma drug levels will be maintained for prolonged periods; thus, flecainide is likely to provide sustained therapeutic activity and should be suitable for twice daily dosage during chronic treatment of cardiac arrhythmias.

(b) R-818-005-01, vol. 2.8 p. 186
"Plasma Concentrations of R-818 in Man Following Single Oral Doses"

George P. Lewis, M.D.
Tufts University
Clinical Pharmacology Research Unit
Lemuel Shattuck Hospital
Boston, Massachusetts

Study Design: Sixteen healthy, adult male subjects were included in this open label study. Each subject received a single oral dose of formulated R-818 with 200 ml of water. Four different subjects were included in each of the four dose level groups; the dose levels employed were 60, 120, 180 and 240 mg of R-818 for Subject Groups A, B, C and D, respectively. Six weeks after the 180 mg dose, the four subjects in Group C also received a second oral dose (200 mg). Since this second dose level is not greatly different from the 180 mg dose, the plasma samples obtained from these four subjects (Group C) following the 200 mg dose were not analyzed. All subjects received the oral doses under fasting conditions, and no food was ingested for at least four hours following dosage.

Seven days following the single oral dose, subjects in Groups A (60 mg) and B (120 mg) also received a corresponding dose of R-818 by the intravenous route. The intravenous dose was administered intravenous solution over an approximately 5 minute period. Intravenous drug administration was done under the same fasting conditions that were used for oral dosage.

Blood Sampling: For determination of plasma drug concentrations, venous blood samples were obtained at various times following the single oral or intravenous doses:

> pre-dose at 5, 10, 15, 30, 45, 60 and 90 minutes and at 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours following the oral dose or following termination of the intravenous dose.

Urine samples were also collected on a limited basis (pre-dose and during the initial 24 hours following dosage) from each subject.

Results:

Following oral dosage (0.65 to 3.53 mg/kg) of the 16 subjects, peak plasma levels of flecainide acetate (69 to 463 ng/ml) are usually attained at 1.5 to 3.0 hours (mean, 2.6 hours). Intrasubject comparisons of oral and intravenous plasma AUC values (zero to infinity) for eight of the subjects indicate that, on an average, 95% of the oral dose is absorbed and delivered to the systemic circulation as unchanged flecainide (oral/intravenous AUC ratio range, 0.71 to 1.24). Plasma AUC values and peak levels are reasonably proportional to oral doses.

Following oral dosage (16 subjects), the plasma half-life of flecainide during the terminal elimination phase was found to range from [redacted] hours (mean 14.2 hours); after intravenous dosage (8 subjects), the plasma half-life was found to range from [redacted] hours (mean 14.1 hours). The plasma half-life is similar for both routes of drug administration in a given subject and is apparently independent of dose level.

A summary of plasma pharmacokinetic data for all sixteen subjects following single oral doses (60 to 240 mg) is shown in Table 6. Table 7 shows comparison of plasma pharmacokinetic data for the eight subjects that also received a single intravenous dose (60 or 120 mg). Plasma R-818 concentrations in seven of eight subjects decrease very rapidly during the first 30 to 60 minutes following intravenous drug administration. The relatively high plasma levels of R-818 in most subjects at early times following dosage are associated with mild and transient side effects observed in some of the subjects. The intersubject variation in half-life values found in this study is approximately three-fold. Although variations in plasma R-818 half-life exist between subjects at different dose levels, no apparent dose-dependent elimination kinetics are detectable in these sixteen subjects at dose levels ranging from 0.65 to 3.53 mg/kg and with peak plasma concentrations up to approximately 450 ng/ml. With oral doses of 60 to 240 mg (0.65 to 3.53 mg/kg), peak R-818 levels of 69 to 463 ng/ml are usually attained at 1.5 to 3 hours (mean, 2.6 hours). The terminal phase of drug elimination from plasma is relatively slow and is reasonably linear (r^2 values range from 0.90 to 0.99) for all subjects; thus, terminal elimination of R-818 from plasma is apparently a first order process.

The terminal plasma half-life of unchanged R-818 was found to range from [redacted] hours (mean 14.2 hours) in the sixteen subjects following oral dosage (Table 6). Similarly, the terminal plasma half-life after intravenous drug administration (Table 7) was found to range from 6.9 to 19.1 hours (mean, 14.1 hours) in eight of these sixteen subjects.

For 11 subjects, the average percent of dose excreted in urine by 24 hours after oral administration (60, 120, or 240 mg) was 24.39 + 10.06%; values for individual subjects range from 9.09 to 43.98%. In four of these subjects following intravenous dosage (60 or 120 mg), the average was 30.86 + 7.25% (range, 21.33 to 38.76%) of the dose within 24 hours. Table 8.

An intrasubject comparison for oral and intravenous dosage was made for four subjects; for Subject Nos. 1 and 7, the extent of urinary excretion (percent of dose excreted unchanged) was nearly equivalent, while for Subject Nos. 5 and 6, the extent of excretion was about three-fold greater following intravenous dosage. This difference was not explainable by the previously reported plasma pharmacokinetic data for these subjects.

No drug-related changes occurred in any of the physical findings or clinical laboratory tests during the study with either oral or intravenous dosage. No clinically significant changes in vital signs or evidence of rhythm disturbances occurred during the eight hour observation period. Minor variations (increases or decreases) were observed in ECG intervals. No other electrocardiographic changes were found. Correlation of changes in ECG intervals with dose or time of drug administration was extremely poor.

Conclusion:

The prompt and extensive delivery of unchanged drug to the systemic circulation following oral administration and the relatively slow plasma elimination of R-818 in man provide the further evaluation of the drug in oral, prophylactic treatment of cardiac arrhythmias.

(c) Intravenous Pharmacokinetics of Flecainide after Single-Dose Administration (2 mg/kg - over 5 minutes) #82-105-FRV-BE-002

by T.B. Tjandramaga, M.D., Ph.D. et al,
Division of Clinical Pharmacology
Katholieke Universiteit Leuven, Belgium

This single dose (2 mg/kg) intravenous study in 5 healthy male volunteers showed that an average peak plasma level of 1710 ng/ml was attained at the end of 5 minute period of IV-injection. The decline in plasma concentration appeared bi-exponential with a fast (a) distribution phase ($t_{1/2}$ = 0..2 hr) and a slow terminal elimination phase ($t_{1/2\beta}$ = 17.5 hr). Flecainide has a large volume of distribution (Vd_{SS} = 512 liters) with approximately 40% of the drug in the body apparently residing in the central compartment (Vc = 199 liters).

The plasma (total body) clearance data (Cl_{TB} = 355.2 ml/min) versus the renal clearance values of unchanged flecainide (Cl_{renal} = 169.5 ml/min) indicated that in normal subjects, flecainide was eliminated from the body about 50% by renal excretion and approximately 50% by non-renal mechanism(s) ($Cl_{non\text{-}renal}$ = 185.7 ml/min).

The present findings of 169.5 ml/min for average renal clearance of flecainide (range: from 127 to 216 ml/min) which are consistently higher than the corresponding creatinine clearance values ($Cl_{creatinine}$ = 107 ml/min; range from 103 to 111 ml/min) suggest that flecaininde undergoes both glomerular filtration and a tubular secretion for its excretion by the kidneys.

(d) Absolute Bioavailability Estimation of Flecainide: Single Oral Versus Intravenous Dose Administrations
#81-152-FRO-BE-002 (Flecainide - Oral Fasting) and
#82-105-FRV-BE-002 (Flecainide - Intravenous Fasting)
by T.B. Tjandramaga, M.D., Ph.D., et al, Division of Clinical Pharmacology, Katholieke Universiteit Leuven, Belgium.

Intrasubject comparisons of oral and intravenous plasma data [Normalized $(AUC)_0$ X B] for five healthy male subjects following single dose administration orally (200 mg) or intravenously (2 mg/kg over 5 minutes) indicated that, on an average, 91% of the oral dose was available to the systemic circulation as unchanged flecainide (range, 86 to 103 of dose).

These plasma level[illegible], following either oral or intravenous administration, f[illegible]r showed that Flecainide disappearance from plasma was relatively slow. The plasma half-life during the terminal elimination phase was found to range from 9.3 to 13.0 hr (mean, 11.5 hr) after oral dosage and from 15.8 to 23.1 hr (mean, 17.5 hr) after intravenous dosage. The apparently shorter oral dose half-life values may represent under estimation of the true values due to shorter intervals of plasma concentration decay curves available for half-life estimations (from 6 to 24-30 hours after oral dose). After intravenous dose administrations the intervals for the apparent terminal elimination phase available for half-life estimation were considerably longer and extended from approximately 2 to 36-48 hours post-dose.

Estimates of the apparent volume of distribution and total body clearance for flecainide (expressed as Vd_{area}/F and Cl_{TB}/F) are somewhat higher and more variable when derived from oral data. Consistently higher renal clearance values of flecainide after both oral and intravenous dosing, as compared to the corresponding endogenous creatinine clearance values, indicate the presence of both glomerular and tubular mechanisms for the renal excretion of unchanged flecainide. See Table 9.

(2) Safety and Effect of Flecainide on Cardiodynamics:

(a) Study #R-818V-003-01, vol. 2.5, pp. 3-168

Investigator: Paul H. Miller, M.D.

Study Site:

City of Hope Medical Center
Duarte, California

Study Population:

Twelve patients, eight men and four women, completed the study. Their ages ranged from 28 to 65 years (mean 52.2 years). Six of the twelve had coronary atherosclerosis; two patients had generalized atherosclerosis. Eleven patients had some type of cardiovascular abnormality in their medical history; the most common complaint was chest pain.

Study Design:

The study was conducted in an open fashion. Only patients who were undergoing diagnostic cardiac catheterization were admitted into the study. The protocol called for hemodynamic measurements and to HIS bundle electrogram be made prior to drug administration and at 10, 30, 60, 90 and 120 minutes following the completion of the intravenous injection of flecainide. Safety evaluations included prestudy and poststudy clinical laboratory tests and electro-

cardiograms; vital signs were monitored throughout the study period. For purposes of assigning flecainide doses, the twelve patients were to be divided into four groups of three patients each. The first group of patients were to receive 0.5 mg per kg (Group A), the second group 0.75 mg per kg (Group B), the third group 1.0 mg per kg (Group C), and the fourth group 1.5 mg per kg (Group D) over 5 to 10 minutes. Blood samples for the determination of plasma flecainide levels were scheduled to be obtained prior to the injection of flecainide and at 10, 30, 60, and 90 minutes and at 2. 4, 6, and 8 hours following administration.

Results

Interpretation of the results of this study was difficult because the baseline hemodynamic measurements were not obtained immediately prior to the administration of flecainide, there were small number of patients in each of the four dose groups and there was no placebo control group. In addition, the hemodynamic measurements were not obtained beyond 60 minutes and during this period there were numerous data omissions.

Cardiac Effects

Systemic cardiac output at baseline was near normal in ten of the 12 study patients. Patients 9 and 11 (Group D) had low cardiac outputs prior to flecainide administration (3.48 and 3.18 liters/minute, respectively). After flecainide, cardiac output was reduced in 11 of the 12 patients at 10. 30, and 60 minutes postdosing; cardiac output increased in patient 11 at the 30 minute interval. Table 10 presents the mean systemic cardiac output for each dose group (A = 0.5 mg/kg, B = 0.75 mg/kg, C = 1.0 mg/kg, and D = 1.5 mg/kg). The mean C.O. of each groups and mean percent change from baseline are shown below.

Mean and Percent Change of Cardiac Output

Group	BASELINE VALUE	10 MIN AFTER DOSE	30 MIN AFTER DOSE	60 MIN AFTER DOSE
Group A Mean 0.5 mg/kg	5.34	4.80	4.41	4.55 l/min
n=4	0.00	-9.72	-16.61	-14.86%
Group B Mean 0.75 mg/kg	5.42	5.18	4.07	4.76 l/min
n=2	0.00	-4.32	-13.92	-12.09%
Group C Mean 1.0 mg/kg	6.26	5.46	5.64	5.42 l/min
n=3	0.00	-12.92	-9.77	-13.34%

Group D Mean 1.5 mg/kg	4.99	4.00	4.22	3.44 l/min
n=3	0.00	-18.80	-13.40	-29.30%

The reductions in patients 9 and 11 were simlar to the reductions observed in patients with normal baseline cardiac output. The maximum decrease (35%) in cardiac output occurred in patient 12 at 60 minutes following flecainide infusion (Table 10). This patient's baseline cardiac output was unusually high (8.32 l/m) and may not have been measured during a true resting state (heart rate decreased by 12 beats/min [13%] from baseline 60 minutes after flecainide administration). Cardiac output did not further decrease with time in most patients nor does it appear to correlate with the dose of flecainide administered 0.5 mg/kg to 1.0 mg/kg. However 1.5 mg/kg showed further reduction at 60 minutes.

There was a very little change in heart rate or aortic pressure during 60 min. of observation period.

Mean Heart Rate & Aortic Pressure

	Baseline	10 min	30 min	60 min
Group A	77.0 (131/63)	78.5 (131/68)	75.8 (124/71)	76.5 (131/71)
Group B	72.0 (105/65)	74.0	74.0	76.0 (100/60)
Group C	74.7 (133/76)	70.7 (123/72)	72.0 (134/72)	77.3 (124/77)
Group D	77.3 (137/81)	73.3 (135/80)	70.7 (131/77)	66.7 (120/69)

There were significant decrease of BP 1-4 hrs post dose in 5 patients, four of them appeared to be due to concomitant medication (protamine sulfate, nitrates or sedatives). One patient (#4) BP dropped to 86/54 from 104/62, 2 hours post dose associated with unable to void, extremities became cool, weakness and nausea.

Systemic stroke volume was determined by dividing the cardiac output by the heart rate. Because of the decreases in cardiac output and only minor changes in heart rate stroke volume was reduced in all of the patients except for patients 6, 7, and 8 at all three time intervals.

The left ventricular end diastolic pressure data are presented in Table 11. No LVEDP data were obtained for patients 8, 10 and 11. Following the flecainide injection, the LVEDP increased in dose groups C (1.0 mg/kg) and D (1.5 mg/kg) at 10 and 30 minutes before returning to near baseline at 60 minutes (Figure 1 presents the mean percent change for each dose group).

The left ventricular dP/dt ratio data are presented in Table 12. In patients 8, 10 and 11, the aortic dP/dt ratio was measured in place of the ventricular dP/dt ratio. The data are grouped together to display the mean percent change in Figure 2. There was a trend in increase of LVED, reduction of cardiac output, BP and dP/dt after higher doses (Group C & D).

Peripheral Effects

Peripheral resistance (total systemic and pulmonary vascular resistance and pulmonary arteriolar resistance) was generally increased in most of the patients. This would be the anticipated response when cardiac output is reduced. The increases appeared not to be dose related. Changes in the remaining pressure measurements (aortic, pulmonary artery, right atrial, pulmonary wedge, and left ventricular [systolic]) were variable; no obvious trends or conclusions were evident.

HIS Bundle Electrogram

HIS conduction intervals were also determined in 9 of the 12 patients at baseline, and at 10, 30, and 60 minutes postdosing. For patient 5, the intervals were measured at predose and 15, 35, 45, 55 and 65 minutes postdose; no HIS electrograms were obtained for patients 3 and 11.

The P-A interval was included as part of the A-H interval for six patents (Nos. 1, 2, 5, 6, 7, and 12); therefore, the P-A interval was added to the A-H interval in all cases for purposes of analysis and was labeled P-A+A-H.

The conduction intervals were within normal limits at baseline. Following flecainide administration, minor fluctuations in the P-A+A-H, H-V and P-R intervals appeared to be random and unrelated to dose. Table 13 shows P-A+A-H intervals. Only Group D patients showed less than 10% increase afterdosing. There was minor change in H-V intervals.

Safety - Side Effects

The only reported side effects occurred in one patient (#4). The patient became hypotensive approximately 2 1/2 hours following flecainide and also had difficulty voiding urine which started one hour postdosing and lasted four hours.

No changes in blood chemistries, hematologic or urinalysis results could be attributed to flecainide administration.

Following flecainide administration, four patients (nos. 2, 4, 6 and 11) experienced transient episodes of a systolic blood pressure less than 90 mmHg.

Patient 2 reported feeling hot and had warm, moist skin and also complained of chest pain and apnea; patient 4 reported weakness and nausea and later cool extremities; patient 5 was diaphorteic; and patient 6 complained of being very hot. The investigator did not provide any comments regarding severity, duration or drug relatedness.

The mean systolic blood pressure for each dose group began to decrease shortly after the 60 minute postdosing interval and remained depressed compared to baseline for the remaining seven hours. The mean diastolic pressure also decreased after the flecainide injection in dose groups A, B and D; little or no change was observed in dose group C (1.0 mg/kg). Minor random changes were found in the respiratory rate. No changes were found on the poststudy ECG compared to the prestudy ECG.

Plasma Flecainide Levels

Plasma flecainide concentrations rapidly decrease during the first hour (distribution phase) after intravenous dosage. During this dynamic phase, it is unlikely that plasma and tissue levels of flecainide are in equilibrium, thus plasma levels at these early times would not reflect the actual concentration of flecainide at the site of any pharmacologic effects.

The terminal (postdistribution) plasma half-life of flecainide was estimated to range from [redacted] hours (mean, 8.9 hours) in these 12 patients; no sex difference in half-life was apparent. No correlations were attempted between plasma flecainide levels and hemodynamic measurements because, it was likely that during the first hour postdosing when the hemodynamic data was obtained, plasma and tissue levels were not in equilibrium.

Conclusion

Flecainide was administered intravenously to 12 patients with heart disease by dividing the patients into four dose groups in a nonrandomized fashion (0.5 mg/kg, 0.75 mg/kg, 1.0 mg/kg and 1.5 mg/kg). A sustained reduction in cardiac output and an increase in peripheral resistance was observed after flecainide administration. Because of the small number of patients, insufficient duration of hemodynamic observations and lack of appropriate baseline measurements, no firm conclusions can be drawn about the extent of the cardiodynamic effects produced by the drug in this study.

However, high I.V. dose of flecainide (1.0 mg & 1.5 mg/kg) appears to reduce left ventricle function by reduction of cardiac output and dp/dt, and increase of LVED pressure, at 10 and 30 min post dose measurements. No obvious trends were found in the other hemodynamic pressure measurements (aortic, left ventricular [systolic], right atrial, pulmonary artery and pulmonary wedge). HIS bundle

electrogram results (P-A+A-H, H-V and P-R) did not remarkably change following flecainide for 60 min. observation period. Belated hypotensive effect of this drug 3-4 hrs after dosing seen in this study indicates that longer observation should be done to see hemodynamic/electrophysiologic effect of flecainide after I.V. dosing.

(b) Study #R-818-022 (vol. 2.5, pp 169-245)

Investigators: Richard Helfant, M.D.
Monty Bodenheimer, M.D.

Study Site: University of Pennsylvania
Presbyterian Medical Center
Philadelphia, PA

Study Population:

To determine the effect of intravenous flecainide acetate on right and left ventricular performance using radionuclide angiography in patients with suspected or diagnosed heart disease.

Study Population:

Twenty patients, 11 females and nine males, between the ages of 36 and 69 years (mean, 53.7 years) entered and completed the study. All had clinical features suggestive of cardiac disease. None had a history of congestive heart disease. Two of the 20 patients had diagnosed cardiomyopathy and 4/20 had hypertension; the remained patients had diagnosed (3/20) or suspected (11/20) coronary artery disease.

Study Design:

Open-label study. Each patient underwent baseline radionuclide angiography, followed by a single intravenous dose of flecainide and a second angiogram 15 to 16 minutes postdose. The radioactive isotope dose was 12 to 18 mCi of Technetium 99m pertechnetate.

Test dosage: Flecainide acetate 1.0 mg/kg, 1.5 mg/kg, or 2.0 mg/kg (formulation U-1b). Over a 5 to 13-minute period.

Safety evaluations during the study procedure included monitoring heart rate and blood pressure and recording adverse experiences.

Blood sampling times for plasma flecainide administration, 14 to 16 minutes after completion of intravenous dosing (just prior to the second radionuclide angiogram), and 30 minutes after recording the second radionuclide angiogram.

There were no poststudy procedures.

Results

All 20 patients completed the study. Four patients received 1.0 mg/kg of flecainide, five patients received 1.5 mg/kg, and ten patients received 2.0 mg/kg. One patient received only 0.7 mg/kg of flecainide because of a decrease in blood pressure during the five-minute infusion period.

A comparison between the predrug and the postdrug radionuclide angiograms determined the effect of flecainide on right and left ventricular performance. See Table 14 & 15.

Patient No. 2 received 0.7 mg/kg of flecainide. His blood pressure decreased from 140/90 mmHg before dosing to 125/70 mmHg at 14 minutes postdosing. The right ventricular ejection fraction (RVEF) increased from 12% before to 27% after flecainide administration; the wall motion showed diffuse hypokinesis both before and after drug. Left ventricular ejection fraction (LVEF) increased from 17% predrug to 21% postdrug. Left ventricular performance prior to dosing was abnormal with diffuse severe hypokinesis; the postdrug angiogram showed no change from baseline. This patient had a primary diagnosis of hypertensive cardiomyopathy and predrug ejection fractions were extremely low (RVEF of 12%, LVEF of 17%).

Following the administration of 1.0 mg/kg flecainide (patient Nos. 1, 3, 4, and 5), there were no staitstically significant (p greater than 0.05) changes in average heart rate, systemic blood pressure, or right and left ventricular ejection fractions. Global function and wall motion of the right ventricle remained the same in three of the four patients (nos. 3, 4, and 5). The fourth patient (No. 1) developed hypokinesis of the right ventricle, associated with a decrease in the RVEF fraction from 37% to 21%. Three patients (nos. 3, 4, and 5) had normal left ventricular functon before flecainide dosing: two (Nos. 3 and 5) maintained normal contracton patterns postdosing while the third (No. 4) developed abnormal wall motion, accompanied by a decreased LVEF (from 88% to 76%). In one case (patient No. 1), a baseline segmental abnormality worsened after flecainide administration.

Five patients (Nos. 6 through 10) received 1.5 mg/kg of flecainide. There were no statistically significant (p greater than 0.05) changes in averages for systolic or diastolic pressure or heart rate. Within the group, the average RVEF decreased significantly (p=0.019) from 31.2% to 26.2%. Five patients had normal baseline right ventricular functions. Three (Nos. 8, 9, and 10) developed mild hypokinesis with an average decrease in ejection fraction of 6.7%; the other two (Nos. 6 and 7) maintained normal contraction patterns. The average LVEF decreased from 64.4% to 56.4% (p=0.098). Three patients (Nos. 7, 8, and 9) who had abnormal left ventricular performance before

flecainide dosing showed worsening abnormalities of the involved zone associated with a decrease in the ejection fraciton following flecainide administration. Two patients (Nos. 6 and 10) with normal left ventricular performance at baseline maintained normal wall motion postdosing.

Patient Nos. 11 through 20 each received a single intravenous dose of 2.0 mg/kg of flecainide. The averages for both systolic and diastolic blood pressures showed increases following flecainide dosing (Table 15). The systolic pressure increased from 138.4 to 144.9 mmHg (p=0.25). The diastolic pressure increase (from 89.3 to 98.0 mmHg) was statistically significant (p=0.0083). There was no statistically significant (p greater than 0.05) change in average heart rate. On the average, RVEF showed a statistically significant (p=0.0034) decrease from 33.0% to 24.9%. Of the nine patients who had normal right ventricular performance, five (Nos. 13, 14, 15, 18, and 20) maintained normal wall motion after dosing. The remaining 4/9 (Nos 11, 16, 17, and 19) showed a deterioration in performance, accompanied by a 12.5% average decrease in RVEF. A right ventricular baseline abnormality remained stable following flecainide for the tenth patient (No. 12). The average LVEF decreased nonsignificantly (p=0.14) from 65.0% to 59.8% following 2.0 mg/kg of flecainide. Of the ten patients in the dosing group, six had normal left ventricular performance initially: four patients (Nos. 13, 16, 18, and 20) developed anterior and/or apical hypokinesis postdosing; two (Nos. 11 and 15) had no change in wall motion. Of the four patiets who had an initial left ventricular abnormality, three (Nos. 12, 17 and 19) experienced a worsening in wall motion accompanied by a decrease (average of 14.3%) in LVEF; the fourth patient (No. 14) experienced an improvement from abnormal to normal performance.

Plasma Flecainide Levels

The protocol specified blood sampling for plasma flecainide level determinations just prior to flecainide administration, at 14 minutes following completion of the flecainide infusion (just before the second isotope pass), and 30 minutes after recording the second radionuclide angiogram. The timing of the 14-minute postdose blood sample corresponded to that of the second radionuclide angiogram (15 to 16 minutes postdose) and the vital signs (14 minutes postdose) which provided the hemodynamic data following flecainide administration. The 30-minutes postisotope blood sample was equivalent to about 45 minutes postdosing.

Ranges of Plasma Levels (ng/ml), () average

	at 15 min	at 45 min
0.7 mg/kg (n=1)	131	79 ng/ml
1.0 mg/kg (n=3)	89-127 (107)	73-116 (93)
1.5 mg/kg (n=5)	155-286 (232)	108-234 (176)
2.0 mg/kg (n=10)	227-386 (292)	182-392 (256)

Following intravenous drug administration, plasma levels of flecainide decrease rapidly during the first hour (distribution phase) after dosage. During this dynamic phase, it is not likely that plasma levels at these early times would reflect the concentrations of flecainide at the site(s) of pharmacologic effect. Thus, no quantitative correlation of hemodynamic effects and plasma levels was conducted. However, a comparison between the radionuclide angiogram results and the plasma flecainide levels at about 15 minutes postdosing showed that no relationships were evident in the data.

Safety - Vital Signs

Table 16 presents the mean values for heart rate and diastolic and systolic blood pressures at each recording time during the study procedures; results are grouped by the dose of flecainide.

The only data compared statistically for vital signs were the recordings taken within ten minutes after the first isotope pass but just prior to flecainide administration and those at 14 minutes after the completion of the flecainide infusion.

Heart rates during the study showed slight variations from baseline within each of the flecainide dosing groups. There were no statistically significant (p greater than 0.05) changes.

Blood pressure readings for patient No. 2 (0.7 mg/kg dose) showed a decrease during flecainide administration which the investigator felt was definitely related to the rate of infusion. The patient's blood pressure fell from 142/92 mmHg at baseline to 125/70 mmHg at 14 minutes after discontinuing the flecainide infusion. Additional recordings during the final 30 minutes of the study procedure showed a return towards baseline. Additional discussion of this observation follows in the adverse experiences section.

A mild decrease occurred in the average systolic blood pressure following the administration of flecainide 1.0 mg/kg or 1.5 mg/kg (p greater than 0.05). Average diastolic pressures remained relatively unchanged throughout the study.

In contrast, patients in the 2.0 mg/kg dosing group experienced increases, on the average, in both systolic and diastolic blood pressures. The greatest increase in systolic pressure from the baseline (preisotope) reading occurred at 14 minutes following flecainide administration (135.0 to 144.9 mmHg); however, this average change was not statistically significant (p greater than 0.05). The systolic pressure returned to baseline by the end of the study procedure. As discussed earlier in the hemodynamic data section, the increase in average diastolic pressure was statistically significant (p=0.0083, Table 15) when comparing the predose value (89.3 mmHg) to the 14-minute postdosing value (98.0 mmHg). Diastolic pressures had not returned to baseline by the end of the study.

Adverse Experiences

As noted earlier, a decrease in systemic blood pressure was observed during the intravenous administration of flecainide to patient No. 2. The infusion was discontinued after total dose of 0.7 mg/kg over 5 min. There was no symptom. The investigator recorded his observation as hypotension which was moderate in severity, lasted for ten minutes after stopping the infusion, and was difinitely related to flecainide adminstration. This patient had a primary diagnosis of hypertensive cardiomyopathy; predrug ejection fractions were very low (VEF of 17%).

Conclusion:

These hemodynamic data in 20 patients showed that at doses of 1.0 and 1.5 mg/kilogram, R-818 administered intravenously has a minimal effect on normal right and normal left ventricular function during 30 min. post-dosing period. However, if a baseline abnormality is present, there is a tendency for deterioratin, particularly in the abnormal segment to occur. After the administration of 2.0 mgs/kilo approximately one half the patients including those with initially normal right or left ventricular function showed deterioration in both global and regional contraction. Thus, there is the potential for an adverse effect on both regional and left ventricular function if higher doses, that is 2.0 mgs/kilogram of R-818 is required. However, while deterioration in left and right ventricular function was detected, there was no apparent adverse effect on systemic pressure, i.e. systolic or diastolic blood pressure or heart rate.

During clinical efficacy studies with multiple oral doses of flecainide, minimum therapeutic plasma levels (associated with 90% or greater suppression of premature ventricular contractions) ranged from about 200 to 1000 ng/ml (mean, about 500 ng/ml). In this study, the highest plasma flecainide level was 386 ng/ml at 14 minutes postdose for patient No. 19 who received a 2.0 mg/kg dose. Only four patients (Nos. 14, 15, 17, and 19) had plasma flecainide levels above 300 ng/ml.

Relatively short period observation after a single I.V. dose and lower than therapeutic plasma levels observed in this study. The above acute hemodynamic effect could not be applied to chronic oral use of this drug. However, this data suggest need of precaution to detrimental hemodynamic effect of flecainide.

(c) Study R-818-023-01 (vol. 2.5, pp 250-316)

Investigator: Morrison Hodges, M.D.

Study Site: Hennepin County Medical Center
Minneapolis, MN

Study Objective:

The purpose of this study was to compare the effects of a single intravenous dose of R-818 (1.0 or 2.0 mg/kg) and drug vehicle on left ventricular function using catheter tip sensors in patients with suspected or diagnosed left ventricular disease.

Study Population:

A total of two patients with suspected mild to moderate cardiac disease and ventricular arrhythmias who were undergoing diagnostic catheterization completed the study. There were no dropouts.

Study Design:

This was a Phase I, double-blind parallel study to compare the effect of a single intravenous dose of flecainide (1.0 or 2.0 mg/kg) on left ventricular performance to that of drug vehicle, utilizing cardiac catheterization techniques.

Cardiac output was measured by the thermodilution technique. Twelve patients were to have completed this study, the difficulty in obtaining appropriate patients led to the termination of the study after only two patients had completed. Of these two patients one received flecainide (2 mg/kg) and one received drug vehicle.

Results

Patients #	001		002	
age	46		31	
Dx	angina		angina, Hx of MI	
Rx	placebo		flecainide 2.0 mg/kg	
Pressure	pre	30'	pre	30'
Rt atrium	11	12	08	08
PA	37/15	32/13	27/12	26/14
Pulm. wedge	14	13	12	13
LV	153/21	154/23	142/16	148/14
AO	153/90	154/90	142/84	148/92
LV peak DP/DT	1278	0861	ND	ND
HR	78	78	60	60
CO	6.4	5.5	5.5	4.7
SV	82	71	92	78
TSR	1250	1440	1489	1841

Hemodynmic data pertaining to the effects of flecainide on left ventricular function are difficult to analyze as only one patient received flecainide. Cardiac output and stroke volume were decreased (both by 15% at 30 minutes postdose) and total systemic and total pulmonary resistance were increased (by 24% and 32% respectively at 30 minutes postdose) during all of the measurements in the 30 minutes following drug administration in this patient. Cardiac output and stroke volume were also decreased (by 14% and 13% respectively at 30 minutes postdose) in the patient who received placebo. There were no other apparent cardiodynamic changes in the flecainide patient.

Adverse Experiences

No adverse experiences were reported for the patient who received flecainide.

The patient who received drug vehicle had an episode of angina early in the catherterization and a second episode toward the end of the drug infusion. Both episodes were promptly relieved by nitroglycerin.

Conclusion

Because only one patient received flecainide in this study, no conclusions can be drawn about the effects on intravenous flecainide on left ventricular function. No adverse experiences were reported in this patient.

(d) Study #R-818-024-01 (vol. 2.6, pp 1-249)

Investigators Morrison Hodges, M.D.

Study Site: Hennepin County Medical Center
Minneapolis, Minnesota

Study Objective

To compare the effects of oral flecainide and placebo on left ventricular function using non-invasive techniques.

Study Population

Ten healthy subjects and 20 patients with diagnosed cardiac disease.

Study Design

Double-blind, placebo-controlled two period crossover. Single oral dose flecainide (250 mg) and placebo were administered to each subject and patient at two different study times separated by at least three, but not more than 7 days. Left ventricular performance was measured using M-mode and two-dimensional echocardiography; peripheral venous effects were measured using forearm venous plethysmography. In addition, EKG rhythm strips (Lead II) and blood samples for plasma flecainide levels for the evaluation of the potential relationship of plasma flecainide levels to pharmacological effecct were obtained before and after dosing. The duration of the study on each study day was 9-1/2 hours; 90 minutes before to 8 hours after study drug administration.

Results

Ten healthy, volunteer subjects and 20 patients completed the study. The subject group consisted of seven men and three women, age ranges from 26 to 72 years.

All patients had some type of cardiovascular abnormality on the medical history. A variety of cardiac and arrhythmia diagnoses were present in this group, and the prestudy physical examination revealed evidence of cardiac disease in all participants. The drug history of this group was quite extensive; twelve patients were receiving digoxin and 12 were receiving diuretics.

M-Mode Echocardiography

Heart Rate

Subjects - Flecainide, 250 mg, po, produced increases in heart rate in this group. Significant increases in heart rate compared to placebo were produced by flecainide at one, two, four five, six, seven and eight hours after treatment (Figure 3). Significant changes from baseline (control) measurements occurred at all times following drug with the exception of the one-half hour measurement.

Patients - The increases in heart rate produced by flecainide in patients were somewhat smaller than those in subjects (Figure 4). The maximum increase in mean heart rate compared to average predose heart rate was 6.5 beats per minute at five hours postdose. Significant increases were noted at four, five, six, seven, and eight hours posttreatment when compared to placebo. Increases in mean heart rate from baseline were significant at all points except one-half hour after flecainide.

Ventricular Dimensions

Subjects - Estimates of left ventricular end systolic diameter in subjects demonstrated a significant increase by flecainide only at three hours when compared to baseline. Although the overall impression is of drug-induced increases in this parameter, none of the other differences was significant either when compared to baseline values or to placebo treatment. No significant drug-induced differences were detected in left ventricular end diastolic diameter in this group from baseline values or from the placebo treatment. Changes in left ventricular diameter with respect to time, dD/dt and d^2D/dt^2, showed little in the way of significant change in his group. These measurements tended to be variable.

Patients - Significant flecainide-induced changes in left ventricular end systolic diameter were observed at one-half, three, six and seven hours compared to placebo. A significant increase in this parameter was produced only at seven hours post-treatment when compared to baseline values. Left ventricular end diastolic diameter showed little or no drug-induced change. Little or no change in LVdD/dt and LVd^2 was produced by flecainide in this group. These measurements showed a high degree of variability in this group also.

Ventricular Function

Subjects - M-Mode indices of ventricular function all showed significant decreases following flecainide administration. Percent shortening of left ventricular diameter (% D) was significantly decreased by flecainide when compared to placebo at one-half, three and six hours following treatment in this group (Figure 5). Significant flecainide-induced decreases from baseline values were noted at one-half, one and three hours after drug. The mean rate of circumferential fiber shortening (mean V_{cf}), an index of contractility, was significantly decreased by flecainide in comparison to placebo at one-half and six hours (Figure 6).

Significant flecainide-induced changes compared to baseline were observed at one-half hour (decrease) and four hours (increase) post-treatment. Systolic ejection fraction in the subjects was also decreased following flecainide (Figure 7). These changes were significant when compared to placebo at one and six hours post-drug and when compared to baseline at one-half and three hours post-drug.

Patients - As in the subject group, M-mode estimates of ventricular function were depressed in the patient group. Percent D (Figure 8) was significantly decreased by flecainide administration compared to placebo at one-half, three and seven hours after treatment. No drug-induced decrease from baseline values reached statistical significance. Mean V_{cf} was also decreased by flecainide (Figure 9). Significant decreases compared to placebo were observed at one, three and seven hours after administration. Again, no drug-induced decreases from baseline were significant. Systolic ejection fraction showed significant decreases compared to placebo at one and seven hours following flecainide administration (Figure 10). As with the other indices of ventricular function, no significant changes from baseline were produced in ejection fraction by flecainide.

Systolic Time Intervals

Subjects - The index of total electromechanical systole (QS_2I) in this group tended to be increased by flecainide. A significant increase from baseline occurred at one hour following flecainide administration. Significant increases compared to placebo were observed at one, two, four and five hours after treatment. Left ventricular ejection time index (LVETI) was variably affected by flecainide. A significant decrease compared to placebo and to baseline was observed at three hours post-treatment; flecainide treatment produced significant increases compared to baseline at four, five, six, seven and eight hours. The pre-ejection period index (PEPI) in subjects was increased by flecainide. These increases were significantly different from placebo at only seven hours postdrug and from baseline at one, two and three hours postdrug. The PEP:LVET ratio in subjects was increased, largely reflecting the above changes in PEPI. Flecainide treatment produced a significant difference from placebo values of PEP:LVET at the three and seven hour periods only.

Patients - Flecainide administration significantly increased QS_2I values from baseline at seven hours only. Significant increases in QS_2I compared to placebo were observed at all times but the one-half and three hour periods following flecainide administration. LVETI was reduced by flecainide administration in patients. LVETI was significantly different from placebo only at the seven hour time following flecainide. Significant decreases from baseline did occur at all times of measurement. PEPI was significantly increased by flecainide in comparison to placebo at one, two, three, four, five,

and six hours after administration. When compared to baseline values, post-flecainide measurements of PEPI increased significantly at all times. PEP:LVET ratio was increased by flecainide, largely due to the increases in PEP. These increases were significant in comparison to placebo at one, three, four, five and six hours postdrug.

Plasma Flecainide Levels

Following the single 250 mg oral dose, the mean plasma concentrations of unchanged flecainide for both subjects and patients are plotted versus time on a rectilinear scale in Figure 11. Mean plasma levels for the subjects and patients are similar over the eight hour period after dosage. For the 10 subjects, the mean (± s.d.) peak flecainide level at 3 hours is 346 ± 59 ng/ml, and for the 20 patients, the mean (± s.d.) peak level at 4 hours is 374 ± 79 ng/ml. Overall, for a 250 mg oral dose, these levels and peak times are reasonable and are in good agreement with previously reported data for subjects. The relatively small differences between subjects and patients in this study are of no consequence with respect to the pharmacodynamic aspects of this study.

Plasma Level - Pharmacologic Effect Correlation Results

For both subjects and patients, the results (Table 17) from correlation analyses between plasma flecainide levels and pharmacologic effects (drug-placebo differences) show significant correlations (p less than 0.05) for heart rate (M-Mode, but not 2-D echocardiography), QS_2I, PEPI, PEP:LVET ratio, atrial and ventricular rates, PR interval, QRS duration and QTc. For subjects only (not patients), the results from correlation analyses between plasma levels and pharmacologic effects (drug-placebo differences) show significant correlation (p less than 0.05) for forearm blood flow only. For patients only (not subjects), the results from correlation analyses are significant (p less than 0.05) for systolic blood pressure only. All other correlations were not significant (p greater than 0.05).

These effects were not clinically noticeable and overall pump function was maintained. Little or no effect was observed on systolic or diastolic blood pressure and effects on the peripheral venous system observed were limited to an increase in forearm blood flow and decrease in forearm venous resistance in the subject group only. Increases in PR interval, QRS duration and QTc interval were observed in both subjects and patients. Side effects reported were mild and infrequent. Overall, the results from correlations between plasma flecainide levels and pharmacologic measurements (drug-placebo differences) were consistent with the magnitude of the differences between drug and placebo measurements.

Blood Pressure

Subjects - Systolic blood pressure did not change appreciably after flecainide administration. Small but significant increases from baseline were recorded at five and six hours postdrug. No differences were observed between flecainide and placebo. Diastolic blood pressure was not significantly different after flecainide than after placebo administration.

Patients - No differences in systolic blood pressure were observed in patients between flecainide and placebo or from baseline. Diastolic blood pressure was variably affected; it was significantly increased compared to placebo at one, three, seven and eight hours after flecainide.

Two-Dimensional (2-D) Echocardiography

End Systolic and Diastolic Volumes

Subjects - Although none of the differences was significant compared to placebo and baseline values, end systolic volume tended to increase following flecainide. A similar result was observed with measurements of end diastolic volume.

Patients - A significant increase in end systolic volume compared to baseline was noted at one hour after flecainide. At later intervals, no significant differences were apparent. End diastolic volume was not appreciably affected by flecainide.

Ventricular Function

Subjects - Ejection fraction was unchanged by flecainide. Similarly, although stroke volume and cardiac output tended toward slightly higher values after flecainide administration, none of the differences was significant.

Patients - Ejection fraction was significantly decreased compared to baseline at one hour after flecainide administration. No other changes were significantly different from placebo or baseline. No differences were observed in stroke volume or cardiac output between flecainide and placebo or from baseline values in this group.

Effects on Peripheral Venous System

Forearm blood flow and forearm venous resistance were significantly increased after flecainide in the subject group, but not in the heart disease group, suggesting a possible vasodilating action of flecainide in normal subjects.

Electrocardiographic Results

Mean heart rates were significantly increased following flecainide in both subject and patient groups compared to placebo.

Flecainide significantly increased the PR interval, QRS duration and the corrected QT intervals in both the normal subjects and the patients with heart disease when compared to placebo.

Side Effects

After the 250 mg flecainide dose, side effects included: drowsiness, lightheadedness, headache, dizziness, dry mouth and sleepiness. After placebo dosing, only drowsiness was reported in the same subject reporting this effect on flecainide. These side effects ranged from probably to definitely not drug related.

Conclusions

Single dose of 250 mg flecainide depresses myocardial contractility to a slight degree evidenced by increase of end-systolic left ventricular volume and decrease of ejection fraction increase of PEPI, but overall left ventricular pump function is maintained.

(e) Study #R-818-039-1 (vol. 2.3, pp. 252-442)

Investigator: Joseph A. Franciosa, M.D.

Study Site: Veterans Administration Medical Center
Philadelphia, Pennsylvania 19104

Study Objectives

Following a single, 200 mg oral dose to patients with varying degrees of congestive heart failure (CHF) and to healthy subjects of similar age and weight, the following were assessed: 1) the effects of flecainide on cardiac function and maximal exercise tolerance; and 2) the influence of CHF on the pharmacokinetics of absorption and elimination from plasma and on the urinary excretion of flecainide.

Study Populations

Ten male patients mean age 57.4 yr (47-65) with varying degrees of congestive heart failure based upon exercise capacity (Class III - 9, Class II - 1) and nine healthy male subjects (age and weight-matched to patients) free of cardiac disease.

Study Design

Open-label, cardiodynamic, metabolic, and safety study.

The effect of flecainide on cardiac output (resting and exercising) was determined using a CO_2 rebreathing method. In addition, the ability to exercise maximally was determined and the effect of flecainide on exercise tolerance was assessed.

Vital signs and a one-minute ECG rhythm strip were obtained at 1, 3, 6, 8, and 24 hours following flecainide. Resting cardiac output (supine and sitting) using the CO_2 rebreathing procedure was measured at 2, 4, 8, and 24 hours after flecainide (just following blood sampling). Exercising cardiac output and maximal exercise tolerance were measured at 4 and 24 hours postdose.

For metabolic evaluations, blood samples were obtained predose and periodically during the 48 hours following dosage. Complete urine collections were obtained predose and for 12 or 24-hour intervals during the 72 hours postdose.

Cardiodynamic Results

Cardiac Index

Cardiac index values (individual as well as mean ± S.D.) for both patients and subjects are presented in Table 18.

Mean Cardiac Indices ($l/min/m^2$) + S.D.

		Subjects, n=9	Patients, n=10
Supine	pre	3.33 ± 0.95	1.94 ± 0.49
	4h post	2.75 ± 0.57	1.93 ± 0.30
	8h post	3.62 ± 0.87	2.28 ± 0.63
Sitting	pre	2.76 ± 0.59	1.90 ± 0.55
	4h post	0.58 ± 0.67	1.74 ± 0.45
Maximum Excerise	pre	9.02 ± 1.06	5.14 ± 1.75
	4h post	8.22 ± 2.24	5.71 ± 2.02

Following the administration of the single, 200 mg oral dose of flecainide, cardiac index measured at supine rest was significantly increased (p less than 0.05) from baseline in patients at 8 hours after drug; no other significant changes were noted in this measurement in patients. Cardiac index at supine rest in the subjects was significantly decreased (p less than 0.01) at 4 hours postdrug only.

Stroke Volume

Predrug resting mean stroke volume (ml/beat ± S.D.) in the patient group was 52.6 + 21.3 and in the subject group was 82.6 ± 18.9. A significant (p less than 0.05) decrease from baseline in resting stroke volumes was observed at the 4-hour period in subjects only.

Heart Rate

Predrug mean heart rates (beats/min ± S.D.) were 73.9 ± 14.8 in the patient group and 75.1 ± 12.2 in the subject group at supine rest (Table 19). At maximal exercise, the predrug values were 127.6 ± 17.7 beats/min in the patient group and 172 ± 24.9 beats/min in the subject group. A significant increase in resting heart rate occurred in the patients at the 4-hour (p less than 0.01) and 8-hour (p less than 0.001) postdrug measurements. A significant increase (p less than 0.05) was observed in the subject group at the 8-hour time only.

Mean Arterial Pressure

Baseline (pre-flecainide) mean arterial pressures (mmHg ± S.D.) at supine rest were 97.2 ± 9.1 in the patient group and 92.3 ± 11.9 in the subject group. Significant decreases were observed in the patient group at 2 hours post-flecainide (p less than 0.05) and at 24 hours post-flecainide (p less than 0.05). A significant (p less than 0.01) increase was seen in the subject group at 4 hours post-flecainide only No other significant differences (p greater than 0.05) were noted in resting mean arterial pressures in either group at any other time.

Systemic Vascular Resistance

The baseline (predrug) values in patients at supine rest were 31.9 ± 13.3 units and in subjects 15.6 ± 3.7 units. Significant differences (p less than 0.05) were noted in the patient group at the 8 and 24-hour periods when values had decreased from baseline. A significant (p less than 0.001) increase from baseline was observed in subjects at 4 hours after drug administration only.

Exercise Results

Duration of Exercise and Maximum Workload

The durations of exercise for the patients/subjects and the maximum workloads attained are presented in Table 20 for each exercise period. The mean predrug value for duration of exercise in the patient group was 8:04 ± 3:11 (min:sec ± S.D.) and the mean maximum work load attained was 345 kpm/min ± 123 (S.D.). Corresponding values for the subject group were (duration) 16:36 ± 2:42 min:sec, [illegible] (workload) 683 ± 109 kpm/min. Significant decreases from baseline in the duration of exercise (p less than 0.05) were observed in both groups only at the 4 hour post-flecainide period. No changes in maximum workload attained were noted in either group.

Total Body Carbon Dioxide Production

Individual and mean values for total body CO_2 production (ml/kg/min) for both groups during exercise are presented in Table 20. Mean resting values (ml/kg/min ± S.D.) were 15.0 ± 3.9 for the patients and 27.5 ± 3.8 for the subjects. No significant differences from baseline (p greater than 0.05) were observed in mean values at [illegible] after flecainide administration.

Total Body Oxygen Consumption

Values (individual and mean) for total body oxygen consumption (ml/kg/min) for both patients and subjects are presented in Table 20. Resting mean values (ml/kg/min ± S.D.) were 12.8 ± 2.6 for the patient group and 26.4 ± 4.4 for the subjects. No statistically significant (p greater than 0.05) differences from predrug mean values were observed at any time in either group (Figure 10).

Respiratory Quotient

Table 20 presents individual and mean values for the respiratory quotients in both patients and subjects at the various exercise periods. Respiratory quotient for the patient group Pre-flecainide (mean ± S.D.) was 1.18 ± 0.26; for the subject group this value was 1.05 ± 0.14. No significant changes (p less than 0.05) from baseline were produced in respiratory quotients at any time after drug administration in either group.

Safety Results

Vital Signs and ECG Rhythm Strips

Results from the measurement of vital signs and one-minute ECG rhythm strips (intervals) predose and at 1, 3, 6, 8, and [illegible] hours post-flecainide showed significant increases in heart rate occurred in the patients at 6 hours (p less than 0.01) and 8 hours (p less than 0.01) after drug and in the subjects at 6 hours (p less than 0.05) only. Respiratory rate was significantly increased at 6 hours postdrug (p less than 0.05) in the patients and at 6 and 24 hours after flecainide (p greater than 0.05) were observed in the subjects. No significant changes (p less than 0.05) were observed in systolic blood pressures; diastolic blood pressure was significantly changed (decreased) only at 1 hour post-flecainide (p less than 0.05) in the patients only.

A significant increase (p less than 0.05) in PR interval occurred in the patient group at 3 hours postdrug, QRS duration at 6 hrs postdrug, corrected QT interval at 6 and 8 hrs (p less than 0.05) after flecainide in patients. Only significant change seen in subjects were corrected QT interval at 6 hrs (p less than 0.05).

Adverse Experiences

Only one adverse experience was reported during the study. Subject No. 104 had mild epigastric burning and discomfort which lasted one hour. Although this episode occurred 24 hours after flecainide administration, it was considered to be possibly drug-related.

Poststudy Results

No clinically significant changes were noted by the investigator in poststudy physical examinations, ophthalmologic examinations, or 12-lead ECG. Poststudy hematologic results showed no changes with the exception of one subject (No. 102) who had an increase in eosinophils (3% prestudy to 8% poststudy) which was classified by the investigator as possibly due to flecainide administration. No changes in blood chemistry values were observed, except for Subject No. 104 who had an increase in lactic acid dehydrogenase from 235 units prestudy to 305 units poststudy; the investigator classified this as possibly due to flecainide administration. No changes due to flecainide were detected in the poststudy urinalysis values.

Metabolism Results

The rate of flecainide absorption was assessed by comparison of times to peak drug level and peak plasma concentrations of flecainide and AUC for the two study groups (Table 21).

Mean Values (± S.D.)

	Patients	Subjects
Time to peak level	5.0 ± 1.9 h	4.9 ± 2.1 h
Mean peak drug levels	210 ± 52 ng/ml	216 ± 45 ng/ml
AUC	6653 ± 2692	5077 ± 1428
Adjusted AUC	86.6 ± 26.0	93.6 ± 30.5

Plasma half-life eliminiation rate constant for flecainide plasma clearance of flecainide and volume of distribution are shown in Table 22. The mean and S.D. are shown below:

	Patients	Subjects
Plasma half-life (hrs)	19.4 ± 5.2	13.8 ± 2.9 p less than 0.05
Elimination rate constant	0.0379 ± 0.0095	0.0523 ± 0.0108/h
Plasma clearance (ml/min/kg)	8.1 ± 3.5	10.2 ± 3.8
Volume of distribution (l/kg)	12.4 ± 3.2	11.7 ± 3.6

Except plasma half-life there was no significant difference between two groups (p greater than 0.05).

Volume and pH of 24-Hour Urine Collections

The mean cumulative percent of the dose excreted as unchanged flecainide in urine by 72 hours was 24.1% for the CHF patients and 24.7% for the subjects. Mean renal clearance of flecainide was lower in the CHF patients as compared to subjects (overall mean, 132 versus 176 ml/min), but the difference was not statistically significant (p greater than 0.05).

Conclusions

No detrimental effects on cardiac function or exercise performance were noted following a single, 200 mg oral dose of flecainide in either patients with congestive heart failure or in age and weight-matched subjects free of cardiac disease. No major effects on mean arterial blood pressure or systemic vascular resistance, resting or exercising, were produced in either group. Small, but statistically significant, effects on ECG intervals were produced by the drug.

Congestive heart failure did not appear to alter either the rate or extent of flecainide absorption. However, the rate of flecainide elimination from plasma was somewhat slower in CHF patients than in subjects. No relationship existed between cardiac index (baseline resting) and either plasma half-life or plasma clearance. The extent of urinary excretion of unchanged flecainide was equivalent in CHF patients and aged-matched subjects. Although mean renal drug clearance was lower in patients than subjects, the difference was not statistically significant; renal clearance accounted for the same proportion of total body (plasma) clearance in both groups.

(f) Study #R-818-054-01 (vol. 2.7, pp. 1-167)

Investigator: Bramah N. Singh, M.D., D. Phil

Study Site: Wadsworth VA Medical Center
Los Angeles, California

Study Objective

To quantitatively evaluate the effects of intravenous flecainide on left ventricular function using cardiac catheterization techniques.

Study Population

Eighteen patients with a history of ventricular arrhythmias who were undergoing routine cardiac catheterization for suspected or diagnosed cardiac disease.

Study Design

The study was conducted in a double-blind fashion utilizing three treatment groups. Six patients received 2.0 mg/kg of flecainide, six patients received 1.0 mg/kg of flecainide and six patients received only drug vehicle. At the conclusion of the routine diagnostic catheterization for each patient, the arterial catheter was left in place. After obtaining the baseline measurements, study drug was administered intravenously over five minutes. Heart rate, cardiac output (by thermodilution), pulmonary artery, pulmonary wedge, central aortic and left ventricular pressures were measured

frequently over 30 minutes. Following the 30 minute measurements, patients were transferred to a special study room where cardiac output, pulmonary artery and plumonary wedge pressures were repeated at 1, 2 and 3 hours postdrug administration. Electrocardiogram rhythm strips and vital signs were also measured at frequent intervals. Blood samples for the determination of plasma flecainide levels were obtained just prior to the intravenous infusion (baseline) and at frequent intervals up to eight hours following dosing.

Results

The heart rate mean difference from baseline (predose) for the 2.0 mg/kg flecainide dose group was significantly increased compared to the 1.0 mg/kg and drug vehicle groups at four and five minutes following dosing. The increases were minor (3.0 and 3.6 beats/min, respectively). Fig. 12.

The QTc interval was significantly prolonged in the 2.0 mg/kg dose groups compared to both the 1.0 mg/kg and vehicle groups at 15 minutes following drug administration; the 2.0 mg/kg dose group was also significantly different from the vehicle group at the one and three hour postdosing time intervals (Fig. 13). Changes in the PR and QRS intervals were variable; no significant differences between the three dose groups were noted.

Cuff systolic and diastolic blood pressures did not appreciably change in either of the flecainide dose groups compared to the vehicle group at 30', 1, 2 and 3 hours post dose. A mild but statistically significant decrease in systolic blood pressure occurred in the 2.0 mg/kg group at 15 minutes postdosing which returned towards baseline at the 30 minute interval (Fig. 14). After the 30 minutes, diastolic blood pressure gradually increased in the 2.0 mg/kg dose group, although, the only significant change occurred at three hour postdosing (Fig. 15).

Cardiac output, determined by thermodilution, and stroke volume were not significantly affected in either of the flecainide treatment groups compared to vehicle; however, stroke work decreased at five minutes post-treatment and was significantly reduced at the 15-minute interval (Fig. 16). Stroke work had returned to baseline within one hour (Fig. 17).

Neither the total pulmonary nor total systemic resistances were noticeably affected by flecainide. Cuff systolic and diastolic blood pressures were also not appreciably affected by flecainide suggesting the absence of vascular effects.

Seventeen of the 18 patients had predose left ventricular ejection fraction of greater than or equal to 52%. Twenty minutes after dosing, ejection fraction was repeated and decreased in all three dose groups; the largest reduction (10%) occurred in the 2.0 mg/kg group. None of the reductions in the flecainide dose groups was significant.

Changes in the left ventricular and central aortic pressures were minor and none of the changes in the flecainide groups was significantly different from vehicle (Fig. 18 & 19).

Pulmonary artery systolic and diastolic pressures and pulmonary wedge pressure increased in both the 1.0 and 2.0 mg/kg dose groups (Fig. 20 & 21). Most of the significant changes occurred at five minutes postdosing and returned to baseline by 30 minutes post-treatment.

After the highest measured level at ten minutes, plasma flecainide concentrations rapidly decreased during the first hour (distribution phase) following intravenous dosage. After distribution, the terminal plasma half-life of flecainide was estimated to range from 6.4 to 14.9 hours (mean, 10.5 hours) in 11 of the 12 patients who received flecainide. No dose-related difference in plasma half-life was apparent. Because it was unlikely that plasma and tissue levels of flecainide were in equilibrium during the early times when changes were observed in the hemodynamic parameters, no correlations between these effects and plasma drug levels were attempted.

Adverse Experience

The only reported adverse experience was a fever and rash which was diagnosed as herpes zoster and unrelated to study drug.

Conclusion

Flecainide administered intravenously in doses up to 2.0 mg/kg over five minutes produces a mild transient negative inotropic effect.

(g) Study #R-818-054-02 (vol. 2.7, pp. 168-231)

Investigators: Paul Troup, M.D.

Study Site: Milwaukee County General Hospital
Milwaukee, WI

Study Objective

The purpose of this study was to compare the effects of a single intravenous dose of flecainide (1.0 or 2.0 mg/kg) and drug vehicle on left ventricular function in patients with suspected or diagnosed left ventricular disease.

Study Population

A total of two patients with suspected mild to moderate cardiac disease and ventricular arrhythmias who were undergoing diagnostic catheterization completed the study. The study was terminated prior to enrollment of the proposed 12 patients because of difficulty in enrolling patients.

Study Design

This was a Phase I, double-blind parallel study to compare the effect of a single intravenous dose of flecainide (1.0 or 2.0 mg/kg) on left ventricular performance to that of drug vehicle, utilizing cardiac catheterizaton techniques and radionuclide angiography. Hemodynamic measurements (cardiac output as measured by the thermodilution technique), and ECG rhythm strips (Lead II), heart and respiration rate, were to be recorded prior to drug administration and at various times up to 30 minutes following drug administration in patients. Left ventricular ejection fraction was determined predrug and at 20 minutes following drug administration. The above measurements, with the exceptions of central aortic pressure, left ventricular pressure and LV peak, were also to be made at 1, 2, and 3 hours postdrug.

Results

Although 12 patients were to have completed this study, only two patients had completed. Of these two patients, patient No. 2 (71 y/m) received flecainide (1.9 mg/kg) and patient No. 3 (46 y/m) received drug vehicle.

Hemodynamic data pertaining to the effects of flecainide on left ventricular function were not analyzed statistically as only one patient received flecainide.

Neither patient had stable preinfusion pulmonary wedge pressure measurements but were continued into the study by the investigator. Many of the other intracardiac and great arteries measurements indicated disparities between predrug measurements as well as variable changes after drug or vehicle administration.

No change in ejection fraction was seen with either patient 20 minutes postinfusion.

On comparing the invasive flow measurements for both study patients, no obvious trends were observed.

Conclusion

No prominent effects on hemodynamics were produced by either flecainide or drug vehicle. Because only one patient received flecainide in this study, no conclusions can be drawn about the effects of intravenous flecainide on left ventricular function. No adverse experiences were reported for either patient.

(h) Supporting Studies (vol. 1.7, pp. 232-271)

i The hemodynamic effect of intravenous Flecainide Acetate R-818 in patients with coronary artery disease by P.W. Serruys et al at Erasmus University, Netherlands.

Ten patients with coronary artery disease but without cardiac failure were given intravenous FA (2 mg/kg). Stroke Index (SI), left ventricular systolic pressure (LVP), end diastolic pressure (EDP) and LV contractility indices (max dP/dt, VCE 40 mmHg, peak VCE, Vmax from total pressure (TP) were measured immediately before and ten minutes after FA, under resting (R) conditions and during atrial pacing (P) with heart rates up to 133 ± 4.2 beats per minute (mean ± SEM). The data are given in the following table:

	pre FA	post FA	p value
SI -R ml/m^2	49 ± 3	45 ± 3	.005
EDP -R mmHg	14 ± 1	16 ± 1	.05
LVP -R mmHg	133 ± 5	129 ± 4	NS
dP/dt-R mmHg/s	1705 ± 109	1366 ± 97	.0005
-P	1936 ± 130	1692 ± 90	.01
peak VCE sec^{-1}			
-R	42 ± 4	31 ± 3	.002
-P	56 ± 5	46 ± 4	.001
Vmax TP sec^{-1}			
-R	53 ± 4	41 ± 3	.0002
-P	66 ± 5	54 ± 4	.001

The investigators concluded that FA has a negative inotropic effect not only under resting conditions but also during pacing-induced tachycardia. The effect appears to be dose related and may result in a reduction of cardiac performance. It would seem advisable to administer this drug slowly (equal to or less than 0.2 mg/kg/min) when given by the intravenous route and to exercise greater caution in both total dose and speed of intravenous administration in patients with compromised ventricular function.

ii Hemodynamic effects of flecainide in ischemic heart disease by V. Legrand et al the University of Liege, School of Medicine, Belgium

The hemodynamic effects of flecainide acetate were studied in 10 patients with recent myocardial infarction (n=43 days) with right and left heart catheterization. The drug was injected intravenously at a dose of 2 mg/kg over 30 minutes. The mean drug plasma level achieved was 394 ng/ml (range 329 to 470 ng/ml). The heart rate did not change but a significant increases (p less than 0.001) in PR duration (+17%), QRS duration (+15%) and QT (+7%) were noted after drug administration. Negative inotropic effects were also observed and consisted in increase (p less than 0.01) to pulmonary wedge pressure (+27%), decreased (p less than 0.01) of stroke index (-10%), left ventricular stroke work index (-12%) and left ventricular ejection rate (-11%). No significant changes in mean aortic pressure, systemic and pulmonary vascular resistances were noted. The left ventriculogram performed after the drug infusion revealed a significant (p less than 0.01) increase in systolic volume (+9%) and a fall of ejection fraction (-9%) and mean Vcf (-13%). A progressive and significant decrease of dp/dt was observed during drug infusion, but 15 minutes after the end of injection dp/dt had returned to near basal values. Figure 22 & 23 shows the individual variations of measurements induced by flecainide infusion before, after infusion, after infusion. The p value indicated is the level of significance of t test for paired data. Thus flecainide acetate appears to have slight, but significant negative inotropic effects, particularly conspicuous during drug infusion. The drug should be administered with caution in patients with poorly compensated heart.

(3) Electrophysiologic Studies

(a) R-818-015-01, vol. 2.7, pp. 275-347

Investigator: Richard H. Helfant, M.D.

Study Site: University of Pennsylvania
Philadelphia, PA

Study Objective

To determine flecainide's effect on the intracardiac conduction system (HIS-bundle electrogram) and sinus node function (sinus node recovery times) when administered as a single intravenous dose (1.0 mg/kg over 5 to 10 minutes).

Study Population

Fifteen patients, eight men and seven women completed the study. Their ages ranged from 36 to 58 years with a mean age of 48.7 years. Five patients had conduction abnormalities on their prestudy ECG. All 15 patients had cardiac related problems in their medical history.

Study Design

The study was conducted open-label. Only patients who were undergoing diagnostic cardiac catheterization procedures were admitted into the study. HIS-bundle electrograms and sinus node recovery times (SNRTs) were obtained prior to and at 10, 20 and 30 minutes following intravenous flecainide dosing (1.0 mg/kg).

Results

His Electrogram

Flecainide administration had no statistically significant effect on the average change in the PA interval. The mean percent increase from baseline at 10, 20, and 30 minutes postdosing was 12%, 15%, and 10%, respectively. The maximum increase in the PA interval was greater than ten msec in four patients; the largest increase was 15 msec which occurred in 1 patient. The remaining patients demonstrated little or no change. When considering the five patients with underlying conduction abnormalities as a separate group (Table 24), flecainide had no effect on the PA interval.

A statistically significant increase was observed in the average change of the A-H interval at 20 minutes postdose. The mean difference was 6.13 msec ($p = 0.016$). The A-H interval did not change significantly at ten or 30 minutes. The mean percent increase from baseline at 10, 20 and 30 minutes postdosing was 6%, 7%, and 5%, respectively. In seven patients, the A-H intervals increased 10 msec or more; the largest increase was 20 msec which occurred in 3 patients. Flecainide had no significant effect on the A-H interval when the five patients with underlying conduction abnormalities were considered as a separate group (Table 24). The A-H interval for patient 1, with first degree heart block on the prestudy ECG, was 160 msec at baseline. The interval increased to 175 msec 20 minutes after flecainide administration before returning to 155 msec 30 minutes after dosing. Th maximum increase in the A-H interval for patient 11 who had RBBB and bifasicular block was 10 msec; little change was observed in the three other patients with underlying conduction abnormalities.

Plasma flecainide levels were obtained at approximately tne same time that the conduction intervals were measured. The correlation coefficients between plasma flecainide levels and the changes in the conduction intervals from baseline (predcse) values were calulated for all time points following drug administration (10, 20, and 30 minutes postdrug) for all 15 patients. A significant positive correlation between plasma flecainide levels and changes in A-H intervals from baseline was observed ($p = 0.036$); no significant correlation was found between changes in the PA intervals ($p = 0.97$) or H-V intervals ($p = 0.64$) and plasma flecainide levels.

Sinus Node Recovery Time

Sinus node recovery times (SNRTS) were obtained after atrial pacing at various rates for approximately 30 seconds. The number of pacing rates and the actual paced rate varied for most patients because of underlying conduction abnormalities, intolerance to the pacing procedure or development of heart block during the actual pacing. The protocol required pacing the right atrium at 90 110, 130, and 150 beats per minute to determine the SNRT. The pacing rates that were actually employed varied from patient to patient and generally only one or two lower frequency rates were utilized in the pacing procedure. SNRTs were not obtained in 2 patients because intranodal heart block developed or became progressively worse during atrial pacing.

The corrected sinus node recovery time (CSNRT) at each time period was compared to the baseline CSNRT using the SNRT corresponding to the first atrial pacing rate. (The CSNRT associated with the first atrial pacing rate at each time period was used for comparison rather than using the maximum CSNRTs because pacing rates varied within the between patients.) No statistically significant change was noted ($p = 0.46$, 0.78, and 0.19 at 10, 20, and 30 minutes, respectively) using the Wilcoxon signed-rank test.

Safety - Side Effects

The only side effects reported occurred in one patient. The patient complained of a brief episode of chest discomfort and mild difficulty in hearing. The investigator assessed that these were related to the atrial pacing procedure. There was no clinically significant changes on ECG, laboratory data or vital signs other than a minor decrease in BP in 3 patients.

Conclusion

Fifteen patients participated in this open-label, Phase I, electrophysiologic study designed to assess flecainide's effect on the intracardiac conduction system. Five of the 15 patients had underlying conduction abnormalities on their prestudy electrocardiogram (ECG).

The mean percent change for all three conduction intervals (PA, A-H and H-V) slightly increased (6%, 7%, and 5% respectively); flecainide administration only had a statistically significant effect on the A-H ($p = 0.016$) and H-V ($p = 0.016$) intervals at 20 minutes postdosing. Similar electrophysiologic studies have also demonstrated that flecainide affects the conduction intervals, particularly the H-V interval. Flecainide had no significant effect on the PA interval at any of the postdosing times (10, 20, or 30 minutes). A significant positive correlation between plasma flecainide levels and changes in A-H intervals from baseline was found; no significant correlation was found for the changes in PA or H-V intervals.

Although the data are sparse, flecainide administration appeared to have no effect on the corrected sinus node recovery times (CSNRT). These results suggest that flecainide does not affect sinus node function at a dose of 1 mg/kg within 30 minutes. Plasma flecainide levels did not significantly correlate with the change in the CSNRTs.

No clinically significant side effects relating to flecainide administration were reported. Vital signs, ECG and laboratory parameters did not appear to be significantly affected by a single I.V. dosing of 1 mg/kg flecainide.

(b) Electrophysiologic Effects of Flecainide in Man
by L. Seipel et al [Z. Kardiol 70:524-529, 1981]

The electrophysiological effects of flecainide (R-818) was tested in 27 patients with and without disturbances of sinus node function and intraventricular conduction. Flecainide was given intravenously in a dose of 1 mg/kg and 2 mg/kg. Constant "therapeutic" plasma levels were reached by application of 1 mg/kg as a bolus and an additional infusion of 1 mg/kg during the test period of 20 min.

The drug had no significant effects on sinus node function even in patients with sinus node dysfunction tested so far. Intracardiac conduction time was prolonged within all compartments of the heart in a dose-dependent manner. After bolus injection of 1 mg/kg, the HRA-A interval legthened by 10.4%, the A-H interval by 13.5%, the H-V time by 15.7% and the V-RVA interval by 29.1% of the control value. In addition, the QRS complex widened by 8.1%. After 2 mg/kg flecainide the HRA-A interval was prolonged by 9.0%,, the 24.2%. In contrast, there was only a small and often significant increase in the refractoriness of the different compartments of the heart (5-15% increase of the control value). In two patients with bundle branch block, a higher degree A-V block distal the H potential occurred after 2 mg/kg flecainide.

These electrophysiological effects may explain some antiarrhythmic actions of flecainide and possible side effects of the drug can be assessed. In patients with intraventricular conduction defects the drug should be used with caution especially when given iv in higher doses.

Data of patients with normal conduction time is shown in Table 25.

Effects of flecainide in intraventricular conduction time on patients with bundle branch block is shown below.

	H-V ms	QRS ms
Control n=5	61.7 + 14.0	134.5 + 20.1
1 mg/kg	71.3 ∓ 18.0	155.3 ∓ 25.8
Difference	+ 15.6%	+ 15.5%
Control n=4	71.0 + 38.7	148.5 + 25.6
2 mg/kg	98.0 ∓ 47.0*	171.3 ∓ 32.8*
Difference	+ 38.0%	+ 15.4%

* 2 patients with spontaneous block distal H after flecainide.

(c) Acute electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness in man by K.J. Hellejstrand, R.S. Bexton, A.W. Nathan, and R.A.J. Spurrell, A.J. Camm from the Department of Cardiology, ST. Bartholomew's Hospital, London [Brit. Heart J. 48:140-8, 1982]

The electrophysiological effects of flecainide acetate (2 mg/kg as an intravenous infusion over five minutes) were assessed in 47 patients undergoing electrophysiological study. Seven patients had normal electrophysiology, 16 had a direct accessory atrioventricular pathway, 12 had dual atrioventricular nodal (AH) pathways, five had paroxysmal ventricular tachycardia, six had conduction system disease, and one patient had a left atrial tachycardia.

No significant change occurred in sinus cycle length. The PA interval, AH interval, and HV interval were all significantly prolonged. The QRS complex duration increased significantly. The QT interval showed slight prolongation due entirely to the increase in QRS duration.

Refractoriness of the atrial and ventricular myocardium was slightly prolonged, but was sigificant only at ventricular level. No significant change occurred in refractoriness of the normal AV node. Pronounced prolongation of retrograde "fast" AH pathway refractoriness was observed in those patients with dual AH pathways. Anterograde and retrograde accessory pathway refractoriness were both greatly increased. See Table 26.

These electrophysiological properties strongly suggest that flecainide will be useful in the managment of a wide variety of cardiac arrhythmias. It should be administered, however, with caution to patients with pre-existing conduction system disease. Because repolarization is not delayed flecainide is unlikely to induce ventricular arrhythmias related to prolongation of the QT interval.

(4) Short-Term, Dose-Ranging Studies

(a) R-818-030-01, vol. 2.21, pp 27-158

Investigator — Jeffrey L. Anderson, M.D.

Study Site — University of Michigan Hospitals
Ann Arbor, Michigan

Study Objective

The purpose of this trial was to determine the range of effective multiple oral dosage regimens for flecainide in suppressing premature ventricular contractions (PVCs) (part 1) and to determine safety and continued effectiveness of the dosage regimen determined effective for each patient in part 1 for a two-week period (part 2). Blood samples for plasma flecainide level determination were obtained to determine the pharmacokinetics of flecainide elimination from plasma, to correlate plasma levels with drug effectiveness and, thus, to establish a range of minimum therapeutic plasma levels.

Study Population

Fourteen patients with chronic ventricular arrhythmias enrolled in this trial. Twelve of 14 patients had previously received at least one antiarrhythmic drug prior to entering the study; eight of 14 had previously reported ventricular tachycardia. Of the 14 patients enrolled, two did not meet the inclusion/exclusion criteria requiring more than 600 PVCs per 12 waking hours; two patients discontinued in part 1 because of side effects; and one patient who completed Part 1 had inadequate (less than 80%) suppression of PVCs and therefore could not enter Part 2. Nine of 14 patients completed the entire study.

Study Design

This was a two-part study in patients with chronic ventricular arrhythmias. Part 1 was conducted on an inpatient basis; Part 2, on an outpatient basis. In Part 1 (single-blind), patients were given flecainide in increasing oral doses (from 100 mg bid to a maximum of 300 mg bid) until greater than 80% suppression of their placebo control PVC frequency was obtained, unless precluded by the occurrence of limiting side effects. In Part 2 (open-label), patients were continued for an additional two weeks to determine multiple dose safety and efficacy on the previously determined effective and safe dose. Non-responders (patients having less than 80% suppression of PVCs) at the highest dose used in Part 1 did not continue into Part 2.

Two days of placebo dosing followed by three days of flecainde dosing at each dose until the effective dose was reached followed by three days of placebo, followed by two weeks at the effective dosage regimen of flecainide.

Decisions by the investigator to increase the flecainide dosage or to proceed to Part 2 were made on the basis of data (suppression of PVCs greater than 80% in comparison with placebo) obtained using a Trendscriber (American Optical Company) to sample cardiac activity periodically for 12 waking hours (9 am - 9 pm). Twenty-four-hour Holter recordings, however, provided the basis for definitive analysis of arrhythmia suppression.

Blood samples for plasma flecainide level determination were obtained just prior to and at three hours after the morning dose on the third day of each dosage regimen, and periodically during the placebo washout period following the last dose on the final dose-ranging day (Part 1); predose samples were also obtained on days 7A and 14A (Part 2).

Results

PVCs

Two of 14 patients did not meet PVC frequency qualifications (greater than 600 PVCs per 12 waking hours) during the control period of placebo administration and were not allowed to participate in the study. Of the 12 patients participating in Part 1 (dose-ranging), two patients discontinued due to adverse experiences. However, both completed day 5 Holter analysis, and data were included.

Table 27 shows the percent suppression of baseline PVCs and the average hourly PVC count recorded on each Holter day for the 12 of 14 patients who qualified. The results under a dose heading (eg, 100 mg bid) refer to the 24-hour Holter recording on the third day of that dose. Two patients (Nos. 8 and 14) actually had an increase in PVCs while receiving 100 mg of flecainide.

Figure 24 displays the Table 27 information for ten of 12 patients in graphical form; patients 4 and 14, who did not complete dose-ranging, are not included in this figure. For each patient, the changes in average PVCs/hr over the course of the study can be observed. This graph illustrates the PVC levels at baseline, third day of highest dose during dose-ranging, placebo washout day 3, and outpatient days 7A and 14A. There is a range of baseline levels from 76.0 PVCs/hr to 2541.2 PVCs/hr. Nine of ten patients showed greater than 80% suppression of baseline PVCs on the third day of highest dose; patient 11 had a suppression of 68.0% (median of all ten patients = 99.6%, average =94.9%). The data from placebo washout day 3 indicates that, in all cases, PVCs increased from the drug suppressed levels achieved on the third day of highest flecainide dose.

Patient 11 did not continue into the outpatient portion (part 2) of the study due to inadequate PVC suppression. The PVC history for patient 11 (Figure 25) which relates dose time with PVC suppression indicates a rapid and nearly complete suppression, followed by a rapid return of PVCs to baseline level before the next dose. This data suggests the possibility that more frequent dosing (eg, tid), might have maintained suppression of PVCs in this patient.

Table 28 gives the highest dose administered in Part 1 and the corresponding percent suppression for each patient. The percent suppression from each of the two outpatient Holters is also listed.

Figure 26 shows the dose-response relationship from the dose-ranging part of this study by displaying percent suppression of baseline PVCs versus total daily dosage plotted on a log scale for each patient. Effective flecainide dosage regimens ranged from 100 mg to 250 mg bid; PVC suppression for the nine ranged from 90.2% to 100% (average 94.9%). Two of the nine responding patients achieved greater than 80% suppression at a dose of 100 mg bid, five at 200 mg bid, and two patients at 250 mg bid. The tenth patient who completed dose-ranging experienced a 68% suppression of PVC frequency at a maximum dose of 300 mg bid, and, therefore, did not qualify (greater than 80% suppression required) for the two-week outpatient portion (Part 2) of the study.

Nine of ten patients who completed Part 1 continued into the outpatient portion (Part 2) at their effective doses determined during dose ranging. All nine maintained a greater than 80% suppression of PVCs (range, 80.9% to 100%; average 96.1%) on day 7A. By day 14A, eight of nine patients had maintained greater than 80% suppression with an average of 98.4% (range, 92.9% to 100%). The ninth patient dropped to 69.9% suppression; the average percent suppression of all nine was 95.3%.

Suppression of Multiple PVCs

The analysis of multiple PVCs (denoted MPVCs and defined as those PVCs which occurred in pairs, [illegible]ts, or runs of four or more) is similar to that of total PVCs. Multiple PVCs were calculated by the formula: total PVCs - isolated PVCs. Percents suppression from baseline are given in Table 29. There is a wide range of baseline levels (from zero MPVCs/hr to 1603.6 MPVCs/hr) among the 12 patients. Nine of ten patients who completed dose-ranging, Part 1, exhibited baseline MPVCs and all showed greater than 80% suppression on the third day of highest dose (median = 100.0%, average = 98.5%). On outpatient day 7A, all eight of nine patients remaining in the study, who had baseline MMVCs, achieved greater than 80% suppression (median - 100.0%, average = 98.4%), and on outpatient day 14A seven patients achieved greater than 80% suppression (median = 100.0%, average = 92.8%). The patient not achieving 80% suppression on day 14A (No. 6) had only 4.6 MPVCs/hr at baseline.

Pharmacokinetic Data

During the placebo washout period following the dose-ranging portion (Part 1), the terminal phase (post-absorptive), plasma half-life of flecainide was found to range from [redacted] hours (mean, 18.8 hours) for the nine patients who completed the study. Flecainide disappearance from plasma was reasonably monoexponential for each patient.

Trough and peak plasma concentrations of unchanged flecainide during the dose ranging portion (Part 1) following multiple oral dosage are shown in Tables 30 & 31. Trough plasma concentrations of unchanged flecainide during the two-week outpatient portion (Part 2) following multiple oral dosage is shown in Table 32.

Trough plasma levels in Part 1 varied about two-fold and were roughly proportional to dose. Plasma flecainide levels at tne time of initial return of PVCs (to greater than 10% of baseline and to greater than 30 PVCs per hour) during the placebo washout period ranged from about [redacted] ng/ml (average, about 450 ng/ml). Table 33. Nearly complete suppression of PVCs was obtained at Day 5 (100 mg bid for 3 days) 2 patients, at Day 8 (200 mg bid for 3 days) 5 patients, Day 11 (250 mg bid for 3 days) in 2 patients.

Comparison of trough plasma concentration of unchanged flecainide to the percent suppression of PVCs during the two-week period (Part 2) is shown in Table 34. A higher range in trough plasma levels, from about [redacted] ng/1ml (average, about 800 ng/ml) during the two-week outpatient portion (Part 2) was associated with a very high average degree of efficacy for flecainide and was well tolerated.

Safety

Adverse experiences were evaluated on all 14 patients which include 2 patients who did not meet PVC qualifications for the study but each received by mistake a single 100 mg oral dose of flecainide.

The most common inpatient side effects were lightheadedness (19 occurrences), itchiness (18 occurrences), sleeplessness (17 occurrences) and constipation (13 occurrences).

Patients 1, 3, 5, and 14 reported the most side effects accounting for 62% of the inpatient occurrences. Two patients, numbers 4 and 14, withdrew due to side effects during dose-ranging. Patient 4 was discontinued on day 5 after experiencing partial blindness associated with a transient ischemic attack; the investigator believed that an assoaciation between this incidence and flecainide was unlikely. Patient 14 experienced numerous side effects, as well as an increase in PVCs, while receiving 100 mg bid flecainide.

On the average, there was a 16.4% increase in the PR interval, a 16.9% increase in the QRS duration and 5.1% increase in the QT interval (uncorrected). No apparent effects of flecainide on vital signs or clinical laboratory parameters were observed.

Long-term chronic studies are currently ongoing to assess the continued safety of flecainide.

Conclusions

Flecainide was highly effective in suppressing ventricular arrhythmias with twice daily dosing without limiting side effects. Most patients responded at a daily dose of 400 mg given in divided doses every 12 hours.

The plasma half-life of flecainide was found to be relatively long (mean, 18.8 hours) in patients with ventricular arrhythmias following multiple oral dosage. Minimum therapeutic plasma levels of flecainide for PVC suppression ranged from about [redacted] ng/ml (average about 450 ng/ml); these levels and trough plasma levels up to about 1600 ng/ml were well tolerated.

(b) R-818-030-02, vol. 2.22, pp 1-123

Investigator: Morrison Hodges, M.d.

Study Site: Hennepin County Medical Center
Minneapolis, Minnesota

Study Objective

Same as Study R-818-030-01 above.

Study Population

Fifteen patients with ventricular arrhythmias enrolled in the trial. Three patients did not receive flecainide because they did not comply with all inclusion/exclusion criteria. Eleven of the 12 patients who received flecainide achieved suppression of at least 80% of their baseline PVCs during part 1; the 12th patient (No. 1) discontinued after one dose of flecainide 100 mg because of an increase in frequency of PVCs. Of the 11 patients achieving 80% or greater suppression, one patient (No. 14) was discontinued after receiving flecainide 300 mg bid because the Trendscriber data indicated less than 80% suppression; this was later contradicted when the corresponding Holter recording was analyzed.

Study Design

Same as Study R-818-030-01 above. See Figure 27.

Results

Suppression of PVCs

All 11 patients who were evaluated in Part 1 had an excellent response with a mean and median PVC suppression of 96.3% and 100.0%, respectively (range, 82.2% to 100.0%) and mean and median multiple PVC suppression of 87.2% and 100.0%, respectively (range, -32.5% to 100.0%) at their effective dose (median effective dose was 200 mg bid).

The PVC histories for the ten patients who completed the dose ranging portion of this study and patient 14 are presented in Figures 2 through 12 in vol. 1.22, pp. 60-70. Classical responses seem a few patients are attached in this review Fig. 28, 29, and 30. The Holter data for patient 14 have been displayed in Table 35.

Table 35 shows the percent suppression of baseline PVCs and the average hourly PVC count recorded on each Holter day. The results under a dose heading refer to the 24-hour Holter recording on the third day of that dose. Patients 1, 3, 6, 11, and 13 are not included in the table for a variety of reasons. Patient 1's Holters are not available due to mechanical difficulty with the equipment. This patient was withdrawn after receiving 100 mg bid of flecainide due to a pronounced increase in PVCs as recorded by the Trendscriber. The investigator could not establish if the increase was due to flecainide. Patient 3 withdrew for personal reasons before flecainide was administered. No patient number 6 was entered into the study. Patients 11 and 13 did not have sufficient baseline PVCs to qualify for the investigation.

Figure 31 displays the information from Table 35 in graphical form. For each patient, the changes in average PVCs/hr over the course of the study can be observed. This graph illustrates the PVC levels at baseline, third day of highest dose during dose-ranging, placebo wahsout day 3, and outpatient days 7A and 14A. There is a range of baseline levels from 92.4 PVCs/hr to 2869.0 PVCs/hr among the 11 patients. All completed patients showed greater than 80% suppression of baseline PVCs at the third day of highest dose (range = [redacted] suppression from baseline, average = 96.3%, median = [redacted]. The data from placebo washout day 3 indicates that in all cases, with the exception of patient 14 who did not complete placebo washout day 3, PVCs increased from thejr drug suppressed levels on the third day of their highest flecainide dose.

On outpatient day 7A, eight of ten patients achieved greater than 80% suppression, while patients 12 and 15 had suppression calculated at [redacted] respectively (average of all ten = 94.1%, median = 99.6%). On outpatient day 14A, seven of nine patients for whom data were available achieved greater than 80% suppression, while patients 12 and 15 had suppression of [redacted], respectively (average of all nine = 93.2%, median = 100.0%). The Holter for patient 7 was technically unsatisfactory and not analyzable.

Table 36 gives the highest dose administered in part 1 and the corresponding percent suppression for each patient. The percent suppression from each of the two outpatient Holters is also listed. The median dose and the median and average percent suppression of PVCs from baseline have also been calculated. Two hundred mg bid (400 mg total daily dose) was efficacious in the majority of patients (seven of 11).

Suppression of Multiple PVCs

The analysis of multiple PVCs is similar to that of total PVCs. Percent suppressions from baseline are given in Table 37. There is a wide range of baseline levels (from 1.0 to 771.7 MPVCs/hr) among the 11 patients. All but one patient (patient number 14 who had a baseline of only 1.3 MPVCs/hr) showed greater than [redacted] suppression of baseline MPVCs at the third day of highest dose (average = 87.2%, median = [redacted]. On outpatient day 7A, nine out of ten patients achieved greater than 80% suppression of their MPVCs while patient 15 had a suppression of 46.3% (average = 92.5%, median = [redacted]. On outpatient day 14A, eight patients achieved greater than 80% suppression, while patient 12 had 79.3% suppression (average = 96.0%, median = [redacted]. The Holter for patient 7 was technically unsatisfactory and not analyzable.

Safety - Side Effects

The most common inpatient side effects during part 1 were lightheadedness (nine occurrences), itchiness (seven occurrences), fatique (seven occurrences), constipation (five occurrences), and shortness of breath (five occurrences).

In the entire study and in decreasing order of frequency, the most frequent side effect occurrences were lightheadedness (15), fatigue (11), dizziness (10), itchiness (8) and nervousness (8).

During the outpatient portion of the study, patient 9 had a convulsive seizure while under therapy with flecainide 300 mg bid. Given this patient's history of alcoholism, drug use, and the findings from an electroencephalogram, the investigator was relatively certain flecainide was not the cause.

Safety - Electrocardiographic Data

Patients had electrocardiograms recorded during the prestudy visit and on day 14A. On the average, there was a 24.9% increase in the PR interval, a 17.6% increase in the QRS duration and a 10.1% increase in the QT interval. Four patients (Nos. 4, 7, 14, and 15) had increases in the PR interval consistent with first degree AV block (PR greater than 0.20); a fifth patient (No. 2) who started the study with first degree AV block (PR = 0.206) experienced a 26.2% increase during the poststudy EKG. Eight patients (Nos. 1, 2, 8, 9, 10, 14, 15, and 16) had increases in the QRS duration consistent with incomplete bundle branch block (QRS 0.10-less than 0.12) and two patients (Nos. 2 and 8) had increases in the QT interval outside the normal range.

Safety - Vital Signs

Blood pressure, pulse and respiration were measured on each of the inpatient days of the study at 9 am, 3 pm and 9 pm and at 9 am and 11 am on outpatient days 7A and 14A. No apparent effects of flecainide on vital signs were observed.

Safety - M-Mode Echocardiography

M-mode echocardiography was recorded during one of the two placebo control days (days 1 or 2) and during the two-week outpatient visit when the patient was receiving flecainide. There were no changes in either the ejection fraction or velocity of the contraction (Vcf) which would clearly indicate an effect on left ventricular function.

Safety - Clinical Laboratory Test Results

There were some fluctuation of laboratory data but no significant abnormal clinical laboratory parameters were observed.

Pharmacokinetic Data

Following multiple oral flecainide dosage in the dose-ranging portion of the study (part 1), plasma concentrations of unchanged flecainide acetate determined during the three-day, placebo washout period were measured.

The plasma half-life values range from [redacted] hours (mean, 19.7 hours). No difference in plasma half-life between sexes was found. These half-life data for patients with ventricular arrhythmias following multiple oral dosage are longer, on an average, than those previously reported for 16 healthy, adult male subjects (range, [redacted] to [redacted] hours; mean, 14.2 hours) following single oral doses (60 to 240 mg) in study R-818-005-01 and for 16 different healthy, adult male subjects (range, [redacted] hours; mean, 11.5 hours) following single oral doses (200 mg) in study R-818-026-01. For patients with PVCs, the range and mean plasma half-life data from this study are in very good agreement with similar data from studies R-818-030-01 & 03.

For the ten patients who completed the dose-ranging portion of the study (part 1), trough plasma flecainide levels on days 5, 8, and 11 with multiple dosage regimens of 100, 200, and 300 mg bid, respectively, and trough plasma levels on placebo washout day 1 (part 1) are shown in Table 38. After two days of dosage with each dosage regimen, trough plasma levels ranged from [redacted] ng/ml (mean, 233 ng/ml) for ten patients at the 100 mg bid dosage regimen, from [redacted] ng/ml (mean, 606 ng/ml) for nine patients at the 200 mg bid dosage regimen and were [redacted] ng/ml (mean, 540 ng/ml) for two patients at the 300 mg bid dosage regimen. For the 100 and 200 mg bid dosage regimens, trough levels were roughly proportional to dose level in the nine patients with available data. The trough levels on placebo washout day 1 (one day following the last day of dose-ranging for each patient. This trend of continued increase in trough plasma levels on placebo washout day suggests that plasma levels of flecainide were continuing to increase with multiple dosage following the last day of dose-ranging; this is consistent with the relatively long plasma half-life of flecainide found in these patients.

For the two-week outpatient portion of the study (part 2), trough plasma flecainide levels on days 7A and 14A during multiple oral dosage with multiple dosage regimens of 100 to 300 mg bid, these trough plasma levels ranged from [redacted] ng/ml (mean, 830 ng/ml) on day 7A and from [redacted] ng/ml (mean, 893 ng/ml) on day 14A for the ten patients. Trough plasma levels during the two weeks of multiple dosage were reasonably constant between days 7A and 14A for each patient. However, trough levels on outpatient days (days 7A and 14A) tended to be higher in most patients than those at the end of the dose-ranging portion (part 1) of the study. This is consistent with the relatively long plasma half-life found in these ten patients, and indicates that steady-state plasma levels of flecainide had not been completely attained on the last day of dose-ranging (days 5, 8, or 11).

Plasma Flecainide Level - Effect Relationships

The plasma levels of flecainide at the time of initial reappearance of PVCs (defined as return to greater than 10% of baseline activity and to greater than 30 PVCs per hour) were estimated during the placebo washout period following the 9 pm dose of flecainide on the final dose-ranging day (part 1); these plasma levels are shown in Table 39 along with the times after the last dose for each patient. These criteria for degree of return of PVCs were chosen arbitrarily. Following multiple oral dosage (100 to 300 mg bid), the estimated plasma levels of flecainide at the time of greater than 10% return of PVCs ranged from 184 to 814 ng/ml (mean, 461 ng/ml) for the nine patients with available data; the time to 10% return of PVCs ranged from 10 to greater than 35 hours with a median of 23 hours. These results support the dosing interval of 12 hours.

For the highest dosage regimen required by each patient during the dose-ranging portion (part 1) of the study (100 to 300 mg bid), for the ten patients, trough plasma levels ranged from [redacted] ng/ml (mean, 615 ng/ml) when the 24-hour average suppression of PVCs ranged from [redacted] (mean, 97.7%). A comparison of trough plasma levels to the percent suppression of PVCs on outpatient days 7A and 14A (part 2) is shown in Table 40. The mean suppression of PVCs was found to be 94.1% on day 7A for the ten patients and 93.2% on day 14A for nine patients with available data. On these days, trough plasma levels of flecainide ranged from about [redacted] ng/ml; mean trough levels were 830 and 893 ng/ml on days 7A and 14A, respectively. Overall, these results are in good agreement with similar data from study R-818-030-01 for other patients with PVCs.

The most commonly occurring side effects in decreasing order of frequency were lightheadedness, fatigue, dizziness, itchiness and nervousness.

Electrocardiographic intervals were increased on the average as follows: PR interval, 24.9%, QRS duration, 17.6%, and QT interval, 10.1%. Flecainide administration over the course of the study had little or no effect on vital signs and clinical laboratory parameters. Long-term safety is being assessed on an ongoing basis in study R-818-031-02.

Conclusions

Average PVC suppression for 11 patients at their effective dose during the dose-ranging part of the study was 96.3% (range, [redacted]). In the ten patients who continued, flecainide maintained this excellent suppression during the outpatient part of the study averaging 94.1% on day 7A and 93.2% on day 14A (range, [redacted]). Patients' multiple PVCs were suppressed on the average 87.2% during the dose-ranging portion, and [redacted] and 96.0% on days 7A and 14A, respectively, during the outpatient portion of the study. At the low dose, 100 mg, three of 12 patients treated had increases in PVC frequency (one was very slight). Ten patients who completed the trial have continued into the long term chronic study R-818-031-02.

The plasma half-life of flecainide was found to be relatively long (mean, 19.7 hours) in patients with ventricular arrhythmias following multiple oral dosage. Minimum therapeutic plasma levels of flecainide for PVC suppression ranged from about [redacted] ng/ml (average, about 450 ng/ml); these levels and trough plasma levels up to about 1400 ng/ml were well tolerated.

(e) R-818-030-03, vol. 2.22 pp. 142-242

Investigator: Raymond L. Woosley, Ph.D., M.D.

Study Site: Vanderbilt University Hospital
Nashville, Tennessee

Study Objective and Study Design

Same as study R-818-030-01.

Study Population

Eleven patients with chronic ventricular arrhythmias participated. Ten of 11 patients had received at least three different antiarrhythmics without success prior to entering the study, and five of 11 had previously reported ventricular tachycardia.

Results

PVCs

Table 41 shows the percent suppression from baseline and the number of PVCs recorded throughout the study. For each Holter day (except placebo washout day 1), the results of the Holter monitoring, both average PVCs/hr and percent suppression from baseline, are shown. (Placebo washout day 1 is complicated by the fact that patients were given drug in the morning and placebo at night.) The results under a dose heading (eg, 100 mg bid) refer to the 24-hour Holter recording on the third day of that dose. Five of 11 patients actually had an increase in PVCs (negative suppression) while receiving 100 mg of flecainide. One possible explanation for this observation may be that 100 mg of flecainide is not effective in all patients and random variation in PVCs accounted for the increase. Another explanation may be that plasma levels of flecainide following 100 mg dosage regimen might be too low and potentially arrhythmogenic.

Figure 32 displays the information in Table 41 in graphical form. For each patient, the changes in average PVC/hr over the course of the study can be observed. This graph illustrates the PVC levels at baseline, third day of highest dose during dose-ranging, placebo washout day 3, and outpatient days 7A and 14A. There is a range of baseline levels from 69 PVCs/hr to 2066 PVCs/hr among the 11 patients. All patients showed greater than 80% suppression of baseline PVCs at the third day of highest dose (average = 96.9% suppression from baseline, median = [redacted]). The data from placebo washout day 3 indicates that in all cases PVCs increased from their drug suppression levels on the third day of highest flecainide dose.

On outpatient day 7A, nine of 11 patients achieved greater than 80% suppression, two patients (2 and 11) had suppression calculated at 79.2% and 78.9% respectively (average = 92.6%, median = [redacted]. On outpatient day 14A, all 11 patients achieved greater than 80% suppression (average = 95.8%, median = [redacted].

The dose-response relationship from the dose-ranging part of this study is shown in Table 42 and Figure 33, which displays percent suppression from baseline vs log of total daily dosage for each patient.

The analysis of multiple PVCs (MPVCs) is similar to that of total PVCs. There is a wide range of baseline levels (from 0.8 greater than 80% suppression of baseline MPVCs at the third day of highest dose (average = 99.9%, median = [redacted]). On outpatient day 7A, all patients achieved greater than 80% suppression of their MPVCs (average = 99.5%, median = [redacted]). On outpatient day 14A again all patients achieved greater than 80% suppression (average = 99.2%, median = [redacted]. Table 43 gives the Holter analysis of each patient and percent suppressing multiple PVCs.

Safety - Side Effects

The most common inpatient side effects were blurred vision (13 occurrences), sleepiness (13 occurrences), hot and cold sensations (ten occurrences), nervousness (nine occurrences), constipation (seven occurrences) and shortness of breath (seven occurrences).

Patients 3 and 4 had the most inpatient side effects (39 and 21, respectively). Patient 3's most common inpatient side effects were hot and cold sensations (nine occurrences) while patient 4's most common side effect was sleepiness (nine occurrences).

A positive dose response (an increase in adverse experiences with increasing dose) is apparent if the number of occurrences of adverse experiences while on placebo is compared with the number reported while patients were receiving 100 and 200 mg of flecainide. It is difficult to assess what occurs at doses higher than 200 mg since there is a limted patient population (four patients) at the higher doses.

Side effects observed in the outpatient part were distributed among only five patients (2, 3, 4, 9 and 10): blurred vision, nervousness and dizziness.

Safety - Electrocardiographic Data

Patients had electrocardiograms recorded during the prestudy visit and on day 14A. On the average and independent of dose, there was a 22.7% increase in the PR interval, a 27.7% increase in the QRS duration and a 9.6% increase in the QT interval. Two patients (7 and 8) had increases in the PR interval consistent with first degree AV block, two patients (2 and 3 from 0.08 to 14 and 16 respectively) had substantial increase in the QRS duration consistent with intraventricular block and three patients (3, 7 and 10) had increases in the QT interval outside the normal range.

Safety - Vital Signs

Blood pressure, pulse and respiration measurement indicate that flecainide has very little or no effect on vital signs.

Pharmacokinetic Data

Following multiple oral flecainide dosage in the dose-ranging portion of the study (part 1), plasma concentrations of unchanged flecainide acetate determined during the three day placebo washout period were plotted versus time on a semilog scale in Figures 27 through 37 for each of the 11 patients. (See pages 205-215, vol. 2.22.)

After peak plasma levels were attained and when absorption was essentially complete following the 9 am dose in placebo washout day 1, flecainide disappearance from plasma was reasonably log-linear for each patient. For the terminal phase, Table 44 shows the plasma half-life of flecainide determined from the least squares line for each of the 11 patients which range from [redacted] hours (mean, 20.3 hours); no difference in plasma half-life between sexes was suggested.

Following the last dose prior to the placebo washout period, the time to peak plasma flecainide level was found to range from [redacted] hours (mean, 3.6 hours) for the 11 patients (Table 44). These data indicated that flecainide absorption from the Primojel^{R} capsule was reasonably prompt in patients following multiple oral dosage. After multiple oral dosage, the peak plasma flecainide level following the last dose (100 to 250 mg) prior to the placebo washout period was found to range from [redacted] ng/ml for the 11 patients (Table 44). These peak levels, when normalized to a 200 mg dose, ranged from [redacted] ng/ml (mean, 916 ng/ml).

In addition, the area under the plasma flecainide level versus time curve (AUC) for one dosage interval (zero to 12 hours after the last dose prior to the placebo washout period) for each patient and AUC values normalized to a 200 mg dose are shown in Table 44. After adjustment for differences in plasma elimination rate, these plasma AUC data for patients compare very well to AUC data previously reported for 16 healthy adult subjects following a single, 200 mg dose with the same capsule.

For the dose-ranging portion of the study (part 1), trough plasma flecainide levels on days 5, 8 and 11 with multiple dosage regimens of 100, 200, and 250 mg bid, respectively, are shown in Table 45; in addition, trough plasma levels on placebo washout day 1 (part 1) are shown in this table. Trough plasma levels after two days of dosage ranged from [redacted] ng/ml (mean, 212 ng/ml) for 11 patients at the 100 mg bid dosage regimen, from [redacted] ng/ml (mean, 563 ng/ml)

for ten patients at the 200 mg bid dosage regimen, and from [redacted] ng/ml (mean, 682 ng/ml) for four patients at the 250 mg bid dosage regimen. The average trough levels were roughly proportional to dose level. The trough levels on placebo washout day 1 (one day following the last day of dose-ranging) were higher than trough levels on the last day of dose-ranging on the average. Similarly, approximate peak plasma flecainide levels (at three hours following dosage) on day 5, 8, 11, and placebo washout day 1 showed trend of continued increase in both trough and peak plasma levels on placebo washout day 1 suggested that plasma levels of flecainide were continuing to increase with multiple dosage following the last day of dose-ranging; this is consistent with the relatively long plasma half-life of flecainide found in these patients.

For the two-week outpatient portion of the study (part 2), trough plasma flecainide levels on days 7A and 14A during multiple oral dosage are shown in Table 46; with multiple oral dosage regimens of 100 to 300 mg bid (none patient with 100 mg tid), trough plasma levels ranged from [redacted] ng/ml (mean, 724 ng/ml) for ten patients on day 7A and from [redacted] ng/ml (mean, 761 ng/ml) for 11 patients on day 14A. Trough plasma levels during two weeks of multiple dosage were reasonably constant between days 7A and 14A for each patient. However, trough levels on outpatient days (days 7A and 14A) tended to be higher, on an average, than those on the last day of dose-ranging, and to be similar to the levels reported on placebo washout day 1. This was consitent with the plasma half-life found in these 11 patients, and indicated that steady-satae plasma levels of flecainide had not been completely attained on the last day of dose-ranging (days 5, 8, or 11). During the two-week outpatient portion of the study (part 2), trough plasma flecainide levels, when normalized to a 200 mg bid dosage regimen, on days 7A and 14A during multiple oral dosage (Table [redacted]) ranged from [redacted] ng/ml (mean, 713 ng/ml) and from [redacted] ng/ml (mean, 725 ng/ml), respectively. These dose-normalized plasma levels were reasonably constant, on an average, for these patients.

Plasma Flecainide Level - Effect Relationships

The plasma levels of flecainide at the time of initial return of PVCs were estimated during the placebo washout period following the 9 am dose on placebo washout day 1 (Table 47). Following multiple oral dosage (100 to 250 mg bid), the estimated plasma levels of flecainide at the time of 10% return of PVCs ranged from [redacted] ng/ml (mean, 622 ng/ml) for ten patients (Table 47). The time of 10% return of PVCs ranged from seven to 25 hours with a median of 13 hours. A comparison of trough plasma levels of flecainide to the percent suppression of baseline PVC activity (based

on 24-hour Holter monitoring) is shown in Table 4C for the dose ranging part of the study; for the ten patients with available data, trough plasma levels ranged from [redacted] ng/ml (mean, 613 ng/ml) when the 24 hour average suppression of PVCs ranged from [redacted] (mean, 96.9%). For the 11 patients, the mean suppression of PVCs was found to be 92.6 and 95.8% on days 7A and 14A, respectively. The trough plasma levels of flecainide ranged from about [redacted] ng/ml; mean trough levels were 724 and 761 ng/ml on days 7A and 14A, respectively.

Safety

The most commonly occurring side effects in decreasing order of frequency were blurred vision, nervousness, sleepiness, hot and cold sensations, constipation and dizziness. Blurred vision was persistent in three patients and one of these patients required a dosage reduction.

Electrocardiographic intervals were increased as follows: PR interval - 22.7%, QRS duration, 27.7%, and QT interval, 9.6%. Flecainide administration over the course of the study had little or no effect on vital signs and clinical laboratory parameters. Long-term safety is being assessed on an ongoing basis in Study R-818-031-03.

Conclusion

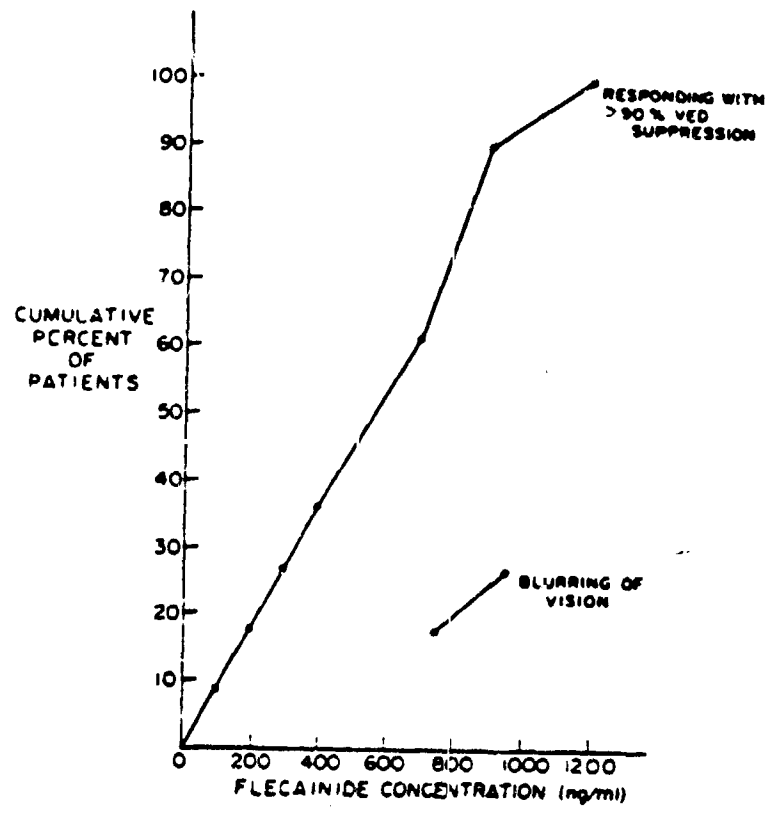
Eleven patients completed the trial and have continued onto the long term chronic study R-818-031-03. Average PVC suppression for all patients at their effective dose during dose ranging part of the study was 96.9% (range 87.8% to 99.9%). This excellent suppression continued during the outpatient part of the study. Patients' multiple PVCs were suppressed on the average greater than 99% over the course of the study. However, at the low dose, 100 mg, five of 11 patients had increases in PVCs; evaluation of this result is ongoing.

The plasma half-life of flecainide was found to be relatively long (mean, 20.3 hours) in patients with ventricular arrhythmias following multiple oral dosage. Drug absorption was reasonably prompt and appeared to be nearly complete. Minimum therapeutic plasma levels of flecainide for PVC suppression ranged from about [redacted] ng/ml (average, about 600 ng/ml); these levels and higher were well tolerated.

The investigator published his data [Duff HJ, Roden DM, Maffucci RJ, RL Woosley et al: Suppression of resistant ventricular arrhythmias by twice daily dosing of flecainide. Am J Cardiol 48(#6):1133-1140, 1981.]

The following additional data were included in pulblication:

1. Using three patients who had transient blurring of vision coincided with arrhythmia abolition therapeutic window was drawn (Figure below). Reducing the dosage and changing the dosing interval from every 12 hours to every 8 hours enabled these patients to continue with outpatient therapy without adverse effects and still provided a mean (+ standard deviation) rate of 94.7 ± 5.8 percent ventricular ectopic beat suppression,



Cumulative proportion of patients responding to flecainide with greater than 90 percent ventricular ectopic beat (VED) suppression as related to plasma flecainide concentration.

2. A paradoxical increase in arrhythmia frequency (relative to placebo) was seen in four patients on the 3rd day of flecainide therapy (100 mg twice daily) and during the decline from therapeutic plasma levels after discontinuation of flecanide during the placebo washout period. The extent of increase in arrhythmia frequency for each patient is indicated in Table below.

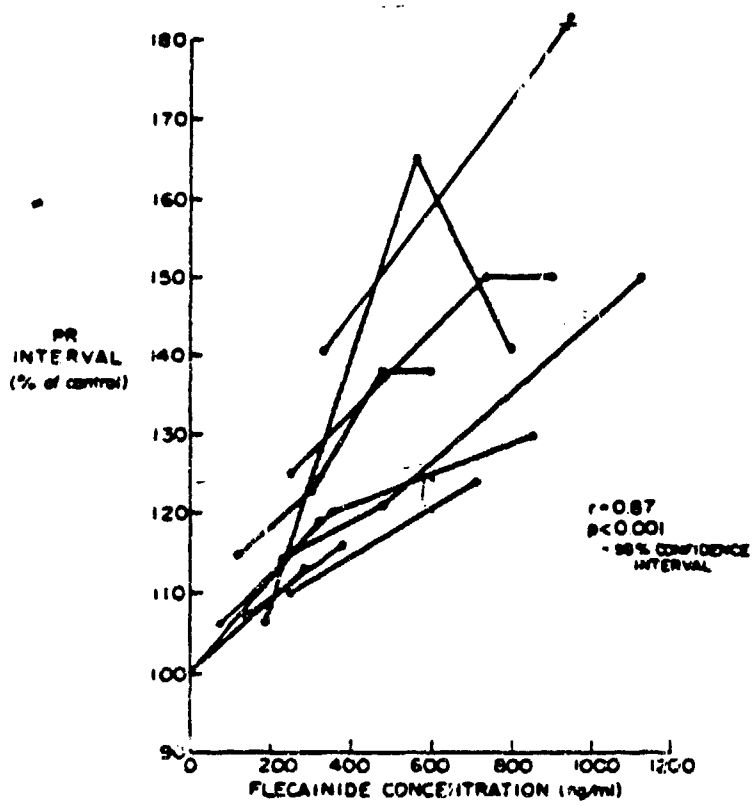
Paradoxical Increase in Arrhythmia Frequency Seen in Four Patients

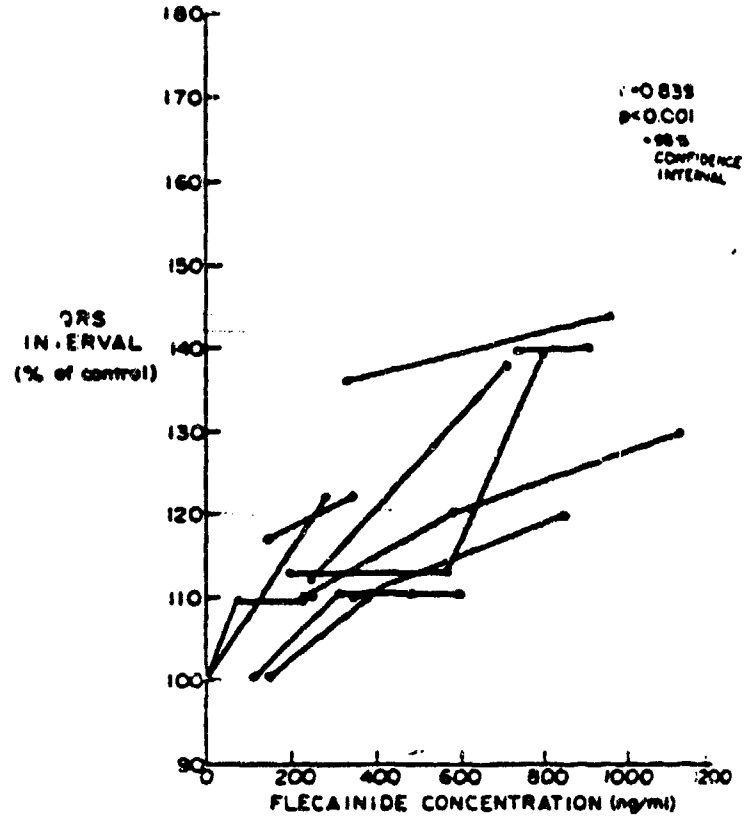
	Ventricular Ectopic Beats/12 hours			Episodes of Ventricular Tachycardia/12 hours		
Case	Placebo	Lowest Dosage	Washout	Placebo	Lowest Dosage	Washout
2	1,343	9,754	13,121	14	11	51
3	8,962	7,409	15,867	5	64	21
6	10,725	14,290	9,807	2.5	7	6*
7	1,139	1,567	4,786	0	6	14

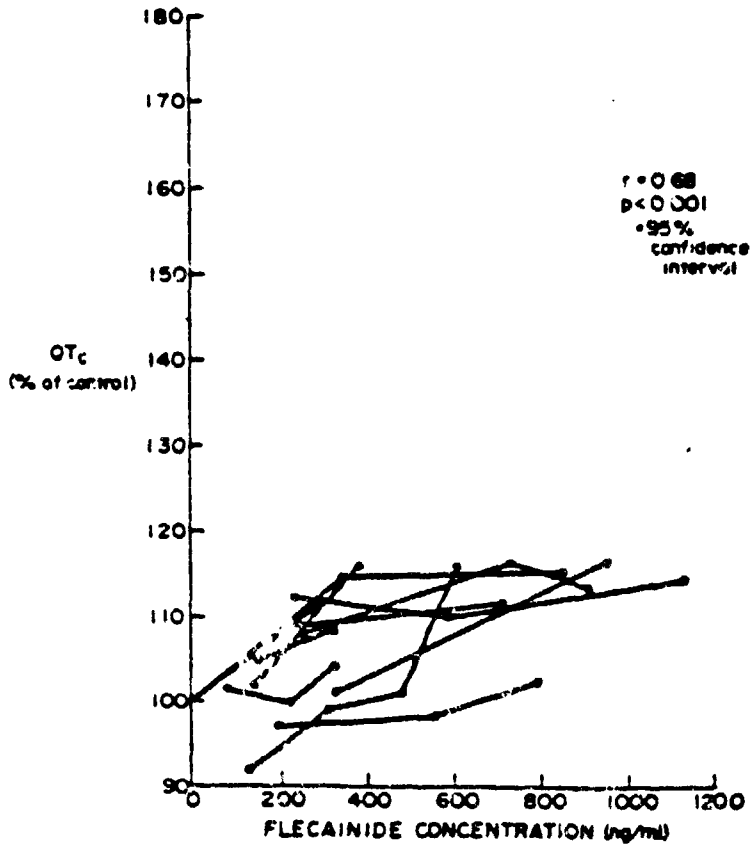
* One episode of sustained ventricular tachycardia.

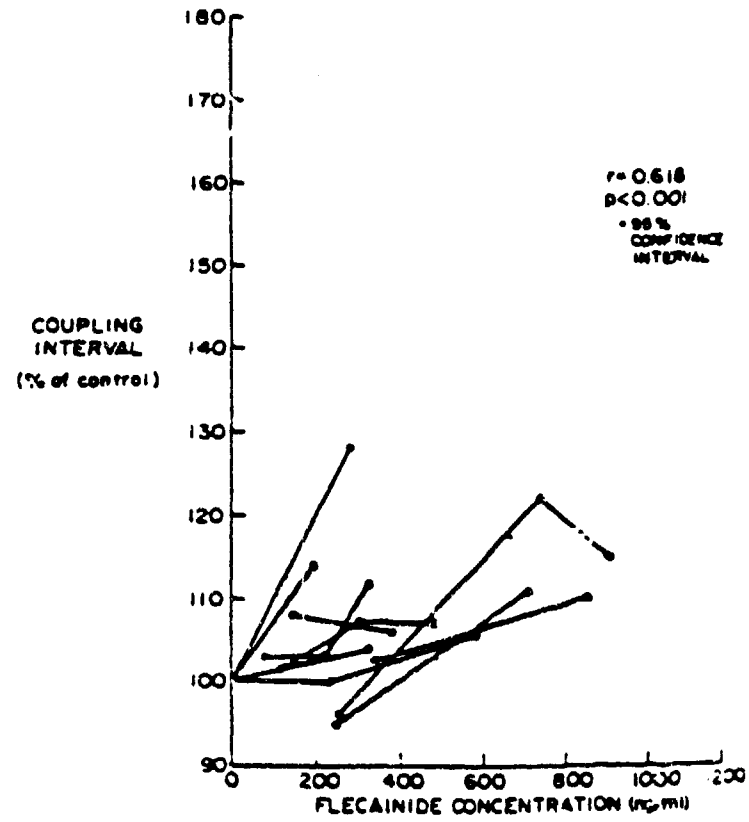
One patient had an episode (1 min.) of self-limited ventricular tachycardia during the decline from therapeutic levels. The patient had never previously manifested episodes of sustained ventricular tachycardia.

3. Concentration-related prolongations of P-R, QRS and Q-Tc intervals were observed in all 11 patients (Figure below). Prior to abolition of ventricular arrhythmias, there was a progressive prolongation in the coupling interval (R-R') of the predominant ectopic focus. The degree of coupling in interval prolongation was linearly related (r=0.61) to the plasma flecainide concentration.









Electrocardiographic interval changes related to plasma flecainide concentrations. Upper left, P-R interval. Upper right, QRS duration. Lower left, Q-Tc interval. Lower right, coupling interval (R-R').

Changes in the Q-Tc interval seen with flecainide therapy are explained largely by changes in QRS duration. Further clinical experience is necessary with flecainide to define completely the clinical significance of these interval prolongations.

4. The arrhythmia frequency in four patients increased with the first dose of flecainide. However, with further increases in the dosage of flecainide and increased electrocardiographic interval prolongation, ventricular arrhythmias were abolished. At times when the QRS and P-R intervals were very prolonged, exercise tolerance and ejection fraction were not significantly changed. No patient manifested bundle branch or A-V block. Transient blurring of vision occurred in three patients at times when the QRS complex was near maximally prolonged.

5. With increasing concentrations of flecainide, there was a progressive prolongation of ventricular ectopic coupling interval prior to arrhythmia suppression. Similar changes in the ectopic coupling interval with procainamide were reported by Giardina and Bigger and imply that the antiarrhythmic action of these drugs depends on effects within a reentrant circuit. It was noted that the extent of QRS widening correlated with antiarrhythmic efficacy of flecainide as well as with steady state plasma concentrations. These data indicate that the electrocardiographic intervals may be accurate predictors of effective myocardial drug concentrations.

6. The extent of antiarrhythmic effect of flecainide was linearly related to both the extent of QRS prolongation ($r = 0.68$) and to the plasma concentration of flecainide ($r = 0.70$). During effective therapy with flecainide, there was a marked prolongation in the P-R interval (mean 37.5 percent, range [redacted]), and QRS duration (mean 26.5 percent, range [redacted]. Less marked changes in the Q-Tc interval (mean 14 percent, range [redacted] were seen but were partially accounted for by changes in QRS duration. No patient manifested Mobitz atrioventricular (A-V) or bundle branch block.

Authors concluded that electrocardiographic intervals as predictors of drug efficacy and effective myocardial drug concentrations without apparent clinical toxicity and may serve as a marker of efficacy. The slow elimination and small incidence of adverse effects allow twice daily dosing with flecainide in most patients treated. Further investigation of the antiarrhythmic efficacy as well as the safety of flecainide is warranted in a broader spectrum of patients.

7. Causes of increased serum alkaline phosphatase: During prolonged flecainide therapy, there was increases in serum alkaline phosphatase. Measurements of 5' nucleotidase and leucine aminopeptidase suggest that the alkaline phosphatase elevation is not due to liver damage. Urinary hydroxyproline excretion in these patients with elevated alkaline phosphatase was normal and therefore does not suggest increased bone turnover as a cause. One could speculate, because flecainide is a fluorinated compound, that fluoride could be liberated during metabolism of the parent compound and alter bone metabolism. Further investigation may be required if these slight elevations of alkaline phosphatase continue to be seen in patients taking flecainide.

(5) Drug Interaction:

(a) R-818-041-01, vol. 2.4, pp. 1-222

Investigator: Jordan L. Holtzman, M.D., Ph.D.
Minneapolis VA Medical Center, Minneapolis, MN

Study Population

Ten healthy male subjects (ages 21-47 years mean 31.3).

Study Design

Because of the unavailability of matching propranolol placebo, this study was conducted in a single-blind fashion. Subjects were institutionalized at the Minneapolis VA Medical Center in the evenings prior to the pharmacodynamic testing and during the days that they received propranolol and flecainide in combination. The following pharmacodynamic tests were conducted on study days 1, 5, 8, 11, 19, 22 and 23 at predose, 1, 2, 3, 5, and 7 hours postdosing: resting supine blood pressure and heart rate, M-mode echocardiographic determination of left ventricular chamber dimensions, systolic time intervals, electrocardiographic effect (ECG rhythm strip) and heart rate response to a standarized bicycle exercise test. Vital signs were also monitored at the same time intervals.

Blood samples were obtained at various times on study days 1, 5, 8, 11, 19, 22 and 23 for the determination of plasma propranolol and/or flecainide levels. Plasma half-life and AUC values were calculated for each drug.

The study drugs were administered according to the following schedule:

Day 1	through 7	Propranolol 80 mg every eight hours and flecainide placebo every 12 hours
Day 8	through 11	Propranolol 80 mg every eight hours and flecainide 200 mg every 12 hours
Day 19	through 221	Flecainide 200 mg every 12 hours
Day 23		Flecainide 200 mg and propranolol 80 mg, single doses

See Table 49 for the study flow chart.

Results

Both propranolol and flecainide demonstrated mild negative inotropic activity. Generally, the effect of administering both drugs concomitantly was additive; there were no synergistic effects of coadministration.

Flecainide slightly increased heart rate, whereas, propranolol markedly reduced heart rate (Fig. 34). The heart rate increase in response to exercise (increase in the heart rate after exercise compared to before), was decreased, as expected, following propranolol and also to a minor extent by flecainde; the effect of coadministration was additive (Fig. 35). Both study drugs widened the PR and corrected QT intervals, although combining the drugs was sub-additive (Fig. 36 & 37). Systolic and diastolic blood pressures decreased after flecainide and more extensively following propranolol. The effect of concurrent administration was additive (Fig. 38 & 39).

In general the effects of propranolol and flecainide on the M-mode echocardiographic measurements were similar; however, the changes following propranolol administration were usually more prominent. Left ventricular end systolic and end diastolic volumes noticeably increased after propranolol and also to a minor extent with flecainide; concurrent dosing resulted in a additive effect (Fig. 40 & 41). Decreases in the mean velocity of circumferential fiber shortening and left ventricular ejection fraction associated with flecainide were slightly less than the reductions attributed to propranolol; their combined effects were additive for both indices (Fig. 42 - 44). Flecainide lengthened the corrected time of total electromechanical systole (QS_2I) and had only a minor effect on the corrected left ventricular ejection time (LVETI), whereas, propranolol shortened both the QS_2I and the LVETI. Because of these changes in the QS_2I and LVETI, the corrected pre-ejection period (PEPI) was increased by flecainide and not appreciably affected by propranolol.

The PEP/LVET ratio was also increased after flecainide and not affected by propranolol; during concomitant administration, the effect on the PEP/LVET ratio was similar to flecainide alone.

Both plasma levels and AUC values for propranolol and flecainide were increased during coadministration. The magnitudes of the higher plasma levels and AUC values of both propranolol (about 30%) and flecainide (about 20%) were small and were unassociated with any synergistic cardiodynamic effects (Fig. 45). Also, the rate of elimination of propranolol and flecainide from plasma did not appear to be significantly altered by concomitant drug administration, since the terminal half-lives of each drug during coadministration with single or multiple doses of the other drug were similar to the values for each drug when administered alone

Adverse Experiences

Frequently reported adverse experiences included lightheadedness, blurred vision, headache and nausea. The lightheadedness and blurred vision were usually attributed to flecainide. When the drugs were coadministered, there was no increase in the reporting of adverse experiences. One episode of lightheadedness was more severe on a study day when both drugs were administered compared to when only one drug was taken; no other adverse experiences were accentuated on days when the drug were administered concurrently.

Conclusion

Individually, both propranolol and flecainide demonstrated mild negative inotropic effects which were frequently additive when the drugs were coadministered; none of the interactions were synergistic even though plasma levels of each drug were slightly increased.

(b) R-818-045-01, pp 223-344, vol. 2.4

Investigator: George P. Lewis, M.D.

Study Site: Clinical Pharmacology Center
Lemuel Shattuck Hospital
Boston, Massachusetts

Study Objective

To determine the possible effect of flecainide acetate on steady-state plasma digoxin concentrations in healthy, male subjects on a maintenance dose of digoxin.

Study Population

Fifteen healthy, adult male subjects. Two other subjects (Nos. 4 and 15) entered the study, but were discontnued.

Study Design

Open-label, metabolic and safety study with multiple oral dosage (digoxin and flecainide).

For metabolic evaluations, blood samples were obtained predose and at 6 hours following the 0800 hours drug (flecainide and/or digoxin) dose on Days 9, 10, 13, 15, 19, and 22 for digoxin level determination and on Days 13, 15, 19, and 22 for flecainide measurement.

Each subject received a single daily oral 0.25 mg dose of digoxin for 22 consecutive days and twice daily oral 200 mg doses of flecainide for 5 days (Days 11 through 15).

To assess safety, physical examinations, ophthalmologic examinations, clinical laboratory tests, and 12-lead electrocardiograms were performed both prestudy and poststudy. Tolerance was monitored by periodically obtaining vital signs and one-minute ECG rhythm strips; side effects were also elicited.

Results

See Table 50 for inidividual data. The mean of plasma digoxin levels (ng/ml) are shown below.

	Pre-flecainide		During flecainide		After flecainide	
Study Day	9	10	13	15	19	22
Predose	0.49	0.42	0.57	0.49	0.51	0.39
6h postdose	0.52	0.64	0.62	0.65	0.55	0.58

Prior to flecainide dosage, plasma digoxin levels at near steady-state on Days 9 and 10 (baseline) were found to range overall from [redacted] (mean, 0.46) ng/ml just prior to morning dosage (trough) and from [redacted] (mean, 0.58) ng/ml at 6 hours postdose in the 15 subjects.

A small, but at some times statistically significant (Wilcoxon signed-rank test), increase in plasma digoxin levels occurred during coadministration of flecainide. On Day 13 (after 2 days of flecainide dosage), digoxin levels were found to range from [redacted] (mean, 0.57) ng/ml predose ($p = 0.014$ compared to baseline) and from [redacted] (mean, 0.62) ng/ml at 6 hours postdose. On Day 15 (after 4 days of flecinide dosage), digoxin levels range from [redacted] (mean, 0.49) ng/ml predose and from [redacted] (mean, 0.65) ng/ml at 6 hours postdose ($p = 0.017$).

Overall, for each subject, the average increase in plasma digoxin levels on Days 13 and 15 compared to baseline is 24.2 $\pm$ 34.9% at the predose time and 13.1 $\pm$ 19.2% at 6 hours postdose.

On Days 19 and 22 (4 and 7 days after flecainide dosage was completed, respectively), plasma levels of digoxin were found to be similar to levels on Days 9 and 10 (baseline); any differences were not found to be statistically significant (p greater than 0.05) either pre- or postdose.

Predose (trough at 0800 hours) plasma levels of flecainide were found to range from [redacted] (mean, 259) ng/ml on Day 13 and from 194 to 531 (mean, 277) ng/ml on Day 15. At 6 hours postdose (0800 hours dose), plasma flecainide levels were found to range from [redacted] (mean, 386) ng/ml and from [redacted] (mean, 397) ng/ml on Days 13 and 15, respectively. These flecainide levels are reasonable for subjects with the dosage regimen employed and are within the range of plasma concentrations associated with suggression of PVCs in patients.

Safety

No flecainide-related changes occurred in any of the physical findings or clinical laboratory tests when pre- and poststudy results were compared. Abnormalities in results from clinical laboratory tests were judged to be not clinically significant. Some minor increases or decreases in vital signs occurred after flecainide and/or digoxin dosage, but these were judged not to be a factor in drug safety.

Transient increases in the PR interval to absolute values above 0.2 second were observed in six subjects during coadministration of drugs. The average QRS interval increased by at most 0.005 second and this was not statistically significant. The QT intervals became continually smaller throughout the study; the most significant decrease ($p = 0.007$) occurred on Day 22, 7 days after flecainide administration was completed. Changes in ECG intervals were not clinically significant.

However shortened, though not significant, QT interval after flecainide seen this study is rather unusualy, because all of previous studies showed some prolongation. I called the sponsor on December 6, 1983 and asked to make comparison with QTc. The sponsor called me back on December 7, 1983, said when compared with QTc there was no difference in QTc.

Side Effects

Adverse experiences were consistent with those observed for flecainide in previous clinical studies. Tiredness and nausea were the most frequent complaints. A total of ten subjects had adverse experiences. All experiences were mild except for a moderate headache for Subject No. 3 and moderate weakness for Subject No. 11.

Conclusion

During coadministration of flecainide to healthy, adult male subjects stabilized on a maintenance dose of digoxin, only a small, but at some times statistically significant, increase in plasma digoxin levels occurred. The magnitude of these changes in digoxin levels with flecainide is markedly less than that found with quinidine and, for flecainide, should be of no clinical consequence for patients receiving chronic digoxin therapy.

Plasma flecainide levels were found to be within the range associated with suppression of PVCs.

No significant changes were observed between pre- and poststudy clinical evaluations. Transient changes in ECGs were noted; these were characteristic of those produced previously by flecainide (increased PR intervals) or digoxin alone ("digitalis effect"; ie, increased PR, sloping of the ST segments). No safety problems were encountered in this study due either to digoxin alone or to digoxin-flecainide coadministration.

B. Controlled Studies, Phase III:

(1) R-818-032-01-17, Multicenter Trial vol. 2.23

TABLE 2: SPECIAL STUDIES

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818V-001	Drug safety & pharmacokinetics in normals	D. Hunninghake	Open	8 subjects	Single iv dose 2 @ 0.5 mg/kg over 5 min 2 @ 1.0 mg/kg over 5 min 2 @ 1.5 mg/kg over 5 min 2 @ 2.0 mg/kg over 5 min
				1 subject	1 @ 5,7.5,10,12.5 mg at 2 hour intervals

Conclusions:
The single, intravenous doses (up to 2.0 mg/kg) were well tolerated by all subjects in the study.

The relatively long plasma half-life of flecainide (mean 11 hours, range 7.3 to 14 hours) indicates that plasma drug levels will be maintained for prolonged periods; thus, flecainide is likely to provide sustained therapeutic activity and should be suitable for twice daily oral dosage during chronic treatment of cardiac arrhythmias.

R-818V-003	Safety & effect of flecainide on cardiodynamics	F. Miller	Open	12 patients	Single iv dose 4 @ 0.5 mg/kg over 5-10 min 2 @ 0.75 mg/kg over 5-10 min 3 @ 1.0 mg/kg over 5-10 min 3 @ 1.5 mg/kg over 5-10 min

Conclusions:
A sustained reduction in cardiac output and an increase in peripheral resistance was observed after flecainide administration. Because of the small number of patients, insufficient duration of hemodynamic observations and lack of appropriate baseline measurements, no further conclusions can be drawn about the extent of cardiodynamic effects produced by the drug in this study.

The only side effects reported by the investigator were difficulty voiding urine and hypotension. The investigator was uncertain whether these side effects were related to flecainide administration.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818V-005	Determine rate & extent of absorption of flecainide. Obtain pharmacokinetic data, assess safety & tolerance.	G. Lewis	Open	16 subjects	Single oral & iv doses 4 @ 60 mg oral, 7 days later 60 mg iv 4 @ 120 mg oral, 7 days later 120 mg iv 4 @ 180 mg oral, 6 weeks later 200 mg oral 4 @ 240 mg oral only

Conclusions:
The plasma level data indicate that flecainide is promptly and extensively absorbed from the capsule formulation and that the drug does not undergo extensive biotransformation in man during absorption or on the first pass through the liver after absorption. The plasma half-life data confirm that flecainide disappearance from plasma is relatively slow in man. From a pharmacokinetic viewpoint, these oral absorption and plasma elimination properties of flecainide demonstrate that the drug is well suited for oral, chronic, treatment of cardiac arrhythmias with twice daily dosage.

The single, oral doses (up to 240 mg or 3.53 mg/kg) and the single, intravenous doses (up to 120 mg or 1.70 mg/kg) were well tolerated by all subjects in the study.

R-818V-015	Effect of flecainide on intracardiac conduction system & sinus node function when administered as a single intravenous dose	R. Helfant	Open	15 patients	Single iv doses of 1.0 mg/kg administered over 5-10 min

Conclusions:
Flecainide administration lengthened the conduction intervals (PA, A-H, and H-V), but only demonstrated a statistically significant increase in the H-V and A-H intervals at 20 minutes postdosing. Flecainide had no significant effect on sinus node function.

TABLE 2 : SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-018	Determine plasma levels of flecainide during seven days of oral dosing. Assess multiple-dose pharmacokinetics of flecainide. Determine safety & tolerance of multiple oral doses of flecainide in subjects	G. Lewis	Open	16 subjects	Seven days of therapy 4 @ 80 mg bid 4 @ 120 mg bid 4 @ 150 mg bid 4 @ 180 mg bid

NDA 18-830

Conclusions:
The plasma level data during multiple oral dosage directly confirm that (consistent with its relatively long plasma half-life) flecainide predictably accumulates in plasma to steady-state levels within a few days; these data confirm that flecainide, from a pharmacokinetic viewpoint, is well suited for twice daily oral dosage for the chronic treatment of cardiac arrhythmias.

The plasma half-life data (for the first and final doses) indicate that multiple oral dosing (up to 180 mg bid) for seven days has no consistent or substantial influence on the rate of flecainide elimination from human plasma (no apparent induction or inhibition of drug elimination processes). The plasma pharmacokinetics of flecainide appear to be independent of dose and to be reasonably linear over a range in multiple oral dosage regimens of 1.1 to 2.8 mg/kg bid. The plasma half-life data are in agreement with previous data for male subjects. This further confirms the relatively long half-life of flecainide in man.

Flecainide was well tolerated by all subjects after single oral doses and during multiple oral dosing regimens (up to 180 mg bid) for seven days. Minor increases in the PR interval were the only electrocardiographic changes observed during the study. Side effects were minor and transient.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818V-022	Determine the effect of intravenous flecainide on right and left ventricular performance using radionuclide angiography in patients with suspected or diagnosed heart disease	R. Helfant M. Bodenheimer	Open	20 patients	Single iv dose 4 @ 1.0 mg/kg over 5-13 min 5 @ 1.5 mg/kg over 5-13 min 10 @ 2.0 mg/kg over 5-13 min 1 @ 0.7 mg/kg over 5-13 min

NDA 18-830

Conclusions:
The investigator made the following conclusion in his report. "These data support the conclusion that at doses of 1.0 and 1.5 mg/kilogram, flecainide administered intravenously has a minimal effect on normal right and normal left ventricular function. However, if a baseline abnormality is present, there is a tendency for deterioration, particularly in the abnormal segment to occur. [illegible] the administration of 2.0 mgs/kilo approximately one half the patients including t[illegible] with initially normal right or left ventricular function showed deterioration in both glob[illegible]nd regional contraction. Thus, there is the potential for an adverse effect on both regional and left ventricular function if higher doses, that is 2.0 mgs/kilogram of flecainide is required. However, while deterioration in left and right ventricular function was detected, there was no apparent adverse effect on systemic pressure, i.e. systolic or diastolic blood pressure or heart rate."

The sponsor concurs, and adds that these data support previous findings of some negative inotropic effect of flecainide. It is difficult to characterize the magnitude of this effect because it varies from patient to patient. In most patients who received the highest dose (2.0 mg/kg), flecainide produced less than a 10% decrease in left ventricular ejection fraction. However, a few patients may experience larger decrements in myocardial performance; therefore, flecainide should be administered cautiously in patients with a history suggesting borderline or compromised myocardial status.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818V-023	To compare the effects of flecainide & vehicle on left ventricular function using catheter tip sensors in patients with suspected or diagnosed left ventricular disease.	M. Hodges	Double-blind, vehicle-controlled, parallel study	2 patients	Single iv dose 2.0 mg/kg over 5 min

Conclusions:
Study terminated because of difficulties in recruiting patients. Because only one patient received flecainide in this study, no conclusions can be drawn about the effects of intravenous flecainide or left ventricular function. No adverse experiences were reported in this patient.

R-818-024	Compare the effects of oral flecainide and placebo on left ventricular function using non-invasive techniques.	M. Hodges	Double-blind, placebo-controlled, two-period, crossover	10 subjects 20 patients	Single oral dose 250 mg

Conclusions:
Flecainide depresses myocardial contractility to a slight degree, but overall left ventricular pump function is maintained.

NDA 18-830

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-026	Compare relative rate & extent of flecainide absorption between a tablet & capsule formulation.	G. Lewis	Open, randomized two-period crossover	17 subjects entered 16 subjects completed	Single dose 200 mg of each formulation

Conclusions:
The plasma level data indicate that flecainide absorption from the wet granulation tablet is essentially complete and that absorption is prompt and reasonably comparable in rate to the capsule. From a drug absorption point of view, this tablet appears acceptable for clinical use.

The plasma half-life data are in good agreement with previous data for male subjects and further confirm the relatively long half-life of flecainide in man.

The 200 mg doses of flecainide (both tablets and capsules) were well tolerated by all subjects in the study.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-038	Determine effect of chronic renal impairment on flecainide elimination. Assess influence of hemodialysis on flecainide elimination. Determine if dosage adjustments are necessary in this patient population.	R. Cutler	Open	10 patients with varying degrees of chronic moderate renal failure. 10 patients with end stage renal disease	Single oral dose 200 mg

Conclusions:
Flecainide absorption (rate and extent) in renal patients appears to be comparable to that in healthy subjects and is reasonably prompt and essentially complete. However, the rate of flecainide elimination from plasma may be slower in some patients with more severe impairment of renal function and the extent of excretion in urine and the renal clearance of unchanged flecainide are both markedly lower in patients with end stage renal disease. For these reasons and because metabolites of flecainide may possibly accumulate in plasma of these patients with multiple dosage, an adjustment downward in drug dosage should be made for renal patients with creatinine clearances, conservatively, of 20 $ml/min/m^2$ or less; initial dosage regimens should be decreased by 25% to 50% and patients should be closely monitored for tolerance.

Hemodialysis does not appear to be an effective means for removal of flecainide from the body.

The single, 200 mg oral dose of flecainide was well tolerated by all patients. No drug-related side effects were reported.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-039	Pharmacokinetics & cardiodynamics of flecainide in healthy subjects & in patients with congestive heart failure.	J. Franciosa	Open	9 subjects 10 patients	Single oral dose 200 mg

Conclusions:
No detrimental effects on cardiac function or exercise performance were noted following a single, 200 mg oral dose of flecainide in either patients with congestive heart failure or in age- and weight-matched subjects free of cardiac disease. No major effects on mean arterial blood pressure or systemic vascular resistance, resting or exercising, were produced in either group. Small, but statistically significant, effects on ECG intervals were produced by the drug.

Congestive heart failure did not appear to alter either the rate or extent of flecainide absorption. However, the rate of flecainide elimination from plasma was somewhat slower in CHF patients than in subjects. No relationship existed between cardiac index (baseline resting) and either plasma half-life or plasma clearance. The extent of urinary excretion of unchanged flecainide was equivalent in CHF patients and aged-matched subjects. Although mean renal drug clearance was lower in patients than subjects, the difference was not statistically significant; renal clearance accounted for the same proportion of total body (plasma) clearance in both groups.

Based on cardiodynamic and pharmacokinetic data from this single dose study, only modest downward adjustments, if any, in initial flecainide dosage regimens for patients with CHF appear to be indicated. Such results, however, may not be predictive of those from continuous administration of flecainide, and downward adjustments in dose may be required in patients with left ventricular dysfunction as dictated in individual cases.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-041	Effects of oral flecainide & propranolol administered alone & concurrently on cardiac function in healthy male subjects.	J. Holtzman	Open	10 subjects	Total of nine days of flecainide 200 mg bid; Total of twelve days of propranolol, 80 mg q8h

Conclusions:
Individually, both propranolol and flecainide demonstrated mild negative inotropic effects which were frequently additive when the drugs were coadministered; none of the interactions were synergistic even though plasma levels for each drug were slightly increased.

R-818-045	Effects of flecainide on plasma digoxin levels when given concurrently to subjects.	G. Lewis	Open	17 subjects entered 15 subjects completed	Five days of flecainide, 200 mg bid; Twenty-two days of digoxin, 0.25 mg

Conclusions:
During coadministration of flecainide to healthy, adult male subjects stabilized on a maintenance dose of digoxin, only a small, but at some times statistically significant, increase in plasma digoxin levels occurred. The magnitude of these changes in digoxin levels with flecainide is markedly less than that found for quinidine and, for flecainide, should be of no clinical significance for patients receiving chronic digoxin therapy.

Plasma flecainide levels were found to be within the range associated with suppression of PVCs. No significant changes were observed between prestudy and poststudy clinical evaluations. Transient changes in ECGs were noted; these were characteristic of those produced previously by flecainide (increased PR intervals) or digoxin alone ("digitalis effect"; ie, increased PR, sloping of the ST segment). No safety problems were encountered in this study due either to digoxin alone or to digoxin-flecainide coadministration.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-049	Comparative oral absorption of three flecainide dosage formulations & the effect of food on drug absorption.	A. Cohen	Open, randomized three-period crossover plus 4th period with food	25 subjects entered 18 subjects completed	Single oral dose 200 mg of each formulation; 200 mg as tablet with food

Conclusions:
The relative bioavailability of flecainide from the final tablet formulation was comparable to that from a reference solution; no statistically significant difference was seen in either the rate or extent of absorption.

The capsule formulation showed a comparable extent of flecainide absorption relative to that from the solution (and tablet), but demonstrated a significantly slower rate of flecainide absorption. The difference in the absorption rate between tablet and capsule should be of no clinical consequence. Similar mean steady-state plasma levels would be expected for both formulations, because they both deliver the same amount of drug to the systemic circulation. A slightly lower peak-trough fluctuation in plasma levels would be predicted for the capsule based on its slower rate of absorption.

Absorption of flecainide from the capsule formulation was compared previously to an intravenous dose in study R-818V-005-01. The capsule was shown to provide nearly complete absorption. Thus, it can be concluded from the similarity of the AUC values in the present study that the extents of flecainide absorption from the tablet and solution were also nearly complete.

When the tablet was administered with a meal, both the rate and extent of flecainide absorption were essentially equivalent to those seen under fasting conditions.

No significant changes were observed between prestudy and poststudy clinical evaluations. No safety problems were encountered in this study due to flecainide administration with any of the three dosage formulations.

TABLE 2: SPECIAL STUDIES (Continued)

Protocol	Study Purpose	Investigator	Study Design	Number of Patients (Subjects)	Duration of Therapy & Dose(s)
R-818-050-03	Metabolic disposition of carbon-14 labeled flecainide.	A. Cohen	Open	4 subjects	Single oral dose 200 mg ^{14}C-labeled flecainide

Conclusions:
Flecainide absorption is prompt and essentially complete following oral dosage. Flecainide and its metabolites are extensively eliminated in urine (about 85% of the dose); only about 5% of the dose is accounted for in feces. On the average, about half of the carbon-14 excreted in urine is accounted for as unchanged flecainide. Much of the remainder of the carbon-14 in urine is accounted for by two major metabolites, one of which is meta-O-dealkylated flecainide; the other metabolite has been identified as 5-hydroxy-N-[2-(6-oxopiperidylmethyl)]-2-(2',2',2'-trifluoroethoxy)-benzamide. Meta-O-dealkylated flecainide exists in urine in both the free and conjugated forms, but is found primarily as the conjugate. On the average, total meta-O-dealkylated flecainide (free and conjugated) in urine accounts for about 14% of the dose. Based upon the previously reported TLC analyses, the other major urinary metabolite represents about the same fraction of the dose as meta-O-dealkylated flecainide and is also found primarily in its conjugated form.

Thus, flecainide undergoes extensive biotransformation in humans and both unchanged flecainide and its metabolites are primarily excreted in urine. In addition, flecainide does not undergo extensive biliary excretion in humans, unless reabsorption occurs after biliary elimination. Also, metabolites of flecainide are present in human plasma and the rate of elimination of total metabolites from plasma is only somewhat slower than that for unchanged drug.

The single, 200 mg oral dose of flecainide was well tolerated by all subjects.

TABLE 5 : CHRONIC-DOSING STUDIES (Continued)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
033-01	Chronic PVCs	B. Beller	Open, long-term safety & efficacy	18	14	Flecainide 100, 150, 200, 300, 400, 500, 600
033-02	Chronic PVCs	M. Hodges	Open, long-term safety & efficacy	21	14	Flecainide 200, 300, 350, 400, 450, 500
033-03	Chronic PVCs	W. Cook	Open, long-term safety & efficacy	4	2	Flecainide 100, 150, 200, 300, 400
033-04	Chronic PVCs	J. Farnham	Open, long-term safety & efficacy	10	9	Flecainide 100, 150, 200, 300, 400
033-05	Chronic PVCs	W. Hart	Open, long-term safety & efficacy	20	15	Flecainide 200, 300, 400, 500
033-06	Chronic PVCs	R. Kalmansohn	Open, long-term safety & efficacy	F 9 Q 1	7[b] 0	Flecainide 200, 400 Quinidine 1200

[a]Also known as R-818-EN-03.

[b]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to adverse experiences.

TABLE 5: CHRONIC-DOSING STUDIES (Continued)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
033-07	Chronic PVCs	J. Laidlaw	Open long-term safety & efficacy	F 16 Q 5	12[b] 5[c]	Flecainide 200, 300, 400, 500, 600 Quinidine 800, 1200
033-08	Chronic PVCs	G. Lee	Open, long-term safety & efficacy	F 11 Q 3	11 1	Flecainide 300, 400, 500, 600 Quinidine 1000, 1200, 1600
033-09	Chronic PVCs	G. Lewis	Open, long-term safety & efficacy	8	6	Flecainide 200, 300, 400
033-10	Chronic PVCs	A. Antlitz	Open, long-term safety & efficacy	F 3 Q 1	3 1	Flecainide 300, 400 Quinidine 1200
033-11	Chronic PVCs	F. Marcus	Open, long-term safety & efficacy	F 7 Q 1	6 1	Flecainide 100, 200, 400 Quinidine 1200

[a]Also known as R-818-EN-03.
[b]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to lack of therapeutic affect.
[c]Number ongoing on quinidine includes one patient who entered study on flecainide and was changed to quinidine due to adverse experiences and lack of therapeutic effect.

TABLE 5: CHRONIC-DOSING STUDIES (Continued)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
033-12	Chronic PVCs	J. Morganroth	Open, long-term safety & efficacy	9	5	Flecainide 200, 300, 400, 500, 600
033-13	Chronic PVCs	C. Oshrain	Open, long-term safety & efficacy	F 15 Q 3	13[b] 2	Flecainide 200, 300, 400 Quinidine 1200, 1600
033-14	Chronic PVCs	P. Reid	Open, long-term safety & efficacy	F 17 Q 2	16 2	Flecainide 200, 250, 300, 350, 400, 500, 600 Quinidine 1200, 1600
033-16	Chronic PVCs	B. Alter	Open, long-term safety & efficacy	4	2	Flecainide 200, 300, 400
033-17	Chronic PVCs	M. Platt B. Rosin	Open, long-term safety & efficacy	F 21 Q 1	17[c] 0	Flecainide 100, 150, 200, 300, 400 Quinidine 1200
Overall Results				F 194 Q 17	F 152 Q 12	

Conclusions: Flecainide remains effective with an acceptable side effect profile and incidence when used chronically in an outpatient population of patients with ventricular arrhythmias requiring antiarrhythmic therapy.

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[a]Also known as R-818-EN-03.

[b]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to adverse experiences.

[c]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to lack of therapeutic effect.

TABLE 5 : CHRONIC-DOSING STUDIES (Concluded)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
R-818-035-01	Chronic PVCs	P. Hugenholtz K. Balakumaran	Open, long-term safety & efficacy	39	28	Flecainide 150, 200, 250, 300, 350, 400
R-818-035-02	Chronic PVCs	P. Hugenholtz F. Hagemeijer	Open, long-term safety & efficacy	7	2	Flecainide 100, 200, 300, 400
R-818-035-03	Chronic PVCs	P. Hugenholtz F. Tencate A. Jovanovic	Open, long-term safety & efficacy	21	13	Flecainide 200, 250, 300, 400

Conclusions: Flecainide was highly effective in suppressing ventricular arrhythmias, without limiting side effects in 43 patients who received long-term treatment and who remain enrolled.

---

[a]Also known as R-818-EN-03.

Table 6

Summary of Plasma Pharmacokinetic Data in Man
Following Single Oral Doses
Lewis #R-818-0C5-01

Subject (and Group) Numbers	R-818 Dose (mg)	(mg/kg)[a]	Plasma Half-life[b] (hours)	Elimination Rate Constant[c] ($hours^{-1}$)	Plasma A.U.C. Values (0-∞)[d] Measured (ng·hours/ml)	per One mg/kg (ng·hours/ml)	per One mg/kg x K_{el} (ng/ml)
1 (A-1)	60	0.65	14.9	0.0464	1327	2057	95.4
2 (A-2)	60	0.85	11.2	0.0621	1182	1385	86.0
3 (A-3)	60	0.84	18.4	0.0377	3443	4114	155.1
4 (A-4)	60	0.78	17.3	0.0400	1734	2228	89.1
5 (B-1)	120	1.64	14.5	0.0479	3356	2042	97.8
6 (B-2)	120	1.70	10.9	0.0638	2985	1754	111.9
7 (B-3)	120	1.70	14.1	0.0493	4350	2552	125.8
8 (B-4)	120	1.32	7.2	0.0957	2474	1876	179.5
9 (C-1)	180	2.26	15.2	0.0457	7557	3338	152.5
10 (C-2)	180	2.57	9.5	0.0731	6097	2371	173.3
11 (C-3)	180	2.22	22.0	0.0315	7354	3309	104.2
12 (C-4)	180	2.95	14.7	0.0471	8697	2947	138.8
13 (D-1)	240	3.53	12.5	0.0555	4309	1221	67.8
14 (D-2)	240	2.25	12.0	0.0579	4460	1981	114.7
15 (D-3)	240	3.41	19.4	0.0357	8783	2573	91.9
16 (D-4)	240	3.41	12.8	0.0543	5102	1495	81.2
Mean			14.2	0.0527		2328	116.6
S_x[e]			± 1.0	± 0.0040		± 197	± 8.5

[a] Dose level (mg/kg) is based on weight at the time of drug administration.

[b] The terminal or beta phase plasma half-life was estimated from the log plasma concentration versus time graph by calculation of the least squares line.

[c] The terminal elimination rate constant (K_{el}) is 0.693 divided by the terminal plasma half-life.

[d] Area under the plasma R-818 concentration-time curve from zero to infinity.

[e] Standard deviation of the mean.

Table 7

Comparison of Plasma R-818 Concentration Data in Man
Following Single Oral and Intravenous Doses
Lewis #R-818-005-01

Subject (and Group) Numbers	R-818 Dose (mg)	R-818 Dose (mg/kg)[a]	Plasma Half-life[b] (hours) Oral	Plasma Half-life[b] (hours) IV	Plasma A.U.C. Values (0 to ∞)[c] (ng·hours/ml) Oral	Plasma A.U.C. Values (0 to ∞)[c] (ng·hours/ml) IV	Ratio Oral/IV
1 (A-1)							
2 (A-2)							
3 (A-3)							
4 (A-4)							
5 (B-1)							
6 (B-2)							
7 (B-3)							
8 (B-4)							
Mean			13.6	14.1			0.947
$S_{\bar{x}}$[d]			± 1.3	± 1.5			± 0.073

[a] Dose level (mg/kg) is based on weight at the time of drug administration.

[b] The terminal or beta phase plasma half-life was estimated from the log plasma concentration versus time graph by calculation of the least squares line.

[c] Area under the plasma R-818 concentration-time curve from zero to infinity.

[d] Standard deviation of the mean.

TABLE 8

Comparison of Percent of Dose Excreted in Urine as Unchanged Flecainide Acetate Within 24 Hours Following Oral and Intravenous Administration of a Single Dose to Human Subjects
Lewis #R-818-005-01

Subject No. (Group)	Dose[a] mg	Dose[a] mg/kg[c]	Percent of Dose Excreted as Flecainide Acetate[b] Oral	Intravenous	Ratio (Oral/IV)
1 (A-1)					
5 (B-1)					
6 (B-2)					
7 (B-3)					
Mean[d]			20.97	30.86	0.673
Std. Dev.			15.90	7.25	0.408

[a] Oral dose (Formulation U-1c 60 mg capsule) was given seven days prior to intravenous dose (Formulation U-1b 10 mg/ml sterile parenteral solution).

[b] Percent of dose excreted in urine within 24 hours following dosage.

[c] Dose level based on weight on dosage day.

[d] Mean values and standard deviations for four subjects.

Notebook Reference: NB-58838-41

Table 9: Kinetic parameters of Flecainide from five healthy male volunteers following intravenous (2 mg/kg in 5 min) or oral (200 mg) single dose administrations (mean ± SD and range values)

Tjandramaga #82-105-FRV-BE-002 & #81-152-FRO-BE-002

		INTRAVENOUS	O R A L
CONDITION		*Fasting*	*Fasting*
C_{max}	(ng/ml)	1710 ± 788	355 ± 48
T_{max}	(h)	-	2.3 ± 0.7
α	(min^{-1})	0.066 ± 0.022	-
$t\ 1/2_{\alpha}$	(min)	12.04 ± 5.70	-
β	(h^{-1})	0.040 ± 0.006	0.061 ± 0.009
$t\ 1/2_{\beta}$	(h)	17.5 ± 3.1	11.5 ± 1.6
$Vd_{\beta\ 2a}/F$	(L)	522.2 ± 69.2	566.0 ± 91.2
	(L/kg)	7.27 ± 1.14	7.83 ± 1.04
Vd_{ss}/F	(L)	512.3 ± 66.2	-
	(L/kg)	7.13 ± 1.11	-
Cl_{TB}/F	(ml/min)	355.2 ± 84.6	563.5 ± 180.4
	(ml/min/kg)	4.96 ± 1.28	7.8 ± 2.6
Cl_R	(ml/min)	169.5 ± 49.3	181.7 ± 63.1
	(ml/min/kg)	2.36 ± 0.76	2.5 ± 0.6

Table 9 continued

Cl_{NR} (ml/min)	185.7 ± 46.2	381.8 ± 183.7
(ml/min/kg)	2.59 ± 0.68	5.4 ± 2.7
AUC_{0-48} (ng/ml.h)	5797 ± 1601 (3761-8149)	-
$AUC_{0-\infty}$ (ng/ml.h)	7201 ± 2305	6047 ± 1566
Normalized $[AUC]_0^{\infty} \times \beta$ (ng/ml)	287 ± 49	361 ± 57
F (%)[a]	91.0 ± 6.7	
Cumulative Urinary Excretion (0 - 48 h)		
(mg)	55.85 ± 9.27	57.46 ± 20.85
(% of dose)	38.39 ± 2.62	28.73 ± 10.42

[a] F = xtent of bioavailability derived from :

$$\frac{[AUC]_0^{\infty} \times \beta \text{ PO}}{[AUC]_0^{\infty} \times \beta \text{ IV}} \times \frac{\text{Dose IV}}{\text{Dose PO}}$$

TABLE 5 : CHRONIC-DOSING STUDIES (Continued)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
033-01	Chronic PVCs	B. Beller	Open, long-term safety & efficacy	18	14	Flecainide 100, 150, 200, 300, 400, 500, 600
033-02	Chronic PVCs	M. Hodges	Open, long-term safety & efficacy	21	14	Flecainide 200, 300, 350, 400, 450, 500
033-03	Chronic PVCs	W. Cook	Open, long-term safety & efficacy	4	2	Flecainide 100, 150, 200, 300, 400
033-04	Chronic PVCs	J. Farnham	Open, long-term safety & efficacy	10	9	Flecainide 100, 150, 200, 300, 400
033-05	Chronic PVCs	W. Hart	Open, long-term safety & efficacy	20	15	Flecainide 200, 300, 400, 500
033-06	Chronic PVCs	R. Kalmansohn	Open, long-term safety & efficacy	F 9 Q 1	7[b] 0	Flecainide 200, 400 Quinidine 1200

[a]Also known as R-818-EN-03.
[b]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to adverse experiences.

TABLE 5: CHRONIC-DOSING STUDIES (Continued)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
033-07	Chronic PVCs	J. Laidlaw	Open, long-term safety & efficacy	F 16 Q 5	12[b] 5[c]	Flecainide 200, 300, 400, 500, 600 Quinidine 800, 1200
033-08	Chronic PVCs	G. Lee	Open, long-term safety & efficacy	F 11 Q 3	11 1	Flecainide 300, 400, 500, 600 Quinidine 1000, 1200, 1600
033-09	Chronic PVCs	G. Lewis	Open, long-term safety & efficacy	8	6	Flecainide 200, 300, 400
033-10	Chronic PVCs	A. Antlitz	Open, long-term safety & efficacy	F 3 Q 1	3 1	Flecainide 300, 400 Quinidine 1200
033-11	Chronic PVCs	F. Marcus	Open, long-term safety & efficacy	F 7 Q 1	6 1	Flecainide 100, 200, 400 Quinidine 1200

[a]Also known as R-818-EN-03.
[b]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to lack of therapeutic affect.
[c]Number ongoing on quinidine includes one patient who entered study on flecainide and was changed to quinidine due to adverse experiences and lack of therapeutic effect.

TABLE 5: CHRONIC-DOSING STUDIES (Continued)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
033-12	Chronic PVCs	J. Morganroth	Open, long-term safety & efficacy	9	5	Flecainide 200, 300, 400, 500, 600
033-13	Chronic PVCs	C. Oshrain	Open, long-term safety & efficacy	F 16 Q 3	13[b] 2	Flecainide 200, 300, 400 Quinidine 1200, 1600
033-14	Chronic PVCs	P. Reid	Open, long-term safety & efficacy	F 17 Q 2	16 2	Flecainide 200, 250, 300, 350, 400, 500, 600 Quinidine 1200, 1600
033-16	Chronic PVCs	B. Alter	Open, long-term safety & efficacy	4	2	Flecainide 200, 300, 400
033-17	Chronic PVCs	M. Platt B. Rosin	Open, long-term safety & efficacy	F 21 Q 1	17[c] 0	Flecainide 100, 150, 200, 300, 400 Quinidine 1200
Overall Results				F 194 Q 17	F 152 Q 12	

Conclusions: Flecainide remains effective with an acceptable side effect profile and incidence when used chronically in an outpatient population of patients with ventricular arrhythmias requiring antiarrhythmic therapy.

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[a]Also known as R-818-EN-03.

[b]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to adverse experiences.

[c]Number ongoing on flecainide includes one patient who entered study on quinidine and later was changed to flecainide due to lack of therapeutic effect.

TABLE 5 : CHRONIC-DOSING STUDIES (Concluded)

(R-818-031, R-818-033, and R-818-035[a])

Protocol	Condition Studied	Investigator	Study Design	Patients Started	Patients Ongoing	Total Daily Dose (mg)
R-818-035-01	Chronic PVCs	P. Hugenholtz K. Balakumaran	Open, long-term safety & efficacy	39	28	Flecainide 150, 200, 250, 300, 350, 400
R-818-035-02	Chronic PVCs	P. Hugenholtz F. Hagemeijer	Open, long-term safety & efficacy	7	2	Flecainide 100, 200, 300, 400
R-818-035-03	Chronic PVCs	P. Hugenholtz F. Tencate A. Jovanovic	Open, long-term safety & efficacy	21	13	Flecainide 200, 250, 300, 400

Conclusions: Flecainide was highly effective in suppressing ventricular arrhythmias, without limiting side effects in 43 patients who received long-term treatment and who remain enrolled.

---

[a]Also known as R-818-EN-03.

Table 6

Summary of Plasma Pharmacokinetic Data in Man
Following Single Oral Doses
Lewis #R-818-005-01

Subject (and Group) Numbers	R-818 Dose (mg)	(mg/kg)[a]	Plasma Half-life[b] (hours)	Elimination Rate Constant[c] ($hours^{-1}$)	Plasma A.U.C. Values (0-∞)[d] Measured (ng·hours/ml)	per One mg/kg (ng·hours/ml)	per One mg/kg x K_{el} (ng/ml)
1 (A-1)	60	0.65	14.9	0.0464	1327	2057	95.4
2 (A-2)	60	0.85	11.2	0.0621	1182	1385	86.0
3 (A-3)	60	0.84	18.4	0.0377	3443	4114	155.1
4 (A-4)	60	0.78	17.3	0.0400	1734	2228	89.1
5 (B-1)	120	1.64	14.5	0.0479	3356	2042	97.8
6 (B-2)	120	1.70	10.9	0.0638	2985	1754	111.9
7 (B-3)	120	1.70	14.1	0.0493	4350	2552	125.8
8 (B-4)	120	1.32	7.2	0.0957	2474	1876	179.5
9 (C-1)	180	2.26	15.2	0.0457	7557	3338	152.5
10 (C-2)	180	2.57	9.5	0.0731	6097	2371	173.3
11 (C-3)	180	2.22	22.0	0.0315	7354	3309	104.2
12 (C-4)	180	2.95	14.7	0.0471	8697	2947	138.8
13 (D-1)	240	3.53	12.5	0.0555	4309	1221	67.8
14 (D-2)	240	2.25	12.0	0.0579	4460	1981	114.7
15 (D-3)	240	3.41	19.4	0.0357	8783	2573	91.9
16 (D-4)	240	3.41	12.8	0.0543	5102	1495	81.2
Mean			14.2	0.0527		2328	116.6
S_x[e]			± 1.0	± 0.0040		± 197	± 8.5

[a] Dose level (mg/kg) is based on weight at the time of drug administration.

[b] The terminal or beta phase plasma half-life was estimated from the log plasma concentration versus time graph by calculation of the least squares line.

[c] The terminal elimination rate constant (K_{el}) is 0.693 divided by the terminal plasma half-life.

[d] Area under the plasma R-818 concentration-time curve from zero to infinity.

[e] Standard deviation of the mean.

Comparison of Plasma R-818 Concentration Data in Man
Following Single Oral and Intravenous Doses
Lewis #R-818-005-01

Subject (and Group) Numbers	R-818 Dose (mg)	R-818 Dose (mg/kg)[a]	Plasma Half-life[b] (hours) Oral	Plasma Half-life[b] (hours) IV	Plasma A.U.C. Values (0 to ∞)[c] (ng·hours/ml) Oral	Plasma A.U.C. Values (0 to ∞)[c] (ng·hours/ml) IV	Ratio Oral/IV
1 (A-1)							
2 (A-2)							
3 (A-3)							
4 (A-4)							
5 (B-1)							
6 (B-2)							
7 (B-3)							
8 (B-4)							
Mean			13.6	14.1			0.947
S_x[d]			± 1.3	± 1.5			± 0.073

[a] Dose level (mg/kg) is based on weight at the time of drug administration.

[b] The terminal or beta phase plasma half-life was estimated from the log plasma concentration versus time graph by calculation of the least squares line.

[c] Area under the plasma R-818 concentration-time curve from zero to infinity.

[d] Standard deviation of the mean.

TABLE 8

Comparison of Percent of Dose Excreted in Urine as Unchanged Flecainide Acetate Within 24 Hours Following Oral and Intravenous Administration of a Single Dose to Human Subjects
Lewis #R-818-005-01

Subject No. (Group)	Dose[a] mg	Dose[a] mg/kg[c]	Percent of Dose Excreted as Flecainide Acetate[b] Oral	Intravenous	Ratio (Oral/IV)
1 (A-1)					
5 (B-1)					
6 (B-2)					
7 (B-3)					
Mean[d]			20.97	30.86	0.673
Std. Dev.			15.90	7.25	0.408

[a] Oral dose (Formulation U-1c 60 mg capsule) was given seven days prior to intravenous dose (Formulation U-1b 10 mg/ml sterile parenteral solution).
[b] Percent of dose excreted in urine within 24 hours following dosage.
[c] Dose level based on weight on dosage day.
[d] Mean values and standard deviations for four subjects.

Notebook Reference: NB-58838-41

Table 9: Kinetic parameters of Flecainide from five healthy male volunteers following intravenous (2 mg/kg in 5 min) or oral (200 mg) single dose administrations (mean ± SD and range values)

Tjandramaga #82-105-FRV-BE-002 & #81-152-FRO-BE-002

	INTRAVENOUS	O R A L
CONDITION	*Fasting*	*Fasting*
C_{max} (ng/ml)	1710 ± 788	355 ± 48
T_{max} (h)	-	2.3 ± 0.7
α (min^{-1})	0.066 ± 0.022	-
$t\ 1/2_{\alpha}$ (min)	12.04 ± 5.70	-
β (h^{-1})	0.040 ± 0.006	0.061 ± 0.009
$t\ 1/2_{\beta}$ (h)	17.5 ± 3.1	11.5 ± 1.6
Vd_{area}/F (L)	522.2 ± 69.2	566.0 ± 91.2
(L/kg)	7.27 ± 1.14	7.83 ± 1.04
Vd_{ss}/F (L)	512.3 ± 66.2	-
(L/kg)	7.13 ± 1.11	-
Cl_{TB}/F (ml/min)	355.2 ± 84.6	563.5 ± 180.4
(ml/min/kg)	4.96 ± 1.28	7.8 ± 2.6
Cl_R (ml/min)	169.5 ± 49.3	181.7 ± 63.1
(ml/min/kg)	2.36 ± 0.76	2.5 ± 0.6

Table 9 continued

Cl_{NR} (ml/min)	185.7 ± 46.2	38..8 ± 183.7
(ml/min/kg)	2.59 ± 0.68	5.4 ± 2.7
AUC_{0-48} (ng/ml.h)	5797 ± 1601 (3761-8149)	-
$AUC_{0-\infty}$ (ng/ml.h)	7201 ± 2305	6047 ± 1566
Normalized $[AUC]_0^{\infty} \times \beta$ (ng/ml)	287 ± 49	361 ± 57
F (%)[a]	91.0 ± 6.7	
Cumulative Urinary Excretion (0 - 48 h)		
(mg)	55.85 ± 9.27	57.46 ± 20.85
% of dose)	38.39 ± 2.62	28.73 ± 10.42

[a] F = extent of bioavailability derived from :

$$\frac{[AUC]_0^{\infty} \times \beta \ PO}{[AUC]_0^{\infty} \times \beta \ IV} \times \frac{\text{Dose IV}}{\text{Dose PO}}$$

STUDY: R-818V-003-01
INVESTIGATOR: PAUL H. MILLER, MD

TABLE 10

SYSTEMIC CARDIAC OUTPUT (1/min)

PATIENT NUMBER	BASELINE VALUE	10 MIN AFTER DOSE	30 MIN AFTER DOSE	60 MIN AFTER DOSE
1				
2				
3				
4				
GROUP A MEAN 0.5 MG/KG	5.34	4.80	4.41	4.55
5				
6				
GROUP B MEAN 0.75MG/KG	5.42	5.18	4.67	4.76
7				
8				
10				
GROUP C MEAN 1.0 MG/KG	6.26	5.46	5.64	5.42
9				
11				
12				
GROUP D MEAN 1.5 MG/KG	4.99	4.00	4.22	3.44

STUDY: R-818V-003-01
INVESTIGATOR: PAUL H. MILLER, MD

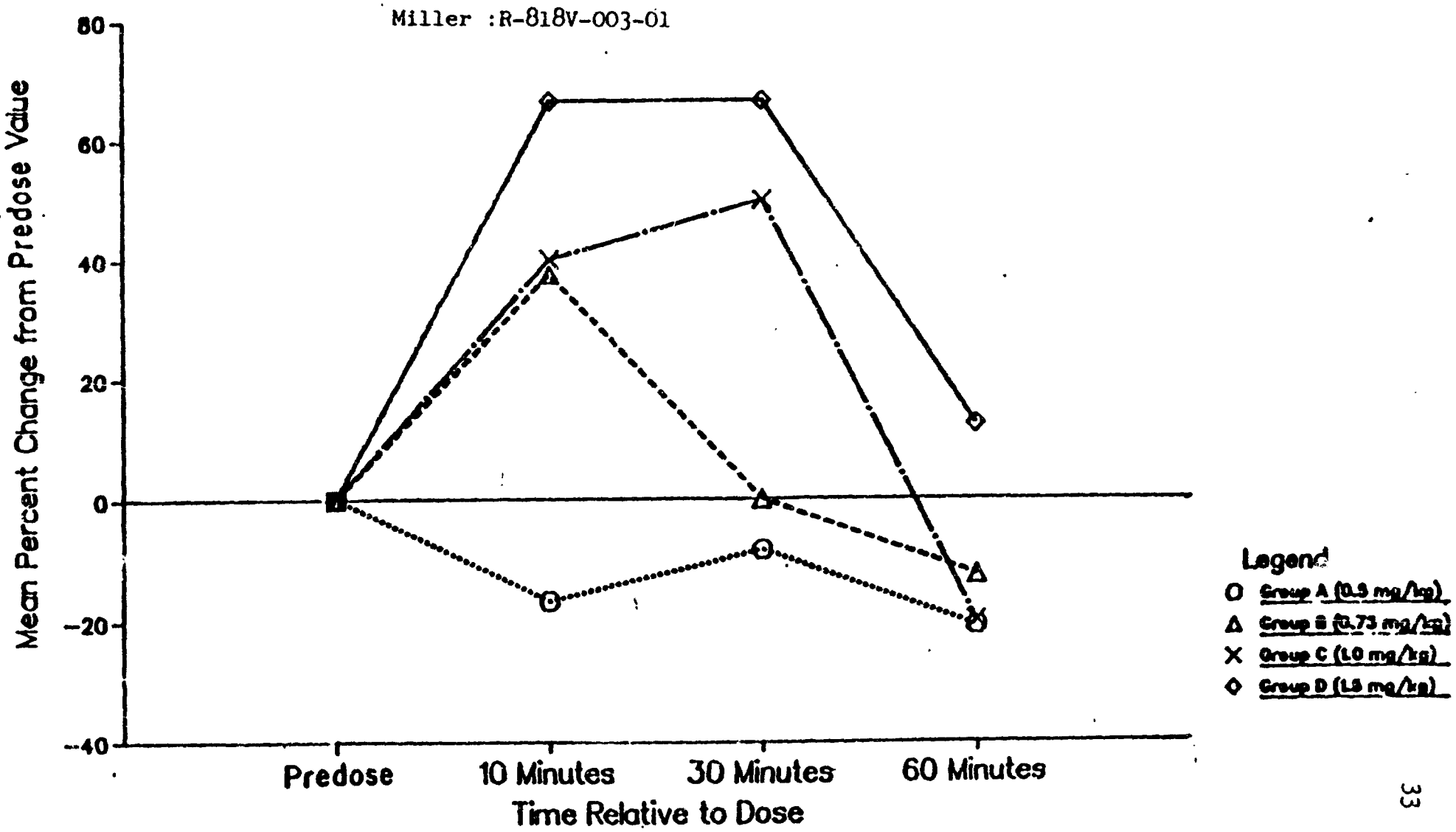
TABLE 11

LEFT VENTRICULAR END DIASTOLIC PRESSURE (mmHg)

PATIENT NUMBER	BASELINE VALUE	10 MIN AFTER DOSE	30 MIN AFTER DOSE	60 MIN AFTER DOSE
1				
2				
3				
4				
GROUP A MEAN 0.5 MG/KG	9.5	7.5	8.5	8.3
5				
6				
GROUP B MEAN 0.75MG/KG	10.0	10.0	10.0	8.0
7				
8				
10				
GROUP C MEAN 1.0 MG/KG	10.0	14.0	15.0	8.0
9				
11				
12				
GROUP D MEAN 1.5 MG/KG	8.0	12.0	12.0	8.5

[a] DATA RECORDED INCORRECTLY ON CASE REPORT FORM AND WAS NOT USED IN THE ANALYSIS.
[b] DATA NOT RECORDED.

Figure 1: MEAN PERCENT CHANGE OF LEFT VENTRICULAR END DIASTOLIC PRESSURE FOR EACH DOSE GROUP



STUDY: R-818V-C03-01
INVESTIGATOR: PAUL H. MILLER, MD

TABLE 25[a]

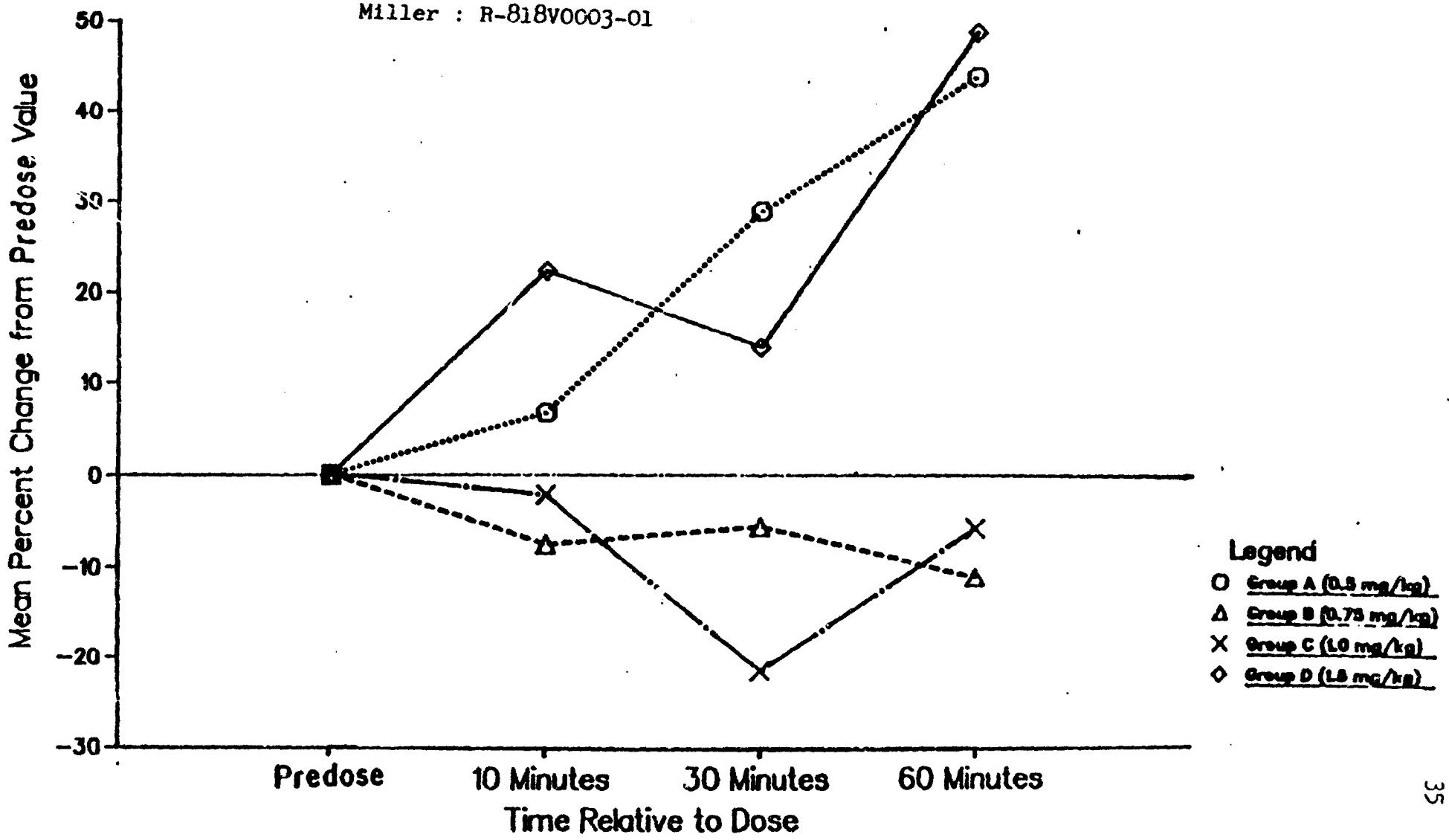
LEFT VENTRICULAR DP/DT RATIO

PATIENT NUMBER	BASELINE VALUE	10 MIN AFTER DOSE	30 MIN AFTER DOSE	60 MIN AFTER DOSE
1				
2				
3				
4				
GROUP A MEAN 0.5 MG/KG	2021.0	2085.0	2380.0	2552.0
5				
6				
GROUP B MEAN 0.75MG/KG	1325.0	1250.0	1250.0	1175.0
7				
8				
10				
GROUP C MEAN 1.0 MG/KG	2300.0	2200.0	2000.0	2100.0
9				
11				
12				
GROUP D MEAN 1.5 MG/KG	1531.3	1768.5	1750.0	1999.5

[a] AORTIC DP/DT RATIO WAS OBTAINED IN PLACE OF THE LEFT VENTRICULAR DP/DT RATIO AND IS DISPLAYED IN TABLE 27.
[b] DATA WAS NOT RECORDED.

Figure 2: MEAN PERCENT CHANGE OF dP/dt RATIO FOR EACH DOSE GROUP

Miller : R-818V0003-01



STUDY: R-818V-003-01
INVESTIGATOR: PAUL H. MILLER, MD

TABLE 13

P-A + A-H INTERVAL (MSEC)[a]

	PATIENT NUMBER	BASELINE VALUE	10 MIN AFTER DOSE	30 MIN AFTER DOSE	60 MIN AFTER DOSE
	1				
	2				
	4				
GROUP A MEAN 0.5 MG/KG		126.7	128.3	124.7	128.3
	5				
	6				
GROUP B MEAN 0.75MG/KG		106.0	112.0	100.0	102.0
	7				
	8				
	10				
GROUP C MEAN 1.0 MG/KG		142.7	145.0	135.7	128.0
	9				
	12				
GROUP D MEAN 1.5 MG/KG		109.0	116.5	117.5	115.5

[a] HIS BUNDLE ELECTROGRAMS WERE NOT OBTAINED FOR PATIENTS 3 AND 11.
[b] DATA NOT RECORDED.

STUDY: R-8139-022-01
INVESTIGATOR: MONTY BODENHEIMER, MD

TABLE 14

SUMMARY OF EFFECTS OF FLECAINIDE ACETATE ON RIGHT AND LEFT VENTRICULAR EJECTION FRACTIONS AND WALL MOTIONS BY DOSING GROUP

PREDRUG		POSTDRUG					
		EJECTION FRACTION			WALL MOTION		
		NO. OF PATIENTS			NO. OF PATIENTS		
WALL MOTION	NO. OF PATIENTS	INCREASE[a]	DECREASE[a]	NO CHANGE[b]	IMPROVED	WORSENED	NO CHANGE
0.7 MG/KG (n=1)							
RIGHT VENTRICLE							
NORMAL	0	0	0	0	0	0	0
ABNORMAL	1	1	0	0	0	0	1
LEFT VENTRICLE							
NORMAL	0	0	0	0	0	0	0
ABNORMAL	1	1	0	0	0	0	1
1.0 MG/KG (n=4)							
RIGHT VENTRICLE							
NORMAL	3	1	1	1	0	1	2
ABNORMAL	1	0	0	1	0	0	1
LEFT VENTRICLE							
NORMAL	3	0	2	1	0	1	2
ABNORMAL	1	0	0	1	0	1	0
1.5 MG/KG (n=5)							
RIGHT VENTRICLE							
NORMAL	5	0	4	1	0	3	2
ABNORMAL	0	0	0	0	0	0	0
LEFT VENTRICLE							
NORMAL	2	0	0	2	0	0	2
ABNORMAL	3	0	3	0	0	3	0
2.0 MG/KG (n=10)							
RIGHT VENTRICLE							
NORMAL	9	1	7	1	0	5	4
ABNORMAL	1	0	1	0	0	0	1
LEFT VENTRICLE							
NORMAL	6	2	3	1	0	4	2
ABNORMAL	4	0	3	1	1	3	0

[a] Includes changes of 4% or more from predrug to postdrug ejection fraction.
[b] Includes changes of 3% or less in ejection fractions.

STUDY: R-818V-022-01
INVESTIGATOR: MONTY RODENHEIMER, MD

TABLE 15

SUMMARY OF EFFECT OF FLECAINIDE ACETATE ON SYSTEMIC PRESSURE, HEART RATE, AND RIGHT AND LEFT VENTRICULAR EJECTION FRACTION BY DOSING GROUP

AGE	BLOOD PRESSURE (MMHG) SYSTOLIC PRE	SYSTOLIC POST	DIASTOLIC PRE	DIASTOLIC POST	HEART RATE PRE	HEART RATE POST	RVEF (%)[a] PRE	RVEF (%)[a] POST	LVEF (%)[b] PRE	LVEF (%)[b] POST
0.7 MG/KG DOSE (n=1)										
54	140	125	90	70	76	75	12	27	17	21
1.0 MG/KG DOSE (n=4)										
56.5	140.0	135.0	82.5	85.5	78.8	78.8	30.0	27.5	58.8	51.5
	± 4.0	± 22.7	± 19.6	± 6.5	± 6.4	± 6.7	± 12.5	± 6.3	± 8.2	± 21.3	± 18.8
		p=0.092		p=0.092		p=1.00		p=0.63		p=0.15
1.5 MG/KG DOSE (n=5)										
54.0	140.0	139.2	89.0	90.0	70.6	72.8	31.2	26.2	64.4	56.4
± 3.7	± 16.2	± 21.5	± 9.6	± 8.6	± 10.8	± 9.8	± 3.4	± 3.8	± 12.4	± 18.6
		p=0.88		p=0.71		p=0.18		p=0.019		p=0.098
2.0 MG/KG DOSE (n=10)										
52.4	138.4	144.9	89.3	98.0	69.9	71.9	33.0	24.9	65.0	59.8
± 8.3	± 21.1	± 24.1	± 10.2	± 12.3	± 11.9	± 7.9	± 6.5	± 5.4	± 7.3	± 11.8
		p=0.25		p=0.0083		p=0.52		p=0.0034		p=0.14

[a] RVEF = Right ventricular ejection fraction.
[b] LVEF = Left ventricular ejection fraction.

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STUDY: R-818V-022-01
INVESTIGATOR: MONTY BODENHEIMER, MD

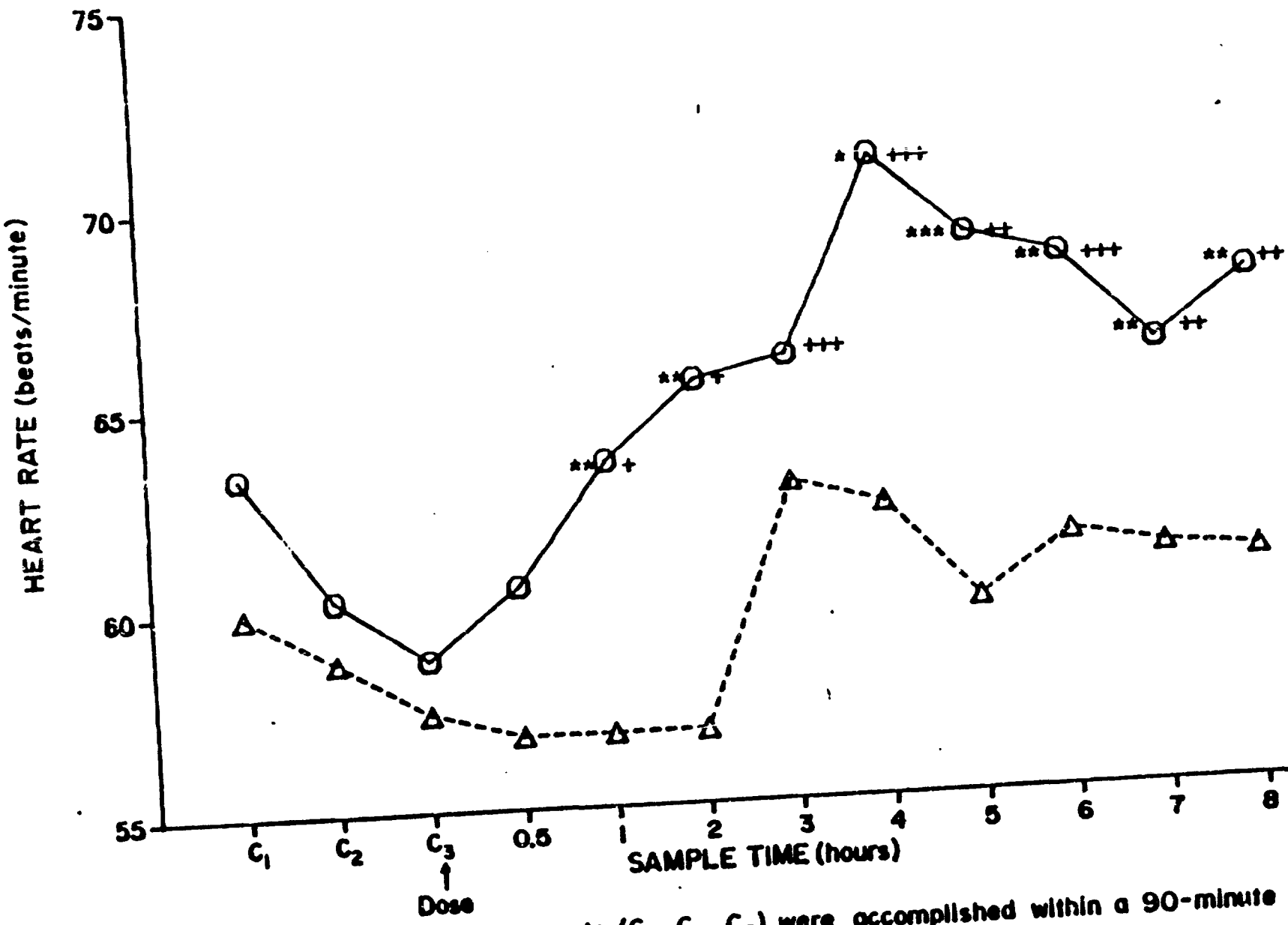
TABLE 16

MEAN VALUES OF HEART RATE AND BLOOD PRESSURE BY FLECAINIDE DOSING GROUP

PROCEDURE SCHEDULE		HEART RATE (±SD)	BLOOD PRESSURE SYSTOLIC (±SD)	BLOOD PRESSURE DIASTOLIC (±SD)
0.7 MG/KG DOSE (n=1)				
BASELINE (PREISOTOPE)	0-30 MIN	75	142	92
FIRST ISOTOPE PASS				
POSTISOTOPE	5-10 MIN	76	140	90
FLECAINIDE ADMINISTRATION				
POSTDRUG	5 MIN	78	125	75
	10 MIN	77	135	75
	14 MIN	75	125	70
SECOND ISOTOPE PASS	15-16 MIN	75	136	75
POSTISOTOPE	10 MIN	75	130	75
	20 MIN	73	135	78
	30 MIN			
1.0 MG/KG DOSE (n=4)				
BASELINE (PREISOTOPE)	0-30 MIN	76.8 (±10.5)	142.5 (±18.3)	85.2 (± 6.6)
FIRST ISOTOPE PASS				
POSTISOTOPE	5-10 MIN	78.8 (± 6.7)	140.0 (±22.7)	82.5 (± 6.5)
FLECAINIDE ADMINISTRATION				
POSTDRUG	5 MIN	80.0 (± 9.9)	133.5 (±15.5)	83.8 (± 8.5)
	10 MIN	82.0 (±10.9)	135.8 (±17.9)	84.0 (± 5.9)
	14 MIN	78.8 (±12.5)	135.0 (±19.6)	85.5 (± 6.4)
SECOND ISOTOPE PASS	15-16 MIN	79.0 (±11.0)	140.5 (±23.8)	90.2 (± 4.6)
POSTISOTOPE	10 MIN	76.0 (±11.0)	132.8 (±23.3)	89.8 (±11.8)
	20 MIN	76.2 (±11.5)	134.0 (±20.3)	88.2 (± 9.6)
	30 MIN			
1.5 MG/KG DOSE (n=5)				
BASELINE (PREISOTOPE)	0-30 MIN	71.2 (±10.6)	144.0 (±22.2)	89.4 (± 8.2)
FIRST ISOTOPE PASS				
POSTISOTOPE	5-10 MIN	70.6 (±10.8)	140.0 (±16.2)	89.0 (± 9.6)
FLECAINIDE ADMINISTRATION				
POSTDRUG	5 MIN	75.4 (± 6.1)	139.8 (±24.7)	91.4 (± 8.8)
	10 MIN	71.8 (± 5.9)	140.4 (±26.2)	89.8 (± 9.0)
	14 MIN	72.8 (± 9.8)	139.2 (±21.5)	90.0 (± 8.6)
SECOND ISOTOPE PASS	15-16 MIN	73.8 (±10.1)	140.0 (±17.9)	89.2 (±11.8)
POSTISOTOPE	10 MIN	68.4 (±11.8)	139.2 (±16.2)	90.4 (±11.8)
	20 MIN	72.4 (± 9.1)	145.6 (±18.1)	92.0 (±12.4)
	30 MIN			
2.0 MG/KG DOSE (n=10)				
BASELINE (PREISOTOPE)	0-30 MIN	69.4 (±12.6)	135.0 (±23.8)	88.0 (± 8.9)
FIRST ISOTOPE PASS				
POSTISOTOPE	5-10 MIN	69.9 (±11.9)	138.4 (±21.1)	89.3 (±10.2)
FLECAINIDE ADMINISTRATION				
POSTDRUG	5 MIN	73.3 (± 5.9)	140.5 (±20.9)	96.4 (±10.9)
	10 MIN	73.2 (± 8.1)	141.9 (±21.0)	97.2 (±11.4)
	14 MIN	71.9 (± 7.9)	144.9 (±24.1)	98.0 (±12.3)
SECOND ISOTOPE PASS	15-16 MIN	71.3 (± 7.1)	141.4 (±21.1)	92.5 (±13.8)
POSTISOTOPE	10 MIN	73.1 (± 6.8)	135 0 (±14.4)	92.9 (± 9.8)
	20 MIN	71.7 (± 8.1)	133.5 (±14.7)	95.1 (± 8.9)
	30 MIN			

Figure 3: MEANS OF HEART RATE IN SUBJECTS DURING M-MODE ECHOCARDIOGRAPHY

Hodges R-818-024-01



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with the last measurement (C_3) made just prior to dose.

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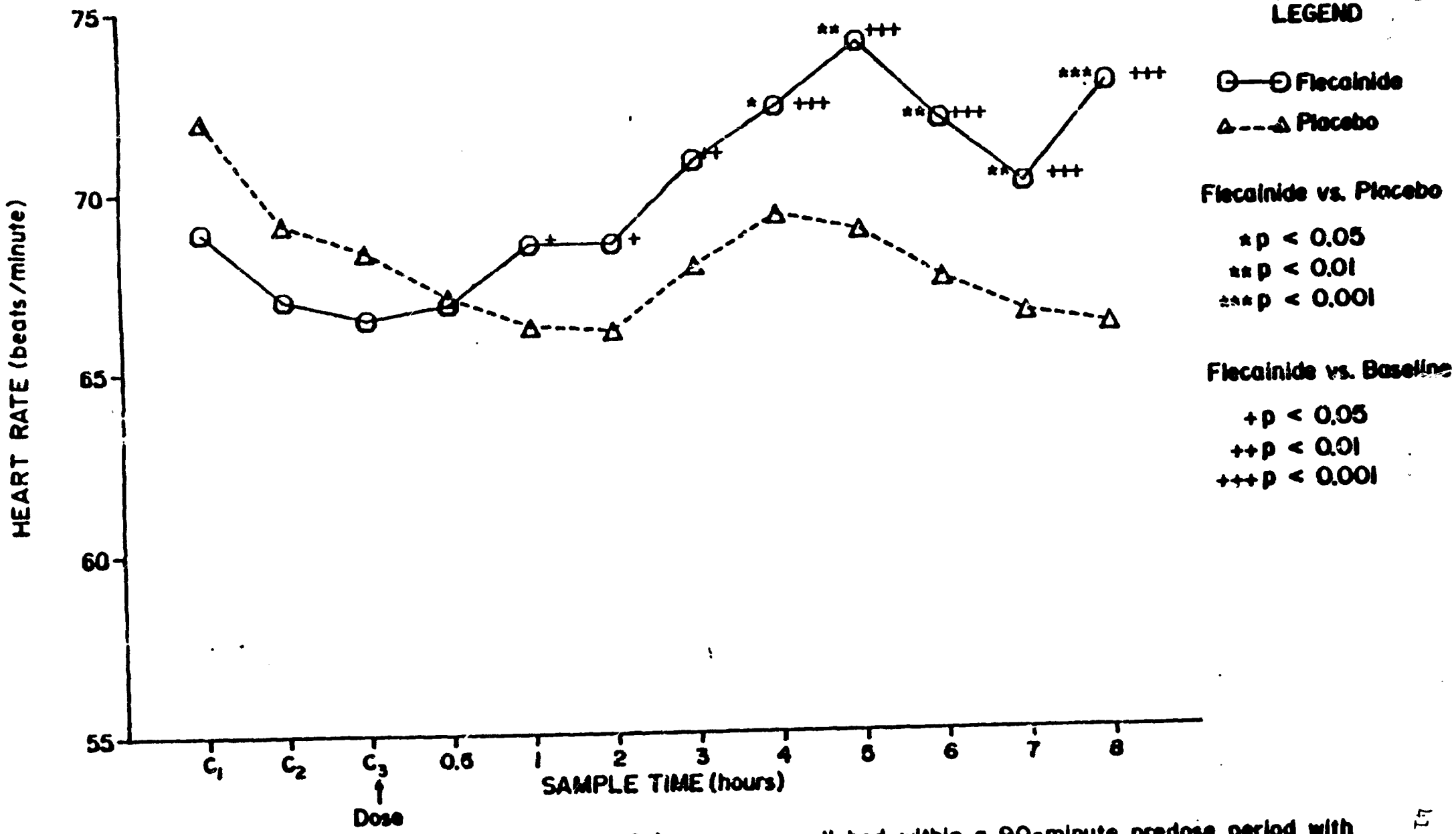
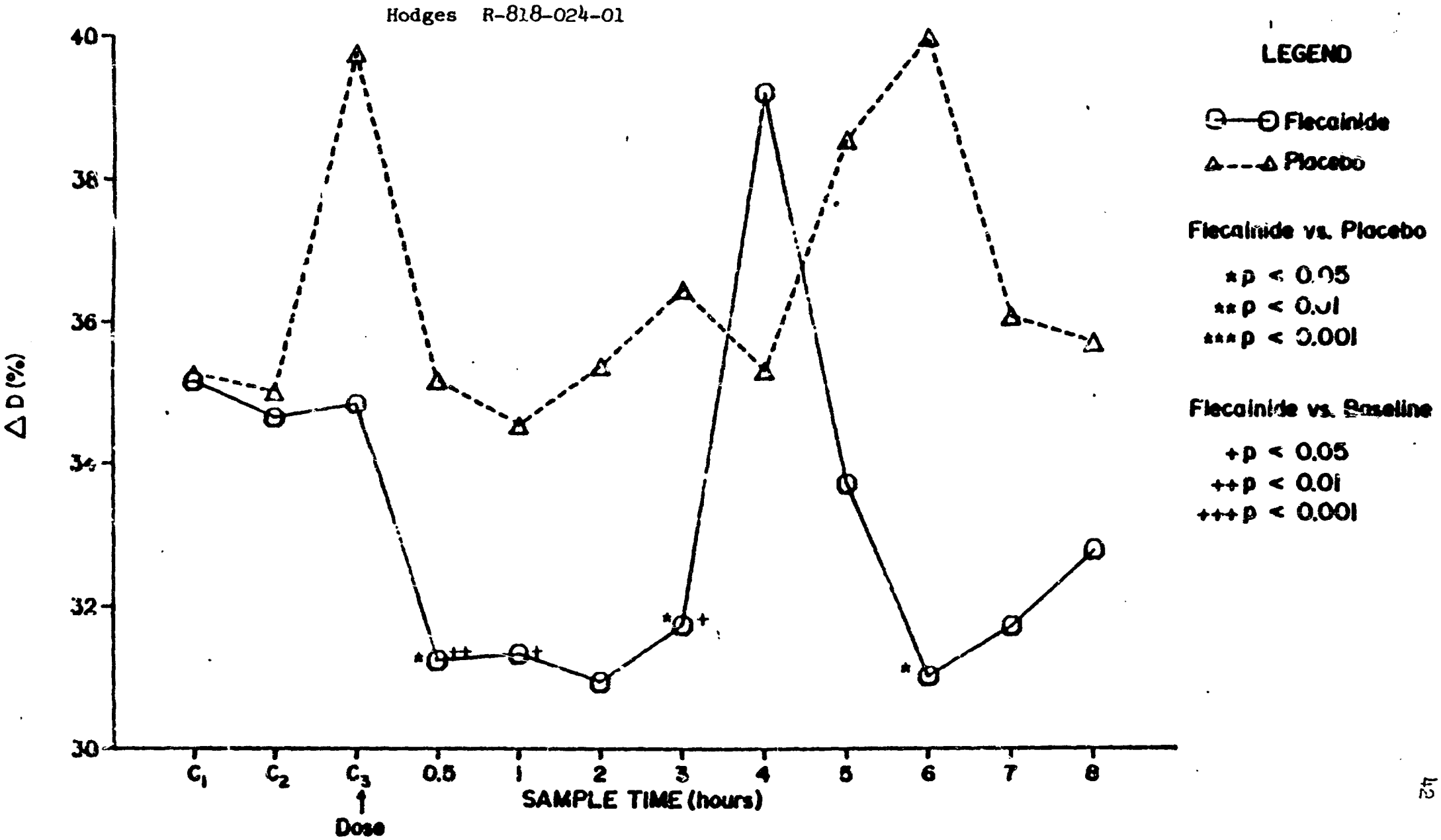
Figure 4: MEANS OF HEART RATE IN PATIENTS DURING M-MODE ECHOCARDIOGRAPHY

Hodgec R-818-024-01



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with the last measurement (C_3) made just prior to dose.

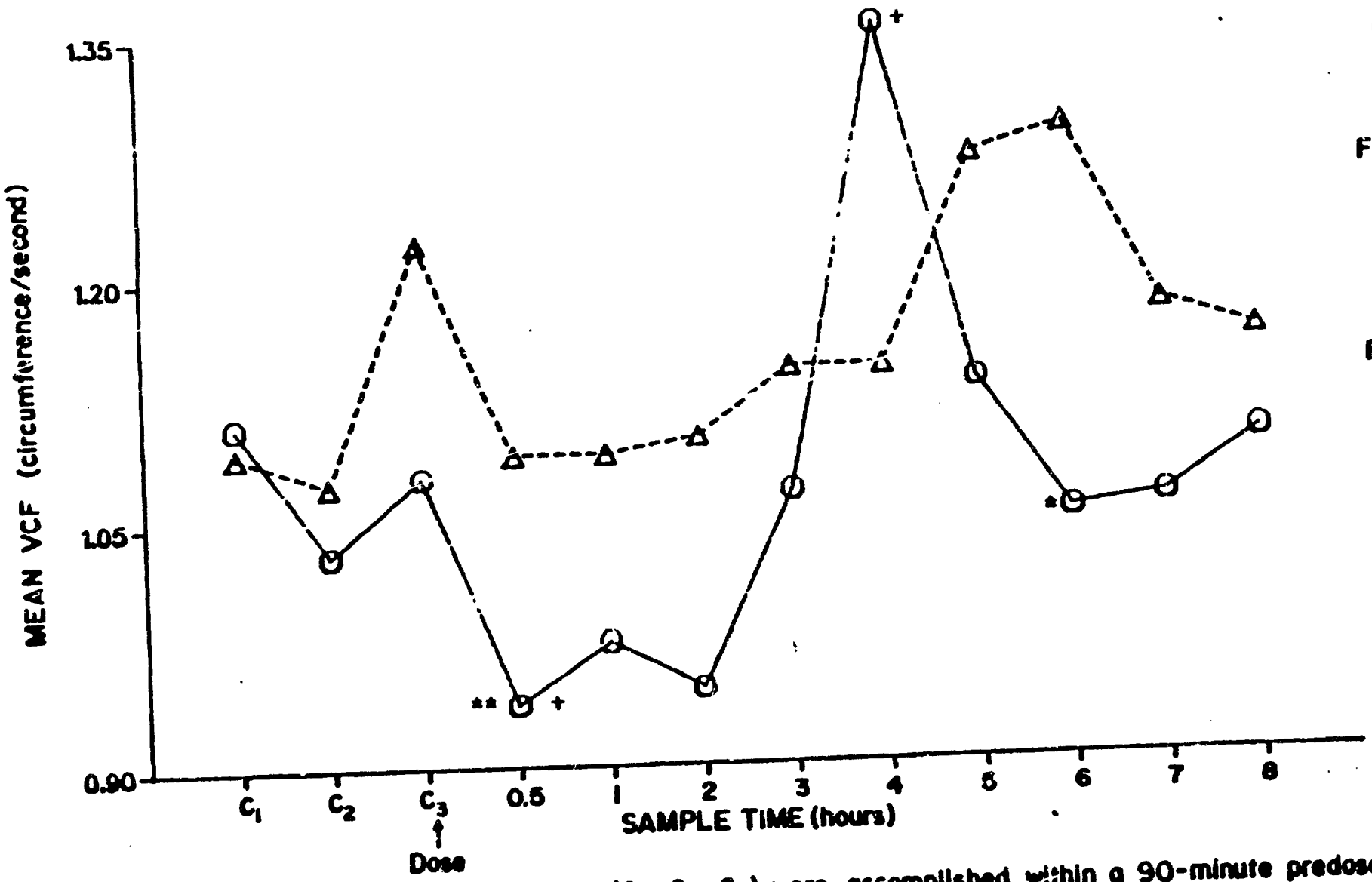
Figure 5: MEANS OF PERCENT SHORTENING OF LEFT VENTRICULAR DIAMETER (%ΔD) IN SUBJECTS M-MODE ECHOCARDIOGRAPHY DATA



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with

Figure 6: MEANS OF MEAN RATE OF CIRCUMFERENTIAL FIBER SHORTENING (MEAN VCF) IN SUBJECTS – M-MODE ECHOCARDIOGRAPHY DATA

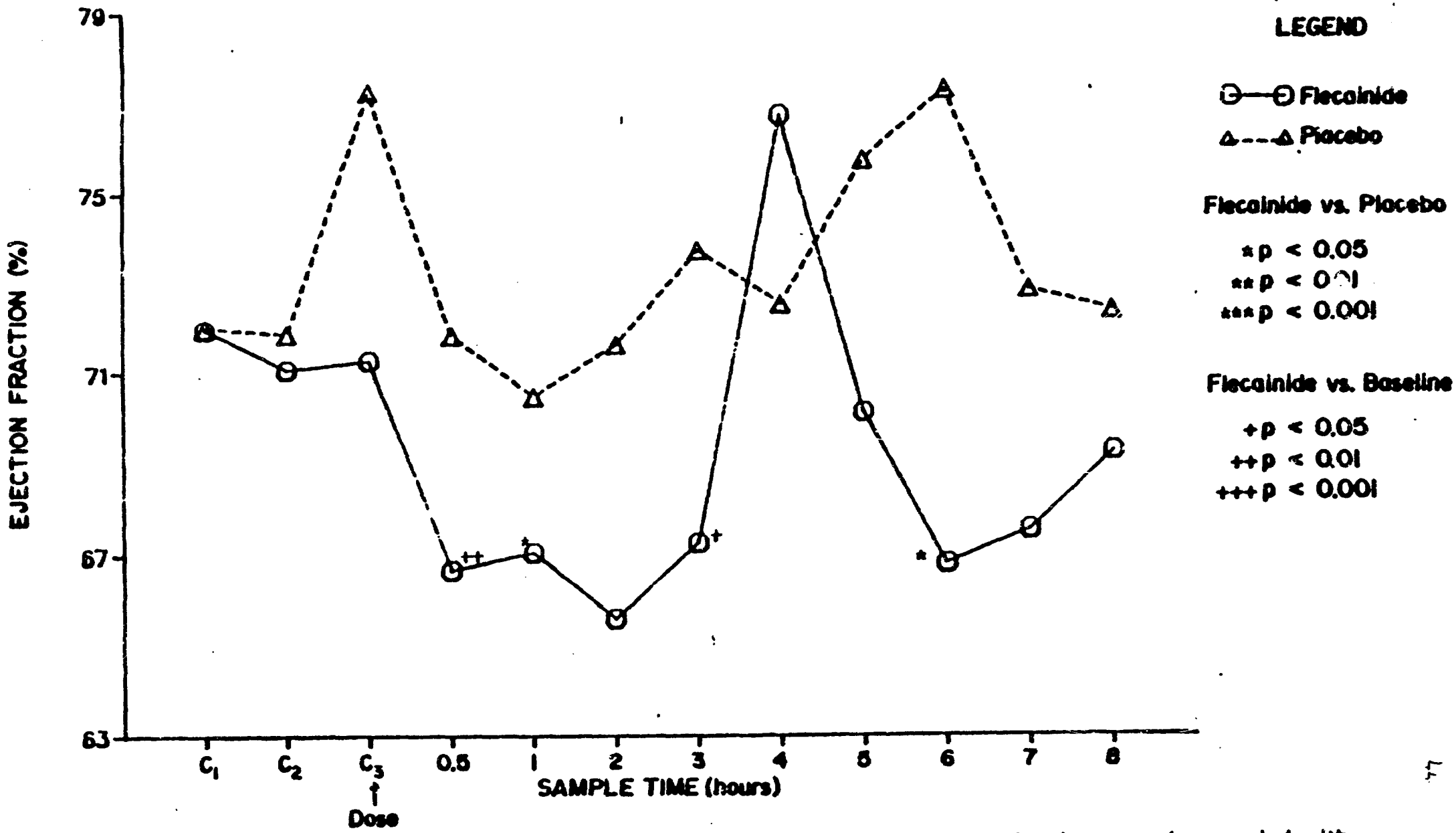
Hodges R-818-024-01



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with the last measurement (C_3) made just prior to dose.

Figure 7: MEANS OF EJECTION FRACTION IN SUBJECTS — M-MODE ECHOCARDIOGRAPHY DATA

Hodges R-818-024-01



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with the last measurement (C_3) made just prior to dose.

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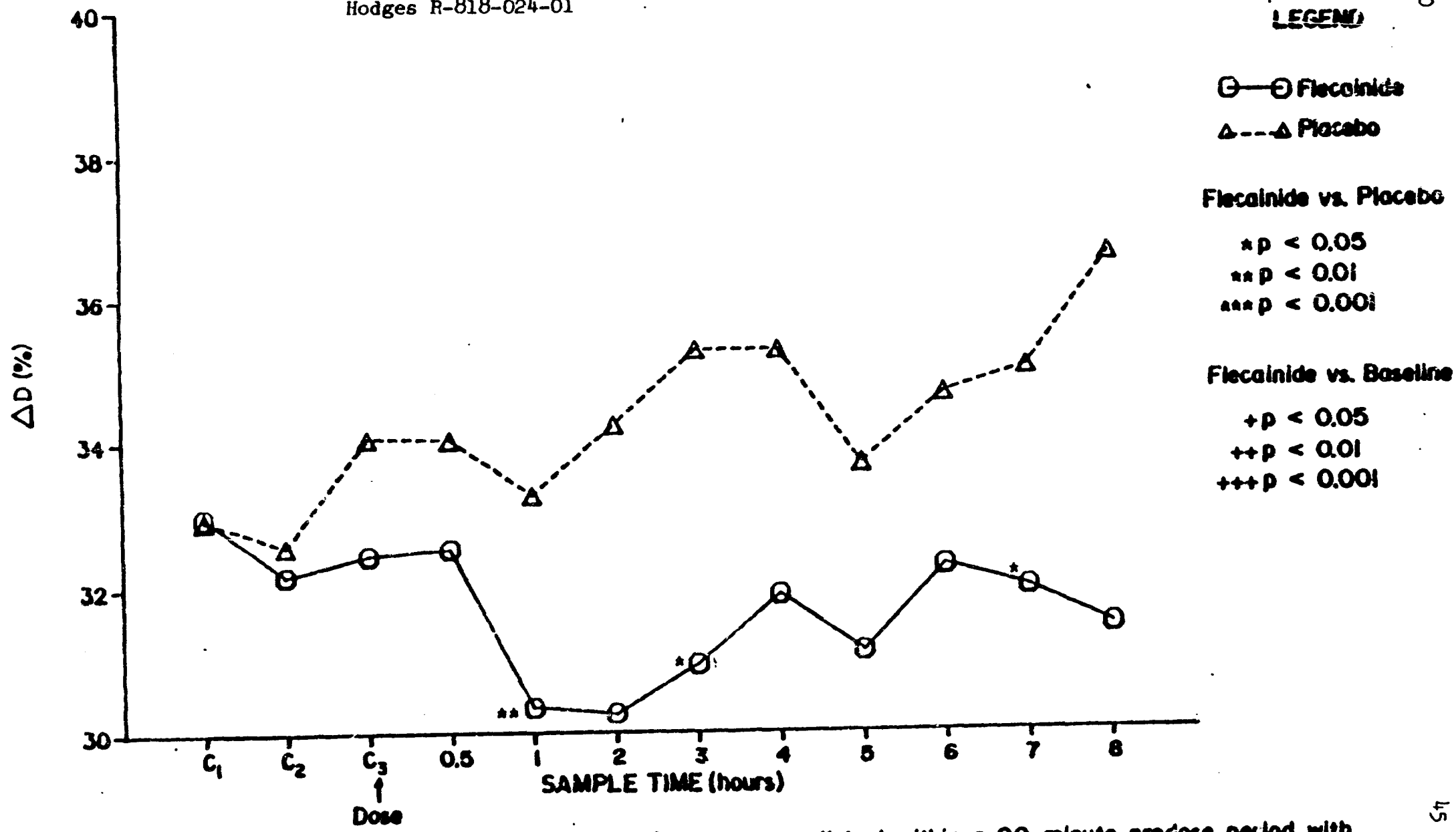
Figure 8: MEANS OF PERCENT SHORTENING OF LEFT VENTRICULAR DIAMETER (%ΔD) IN PATIENTS M-MODE ECHOCARDIOGRAPHY DATA

Hodges R-818-024-01



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with the last measurement (C_3) made just prior to dose.

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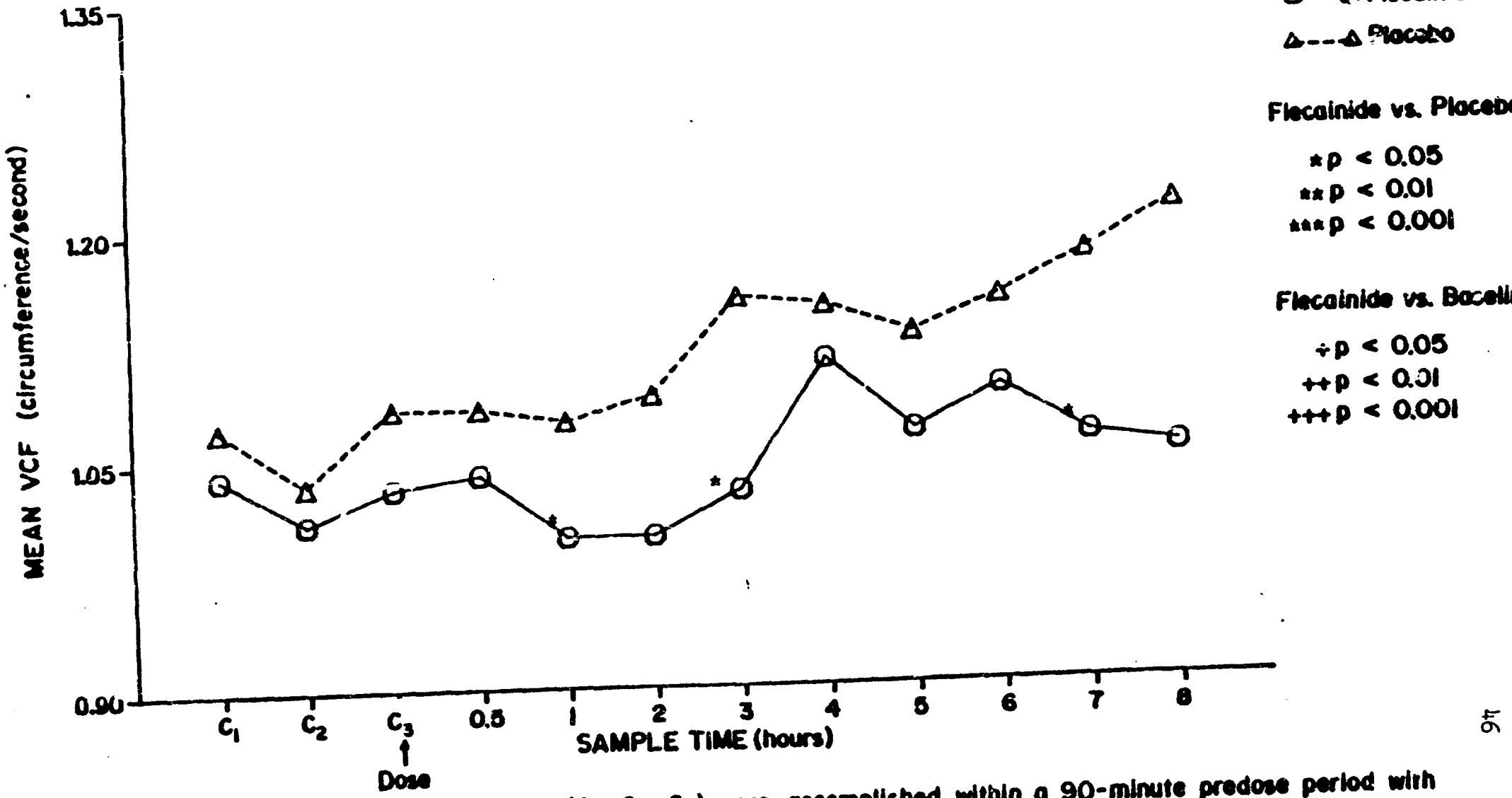
Figure 9: MEANS OF MEAN RATE OF CIRCUMFERENTIAL FIBER SHORTENING (MEAN VCF) IN PATIENTS – M-MODE ECHOCARDIOGRAPHY DATA

Hodges R-818-024-01



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with the last measurement (C_3) made just prior to dose.

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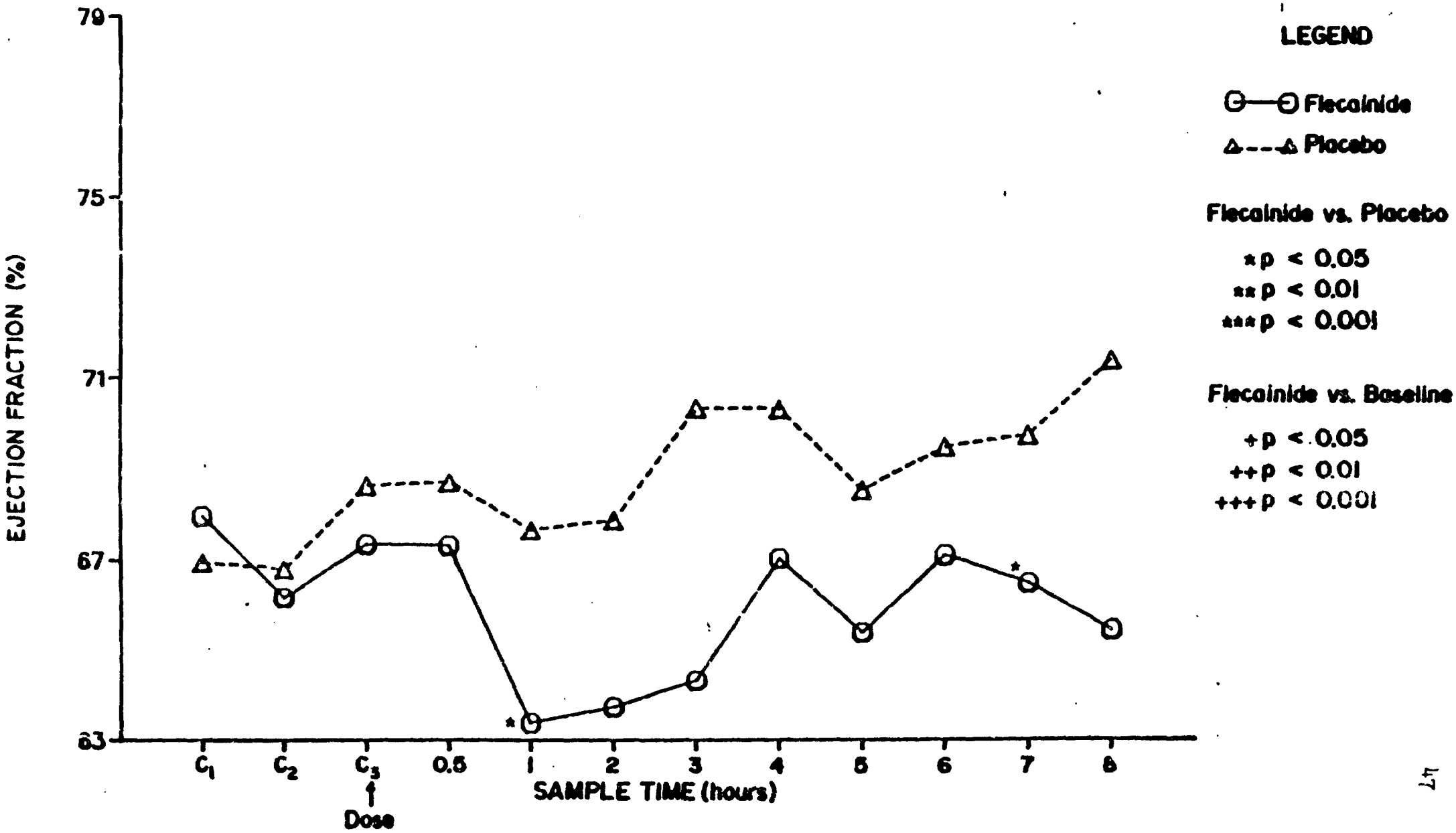
Figure 10: MEANS OF EJECTION FRACTION IN PATIENTS – M-MODE ECHOCARDIOGRAPHY DATA

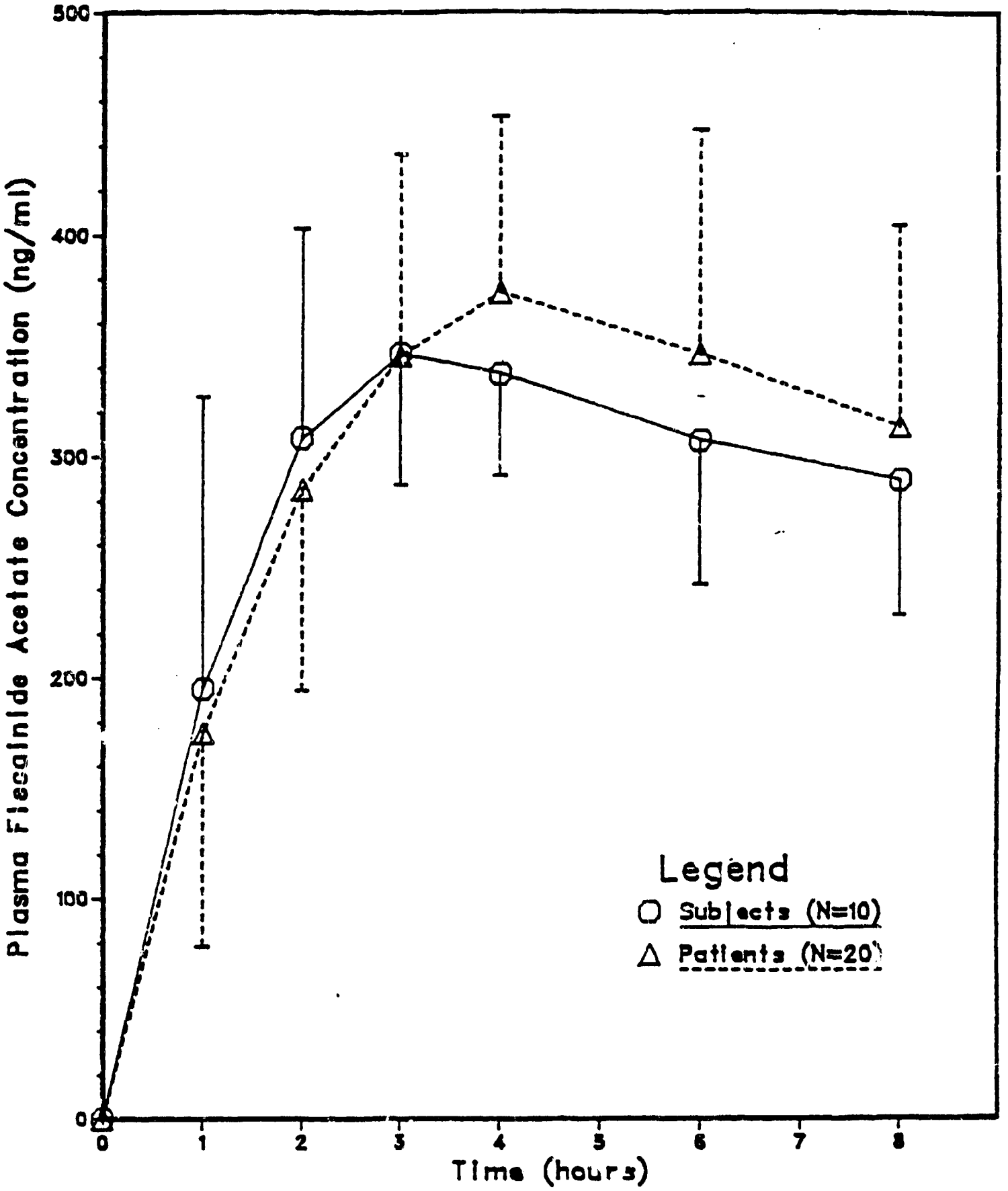
Hodges R-818-024-01



All control or predose measurements (C_1, C_2, C_3) were accomplished within a 90-minute predose period with

Figure 11: Mean Plasma Concentrations of Flecainide Acetate Following a Single 250 mg Oral Dose

Hodges R-818-024-01



STUDY: H-818-039-01
INVESTIGATOR: JOSEPH A. FRANCIOSA, MD

HEART RATE (BEATS/MIN) AT VARIOUS WORK LOAD LEVELS

TABLE 19

PATIENTS	ID NO	PREDRUG SUPINE	PREDRUG SITTING	PREDRUG MAXIMAL EXERCISE	2 HOURS POSTDOSE SUPINE	4 HOURS POSTDOSE SUPINE	4 HOURS POSTDOSE SITTING	4 HOURS POSTDOSE MAXIMAL EXERCISE	8 HOURS POSTDOSE SUPINE	24 HOURS POSTDOSE SUPINE	24 HOURS POSTDOSE SITTING	24 HOURS POSTDOSE MAXIMAL EXERCISE
	1											
	2											
	3											
	4											
	5											
	6											
	7											
	8											
	9											
	10											
	MEAN	73.9	77.6	127.6	77.1	80.8	85.1	136.2	86.5	77.5	83.2	132.4
	STD DEV	14.8	18.0	17.7	19.0	15.9	17.9	12.7	15.0	14.9	13.4	16.1

SUBJECTS	ID NO	PREDRUG SUPINE	PREDRUG SITTING	PREDRUG MAXIMAL EXERCISE	2 HOURS POSTDOSE SUPINE	4 HOURS POSTDOSE SUPINE	4 HOURS POSTDOSE SITTING	4 HOURS POSTDOSE MAXIMAL EXERCISE	8 HOURS POSTDOSE SUPINE	24 HOURS POSTDOSE SUPINE	24 HOURS POSTDOSE SITTING	24 HOURS POSTDOSE MAXIMAL EXERCISE
	101											
	102											
	103											
	104											
	105											
	106											
	107											
	108											
	109											
	MEAN	75.1	83.4	172.0	73.7	74.9	85.0	163.1	87.6	78.4	86.4	164.9
	STD DEV	12.2	9.6	24.9	12.3	8.4	12.8	32.9	9.7	9.7	13.4	25.7

STUDY: R-818-039-81
INVESTIGATOR: JOSEPH A. FRANCIOSA, MD

TABLE 20

DATA AT MAXIMUM WORK LOADS

PATIENTS

ID NO	PREDRUG					4 HOURS POSTDOSE					24 HOURS POSTDOSE				
	DUR	WORK	VCO2	VO2	RQ	DUR	WORK	VCO2	VO2	RQ	DUR	WORK	VCO2	VO2	RQ
1															
2															
3															
4															
5															
6															
7															
8															
9															
10															
MEAN	8:04	345	15.0	12.6	1.15	7:33	345	14.7	13.0	1.13	8:00	360	15.6	13.6	1.15
STD DEV	3:11	123	3.9	2.6	0.26	3:01	123	5.2	2.5	0.21	3:16	145	4.7	3.3	0.19

SUBJECTS

ID NO	PREDRUG					4 HOURS POSTDOSE					24 HOURS POSTDOSE				
	DUR	WORK	VCO2	VO2	RQ	DUR	WORK	VCO2	VO2	RQ	DUR	WORK	VCO2	VO2	RQ
101															
102															
103															
104															
105															
106															
107															
108															
109															
MEAN	16:36	683	27.5	26.4	1.05	14:10	600	24.6	23.8	1.03	15:24	650	26.1	24.8	1.06
STD DEV	2:42	109	3.8	4.4	0.14	3:29	130	6.4	5.7	0.10	2:19	106	4.0	4.3	0.12

NOTE: DUR = DURATION OF EXERCISE (MIN:SEC)
WORK = MAXIMAL WORK LOAD (KPM/MIN)
VCO2 = TOTAL BODY CO2 PRODUCTION (ML/KG/MIN)
VO2 = TOTAL BODY O2 CONSUMPTION (ML/KG/MIN)
RQ = RESPIRATORY QUOTIENT (VCO2 / VO2)

TABLE 21

Time to Peak Plasma Concentration, Peak Plasma Concentration, and Area Under the Plasma Concentration Versus Time Curve (AUC) for Flecainide Acetate Following Oral Administration of a Single, 200 mg Dose to Patients and Subjects

Patient/Subject Number	Dose (mg/kg)	Time to Peak Level (hours)	Peak Plasma Concentration (ng/ml)	Plasma AUC Value Zero to Infinity (ng.hours/ml)	AUC.kel per one mg/kg (ng/ml)
Congestive Heart Failure Patients					
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
Mean	2.79	5.0	210	6653	86.6
Std. Dev.	0.61	1.9	52	2692	26.0
Healthy Subjects					
101					
102					
103					
104					
105					
106					
107					
108					
109					
Mean	2.86		216	5077	93.6
Std. Dev.	0.51	2.1	45	1428	30.5

a Value obtained by interpolation between adjacent time points.

NDA 18-830
R-818-039-01
Investigator: Joseph A. Franciosa, MD

TABLE 22

Plasma Pharmacokinetic Parameters of Flecainide Acetate Following Oral Administration of a Single, 200 mg Dose to Patients and Subjects

Patient/Subject Number	Plasma Half-Life (hours)	Elimination Rate Constant ($hours^{-1}$)	Plasma Clearance[a] (ml/min/kg)	Volume of Distribution[b] (l/kg)
Congestive Heart Failure Patients				
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
Mean	19.4	0.0379	8.1	12.4
Std. Dev.	5.2	0.0095	3.5	3.2
Healthy Subjects				
101				
102				
103				
104				
105				
106				
107				
108				
109				
Mean	13.8	0.0523	10.2	11.7
Std. Dev.	2.9	0.0108	3.8	3.6

a Plasma clearance or total body clearance is the dose divided by the plasma AUC from zero to infinity.

b Apparent volume of distribution is the dose divided by the product of the plasma AUC from zero to infinity and the elimination rate constant.

FIGURE 12

R-818-054-01 SINGH
Means of Heart Rate (beats per minute)

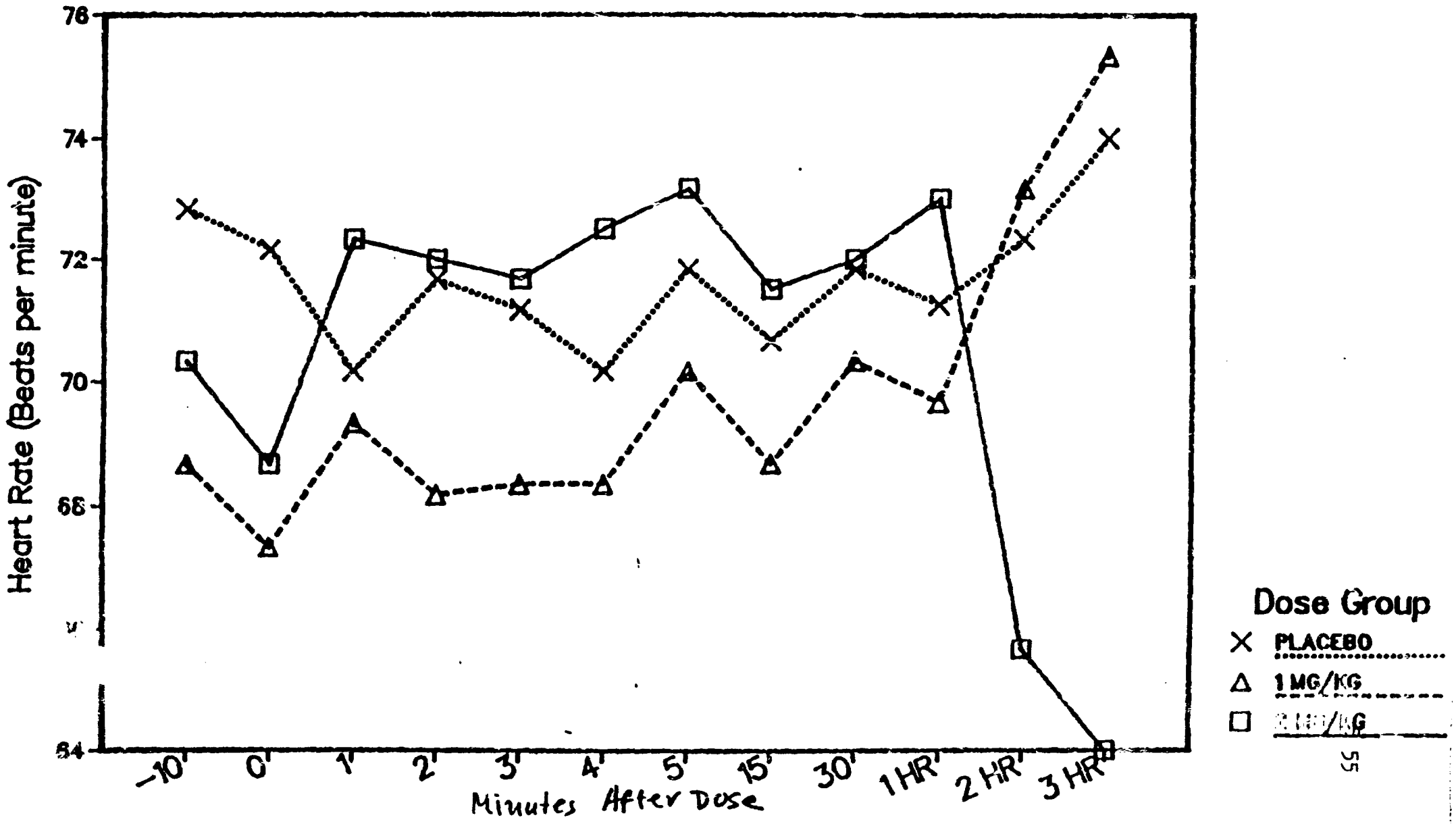


FIGURE 23

R-818-054-01 SINGH
Means of Corrected QT Interval (secs)

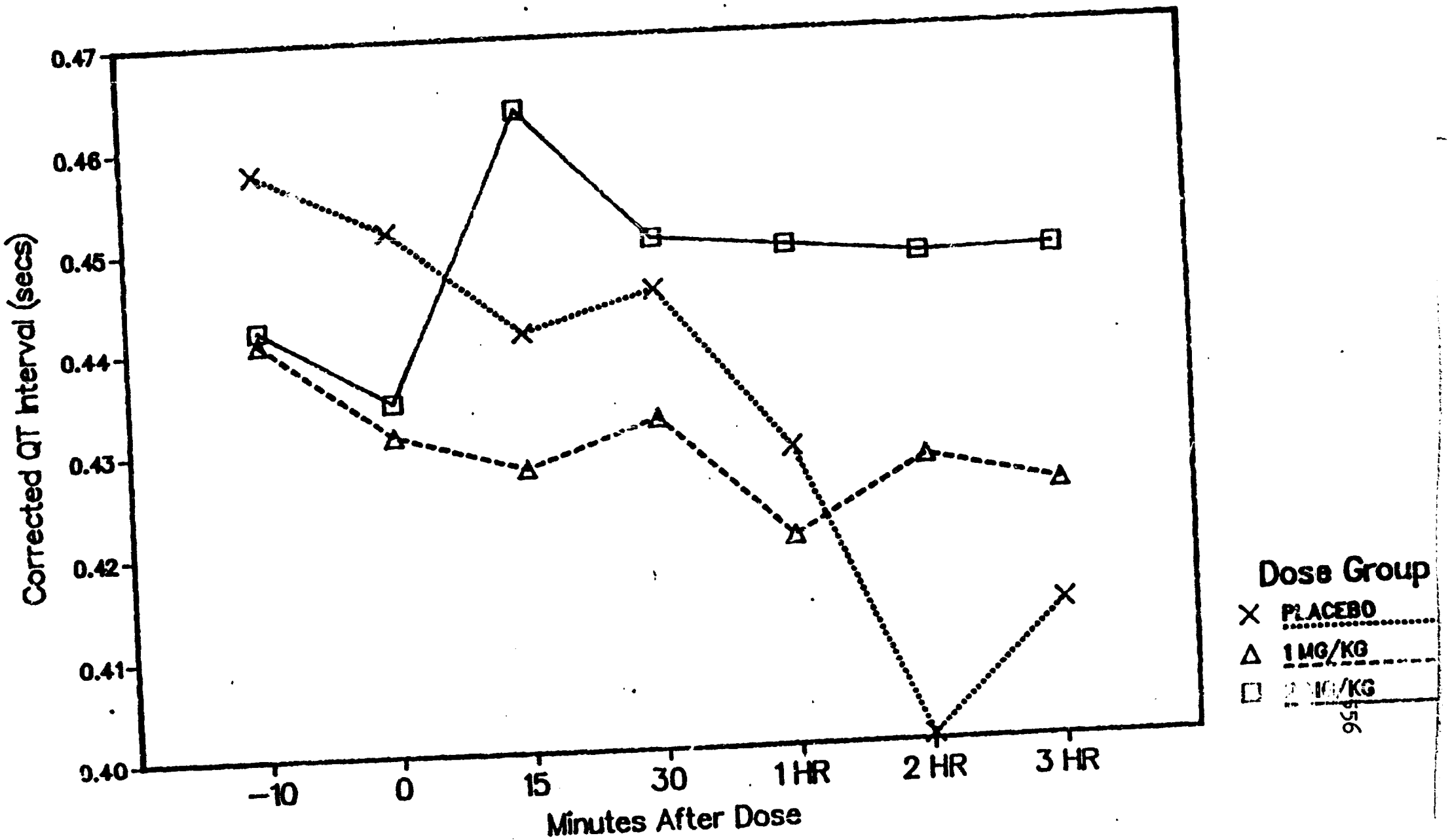


FIGURE 14

R-818-054-01 SINGH
Means of Systolic Blood Pressure (mmHg)

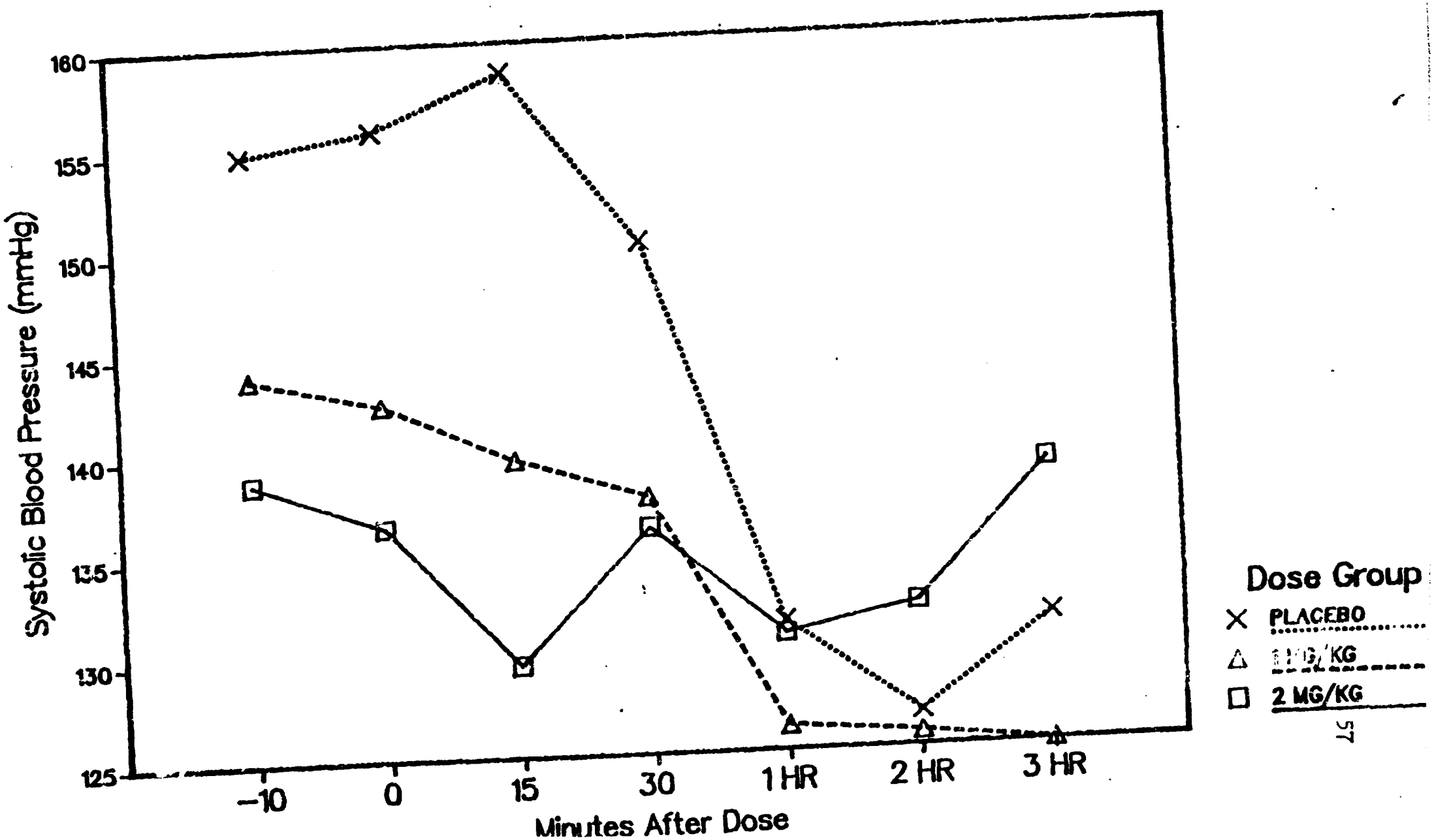


FIGURE 15

R-818-054-01 SINGH
Means of Diastolic Blood Pressure (mmHg)

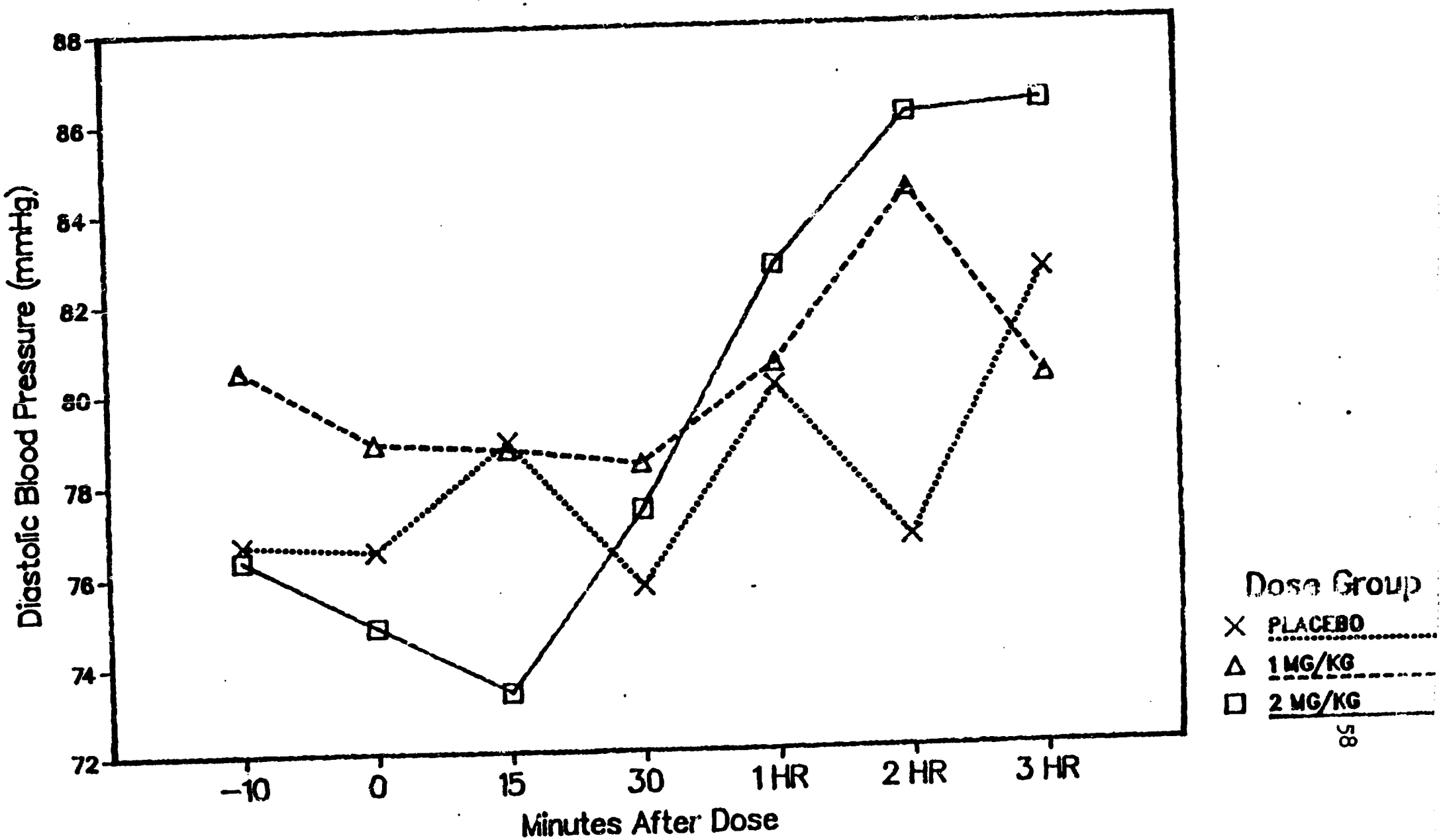


FIGURE 16

R-818-054-01 SINGH
Means of Thermodilution Stroke Volume (ml)

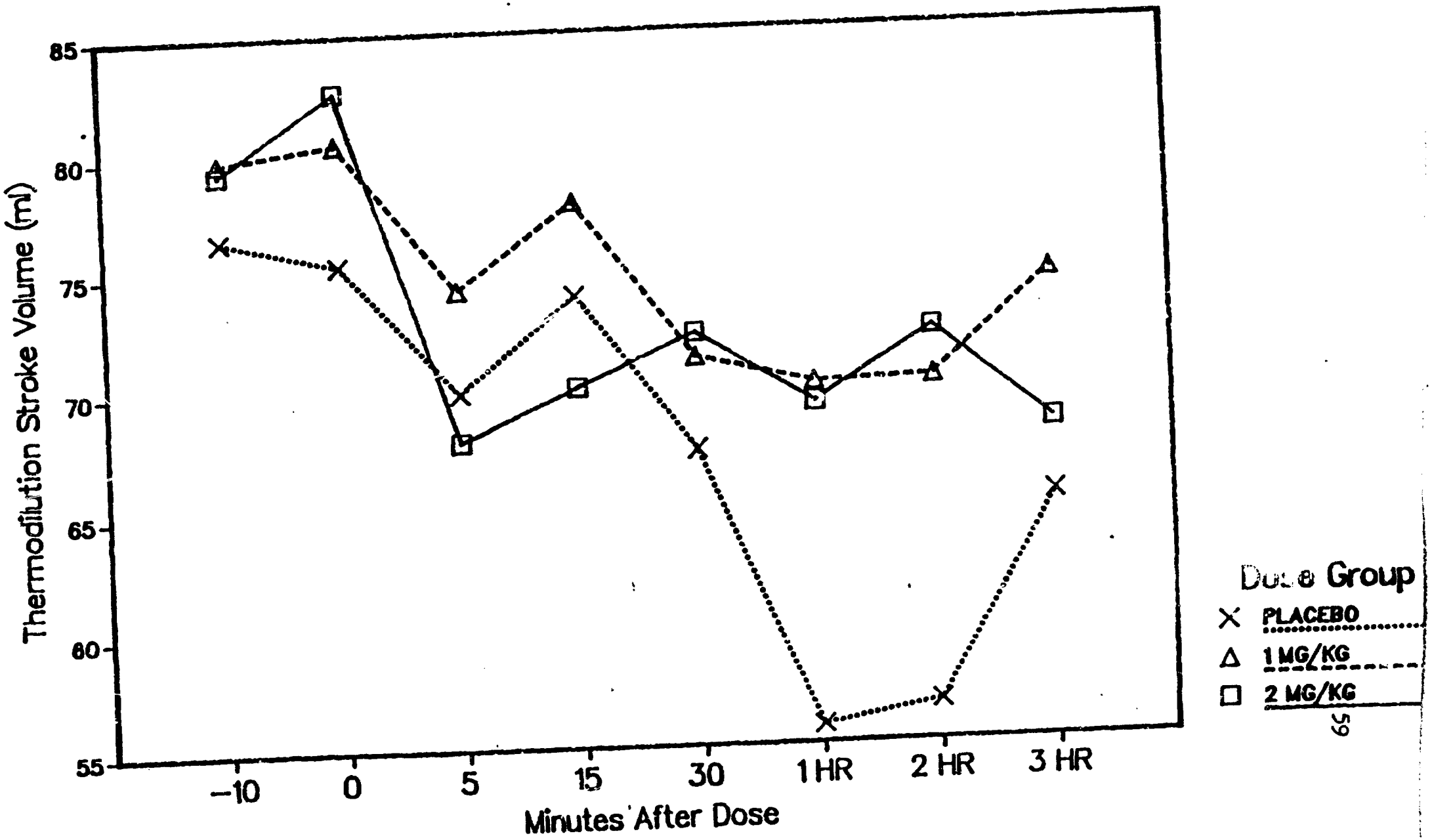


FIGURE 17

R-818-054-01 SINGH
Means of Stroke Work (gram meters)

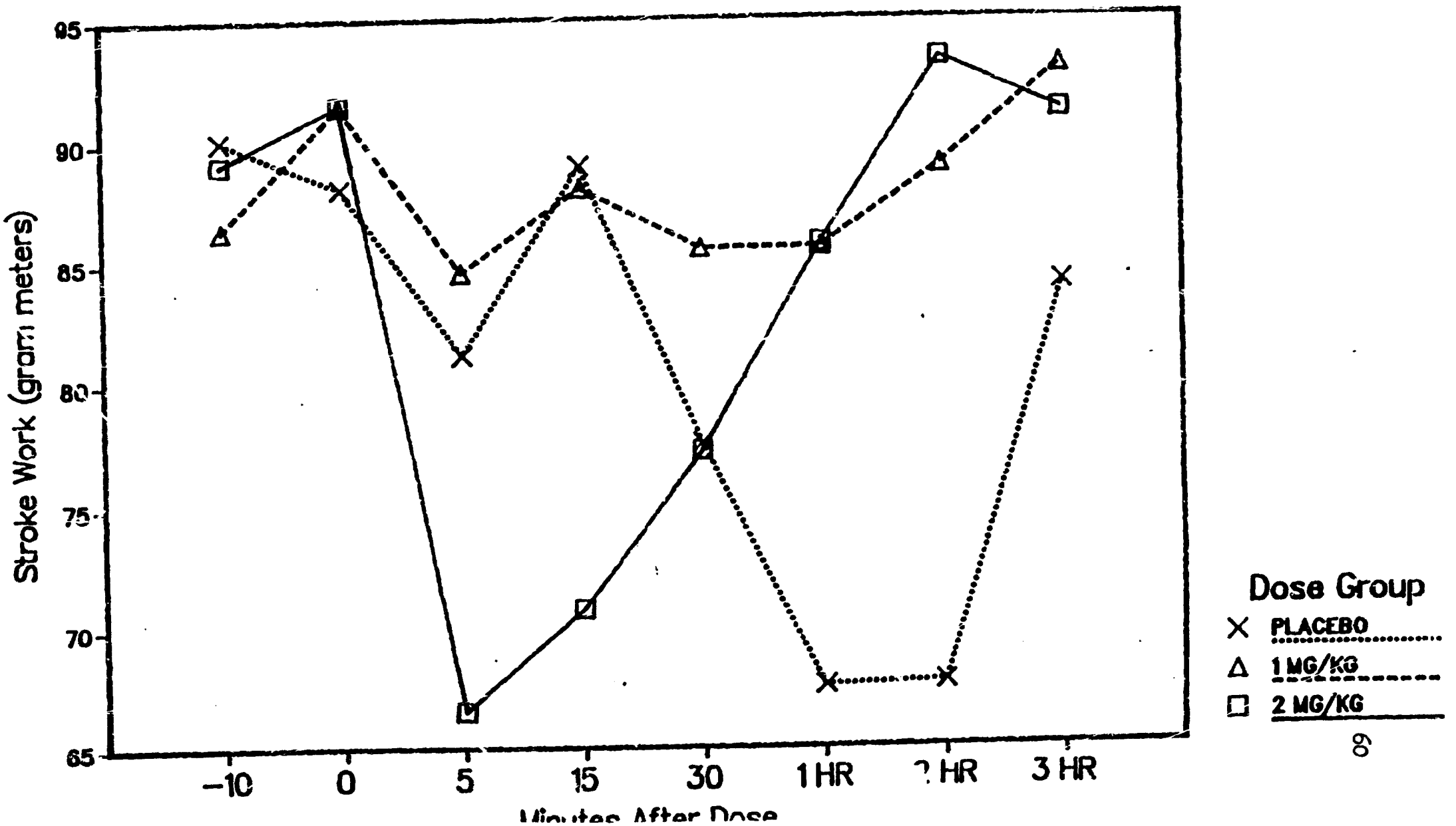


FIGURE 18

R-818-054-01 SINGH
Means of Left Ventricular Systolic Pressure (mmHg)

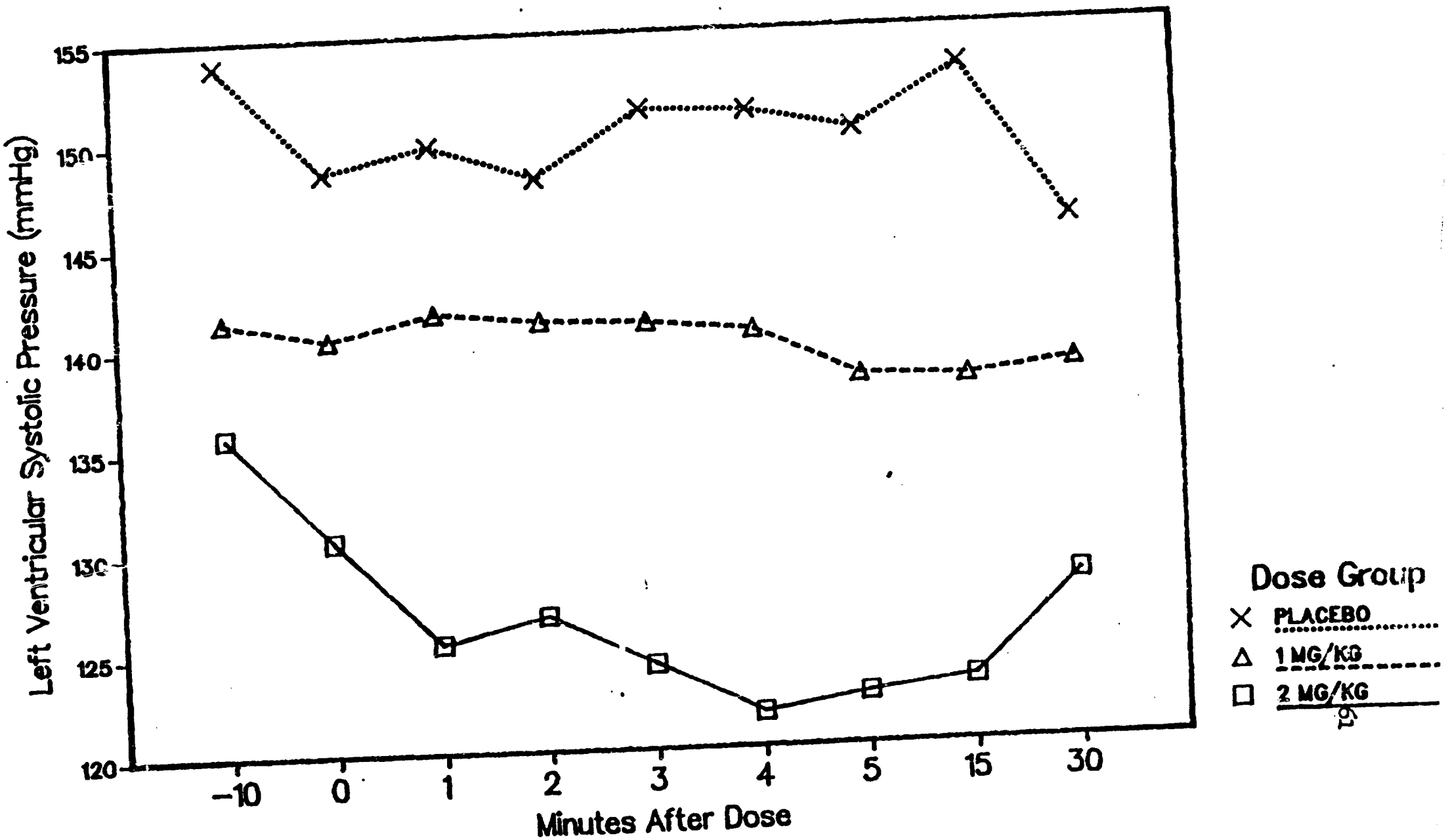


FIGURE 19

R-818-054-01 SINGH
Means of Left Ventricular End Diastolic Pressure (mmHg)

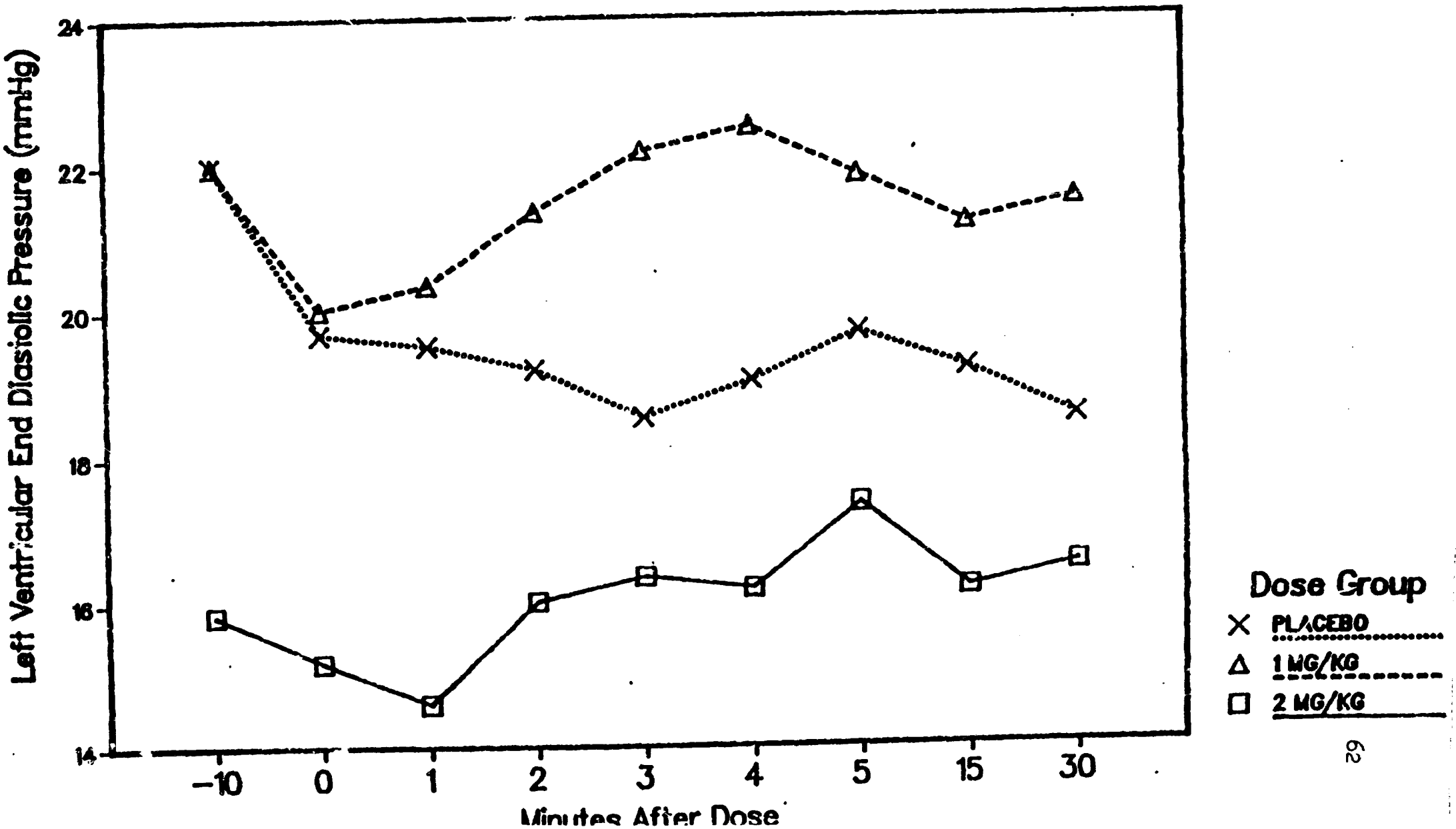


FIGURE 20

R-818-054-01 SINGH
Means of Pulmonary Artery Systolic Pressure (mmHg)

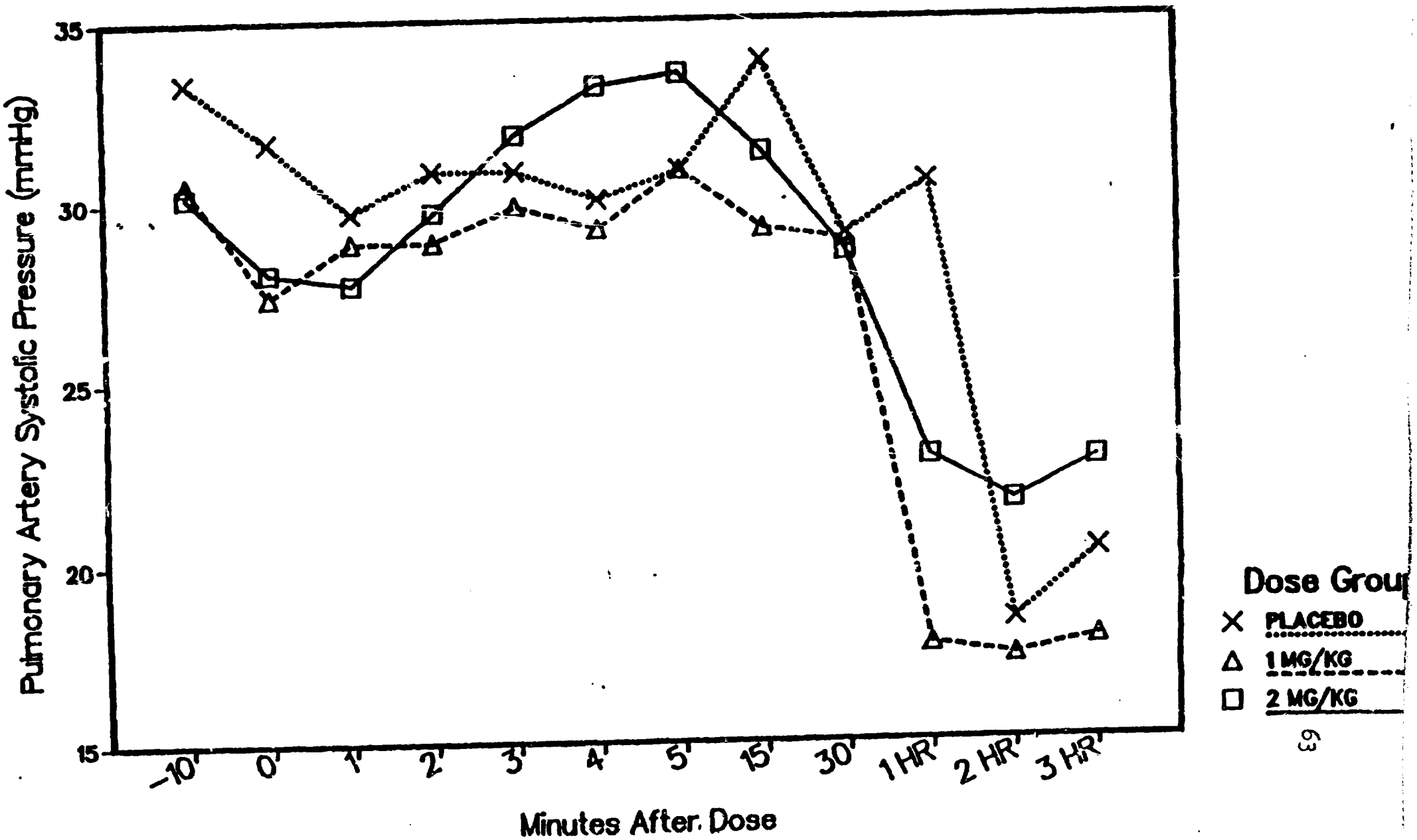


FIGURE 24

R-818-054-01 SINGH
Means of Pulmonary Wedge Pressure (mmHg)

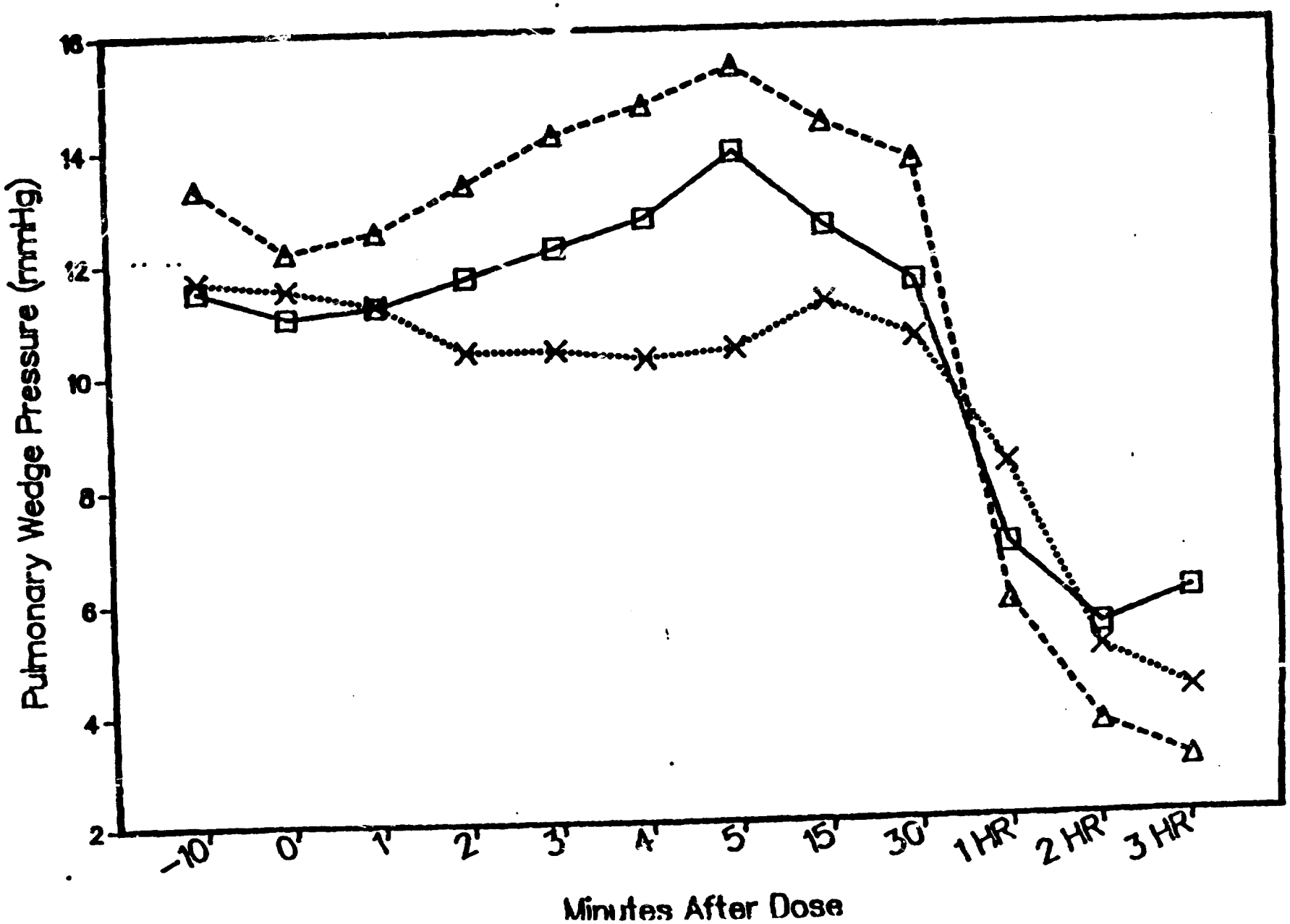


Figure 22:Hemodynamic effects of flecainide

V. Legrand et al.

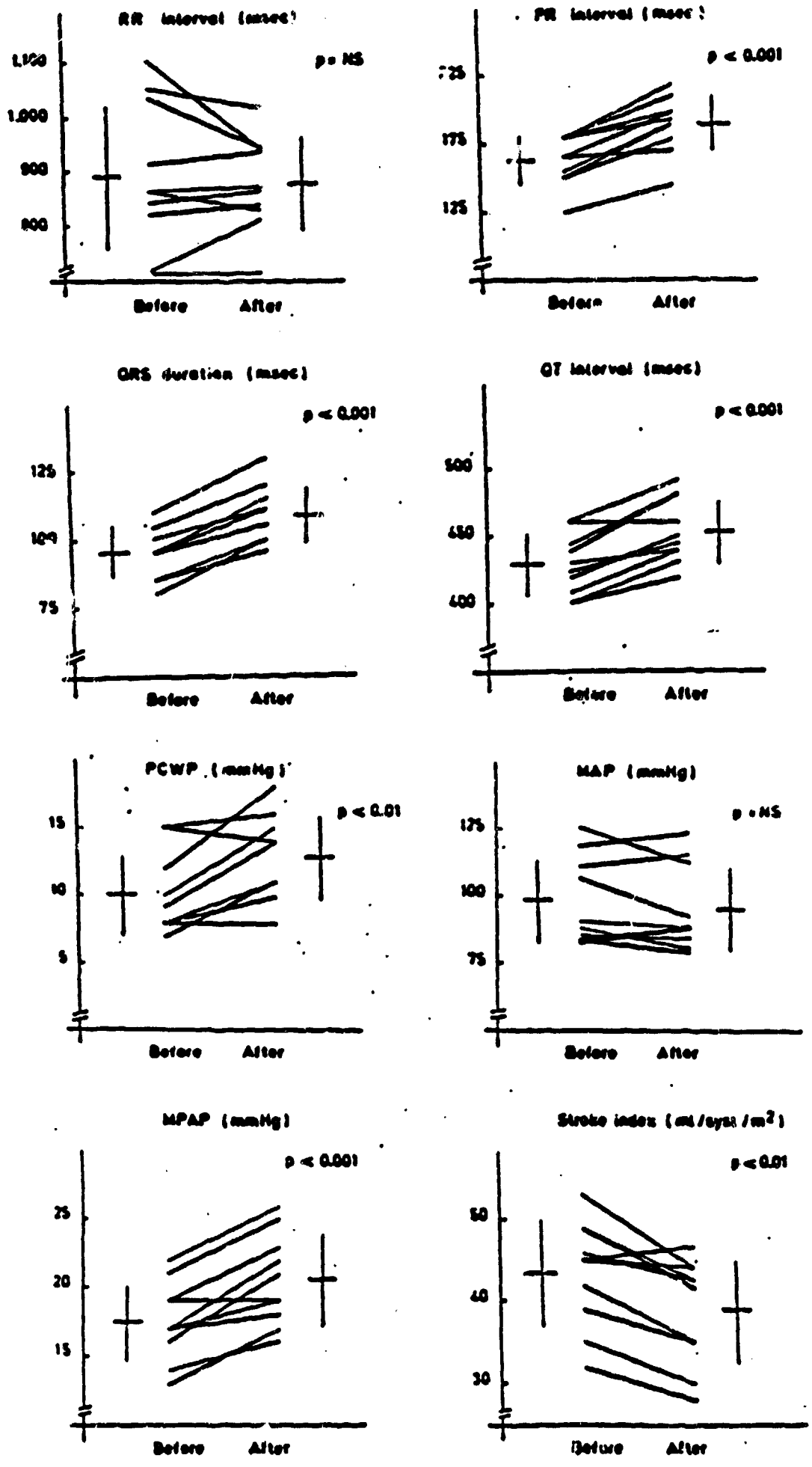


Figure 22 : Hemodynamic effects of flecainide
V. Legrand (continued)

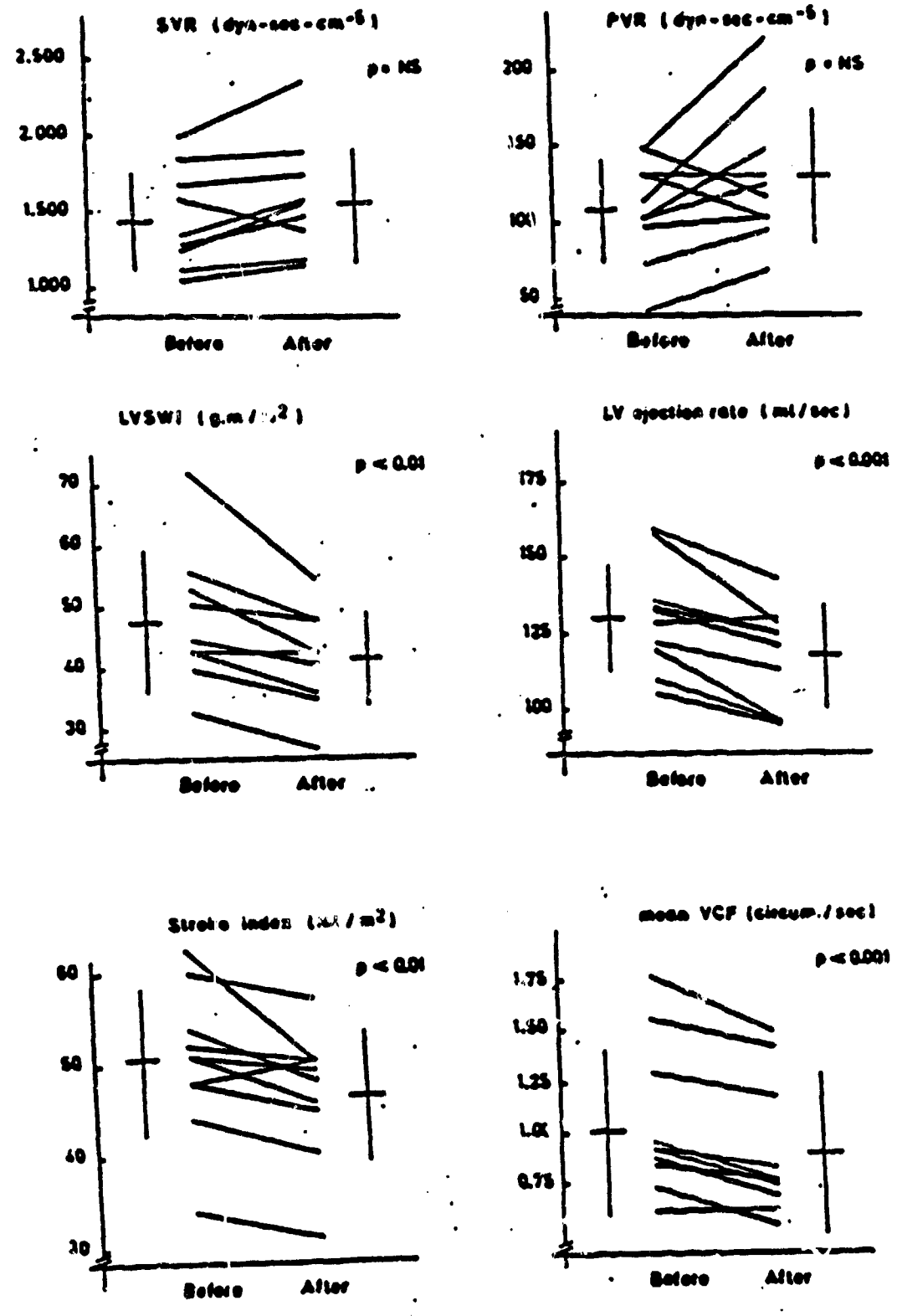
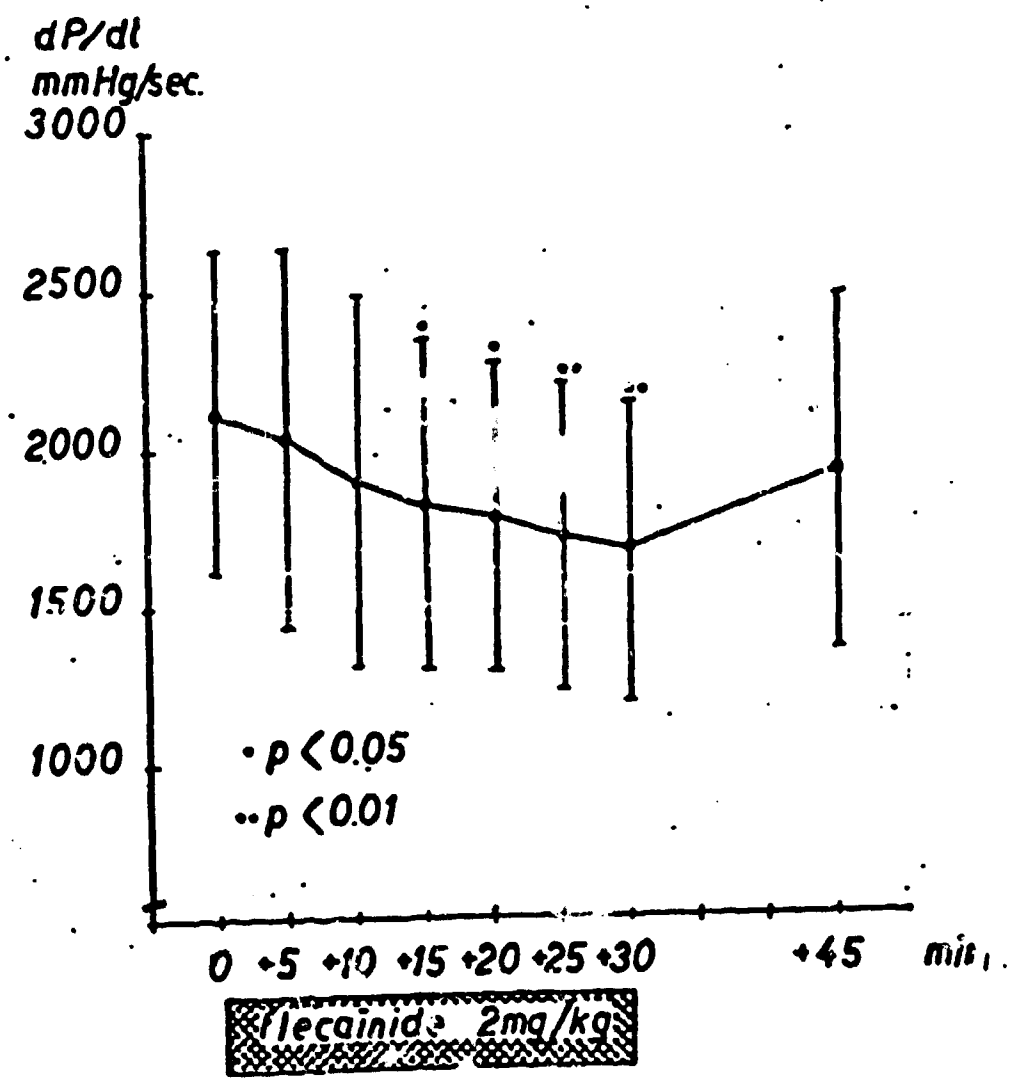


Figure 23: Hemodynamic data (V. Legrand)

Mean variations of dp/dt observed during flecainide infusion and 45 minutes after the end of injection.



The p value indicated is the level of significance of t test for paired data, comparison is made with the basal value before flecainide infusion.

STUDY: R-918-015-01
INVESTIGATOR: RICHARD H. KELFANT, MD

TABLE 24

HIS BUNDLE ELECTROGRAM DATA FOR THE FIVE PATIENTS WITH UNDERLYING CONDUCTION ABNORMALITIES ON PRESTUDY ECG

Patient Number	ECG	PA Interval (msec) Minutes Postdose					A-H Interval (msec) Minutes Postdose					H-V Interval (msec) Minutes Postdose				
		Control	10	20	30	40	Control	10	20	30	40	Control	10	20	30	40
1	'legree lock															
3	Left anterior hemiblock															
5	Left bundle branch block															
7	Right bundle branch block and bifasicular block															
11	Right bundle branch block and bifasicular block															
Mean difference		5.00	3.80	5.00			3.75	5.60	0.00			6.25	7.60	2.00		
Standard deviation		4.08	6.76	4.08			4.79	6.27	3.54			9.46	9.29	14.40		
P-values:(t-test)		0.09	0.28	0.09			0.22	0.12	1.00			0.27	0.14	0.77		
Comparison of all 15 patients																
Mean difference		0.69	0.93	1.46			5.07	6.13	3.93			4.36	6.13	5.00		
Standard deviation		7.50	7.59	6.35			10.25	8.68	8.66			7.84	8.93	9.82		
P-values (t-test)		0.74	0.65	0.42			0.087	0.016	0.10			0.058	0.016	0.069		

[a] Not obtained.

Table 25: Electrophysiologic Effects of Flecainide in Man
Seipel et al.

. Wirkung von Flecainid 1 mg/kg auf die Sinusknotenfunktion bei Patienten mit normaler Ausgangssituation. A-A = spontane Periodendauer; SNRT = Sinusknotenerholungszeit; CSNRT = frequenzkorrigierte SNRT; SACT = kalkulierte sinu-atriale Leitungszeit.

	n	A-A ms	SNRT ms	CSNRT ms	SACT ms
Kontrolle	13	705,2 ± 94,2	1012,3 ± 122,3	307,1 ± 115,1	73,3 ± 17,2*)
1 mg/kg		727,1 ± 91,9	1036,9 ± 179,2	313,9 ± 137,8	75,0 ± 17,4*)
Kontrolle	8	862,5 ± 132,0	1165,0 ± 137,4	296,5 ± 105,8	-
2 mg/kg		831,6 ± 143,9	1238,3 ± 311,5	406,7 ± 267,2	-

*) n = 10

Effekt von Flecainid 1 mg/kg auf die intrakardialen Leitungszeiten bei 12 Patienten mit normaler Ausgangssituation. HRA-A = Leitungszeit vom hohen zum basalen rechten Vorhof; A-H = Leitungszeit vom basalen Vorhof zum Hisschen Bündel; H-V = Zeit von der His-Bündel-Aktivierung bis zur frühesten Ventrikelerregung; V-RVA = Zeit von der frühesten Ventrikelseptumaktivierung bis zur Depolarisation der rechten Ventrikelspitze; QRS = Breite des Kammerkomplexes; S-S 600 = konstante, stimulierte Vorhoffrequenz von 100/min.

		HRA-A	A-H	A-H (S-S 600)	H-V	V-RVA	QRS
Kontrolle	ms	26,0 ± 7,0	83,8 ± 8,1	99,5 ± 18,4	45,1 ± 8,2	21,3 ± 8,4*)	84,5 ± 6,0
1 mg/kg	ms	28,7 ± 8,1	95,1 ± 13,6	119,4 ± 35,0	52,5 ± 6,5	27,5 ± 12,0	91,3 ± 8,4
Differenz	%	+ 10,4	+ 13,5	+ 20,0	+ 15,7	+ 29,1	+ 8,1
Signifikanz	P	< 0,05	< 0,001	< 0,001	< 0,001	< 0,005	< 0,005

*) n = 9

Effekt von Flecainid 2 mg/kg auf die intrakardialen Leitungszeiten bei 6 Patienten mit normaler Ausgangssituation.

		HRA-A	A-H	A-H S-S 600	H-V	V-RVA	QRS
Kontrolle	ms	24,3 ± 6,7	76,5 ± 20,8	102,0 ± 42,1	48,3 ± 10,3	20,0 ± 5,0	84,4 ± 17,7
2 mg/kg	ms	26,5 ± 7,5	95,2 ± 19,6	142,2 ± 82,2	67,7 ± 7,4	23,3 ± 2,8	104,8 ± 21,6
Differenz	%	+ 9,0	+ 24,4	+ 39,4	+ 40,2	+ 16,5	+ 24,2
Signifikanz	p	ns	< 0,005	< 0,005	< 0,001	< 0,05	< 0,005

Wirkung von Flecainid 1 mg/kg auf die effektive (ERP) und funktionelle (FRP) Refraktärzeit von Vorhof (A), A-V Knoten (AVN) und Ventrikel (V) sowie auf den sog. Wenckebach-Punkt (WP) bei 12 Patienten mit normaler Ausgangssituation.

		ERP A	FRP AVN	ERP AVN	ERP V	WP
Kontrolle	ms	205,8 ± 17,8	396,0 ± 43,6*)	278,3 ± 37,6*)	218,9 ± 3,3	341,0 ± 66,6
1 mg/kg	ms	214,6 ± 22,6	427,8 ± 27,4	320,0 ± 43,8	231,1 ± 14,5	371,0 ± 69,6
Differenz	%	+ 4,3	+ 8,0	+ 15,0	+ 5,6	+ 8,0
Signifikanz	p	ns	< 0,05	ns	< 0,05	< 0,01

*) n = 9 (3 Pat. 1:1 Leitung bis ERP A).

Tab. 5. Wirkung von Flecainid 2 mg/kg iv. auf die Refraktärität der verschiedenen Herzabschnitte bei 6 Patienten mit normalen Ausgangsbedingungen.

		ERP A	FRP AVN	ERP AVN	ERP V	WP
Kontrolle	ms	212,0 ± 16,4	435,0 ± 49,5	310,0 ± 36,1*)	219,0 ± 8,9	340,0 ± 46,2
2 mg/kg	ms	246,0 ± 25,1	450,0 ± 14,1	348,3 ± 23,6*)	242,0 ± 16,4	397,0 ± 30,1
Differenz	%	+ 16,0	-	+ 12,4	+ 10,5	+ 16,8
Signifikanz	p	< 0,01	-	ns	< 0,01	< 0,05

*) n = 4 (2 Pat. mit 1:1 Leitung bis ERP A).

Table 26: Acute electrophysiologic effects of flecainide
Hellestrand et al.

Conduction intervals

Interval	*No.*	*Control (ms) (mean ± SD)*	*Flecainide (ms) (mean ± SD)*	*Statistical significance (p)*
Sinus cycle length	47	745 ± 198	734 ± 180	NS
PA	43	41 ± 13	50 ± 13	<0·001
AH (SR)	43	67 ± 21	81 ± 33	<0·001
AH (AP)	43	84 ± 33	101 ± 39	<0·001
HV	39	44 ± 9	61 ± 12	<0·001
QRS	47	96 ± 21	118 ± 30	<0·001
QT (SR)	39	368 ± 43	382 ± 44	<0·02
QT (AP)	39	342 ± 25	349 ± 30	<0·01
QTc	39	427 ± 34	446 ± 40	<0·001
JT	39	246 ± 27	232 ± 33	<0·001
WCL (AV)	19	371 ± 153	410 ± 178	<0·05
WCL (VA)	19	355 ± 91	496 ± 72	<0·001

PA, right intra-atrial conduction time; AH (SR), AV nodal conduction time in sinus rhythm; AH (AP), AV nodal conduction time during atrial pacing; HV, H to V conduction time; QRS, QRS duration; QT (SR), QT interval during sinus rhythm; QT (AP), QT interval during atrial pacing; QTc, the corrected QT interval; JT, the JT interval during atrial pacing (QT–QRS); WCL (AV), anterograde Wenckebach periodicity of the AV node; WCL (VA), retrograde Wenckebach periodicity of the AV node.

Refractory periods

Refractory period	*No.*	*Control (ms) (mean ± SD)*	*Flecainide (ms) (mean ± SD)*	*Statistical significance (p)*
A ERP	47	213 ± 32	219 ± 28	NS
AVN ERP	18	314 ± 66	287 ± 21	NS
V ERP	47	220 ± 22	229 ± 23	<0·01
AHfast (AV)	12	342 ± 59	364 ± 59	NS
AHfast (VA)	11	315 ± 99	450 ± 144	<0·01
AHslow (AV)	6	277 ± 40	293 ± 37	NS
AHslow (VA)	1	280	300	
AP (AV)	8	262 ± 47	361 ± 138	<0·05
AP (VA)	13	300 ± 49	453 ± 169	<0·01

A ERP, atrial effective refractory period; AVN ERP, AV nodal effective refractory period; V ERP, ventricular effective refractory period; AHfast (AV), anterograde refractoriness of "fast" AH pathway; AHfast (VA), retrograde refractoriness of "fast" AH pathway; AHslow (AV), anterograde refractoriness of "slow" AH pathway; AHslow (VA), retrograde refractoriness of "slow" AH pathway; AP (AV), anterograde refractoriness of accessory pathway; AP (VA), retrograde refractoriness of accessory pathway.

R-818-030-01
Investigator: Jeffrey Anderson, MD

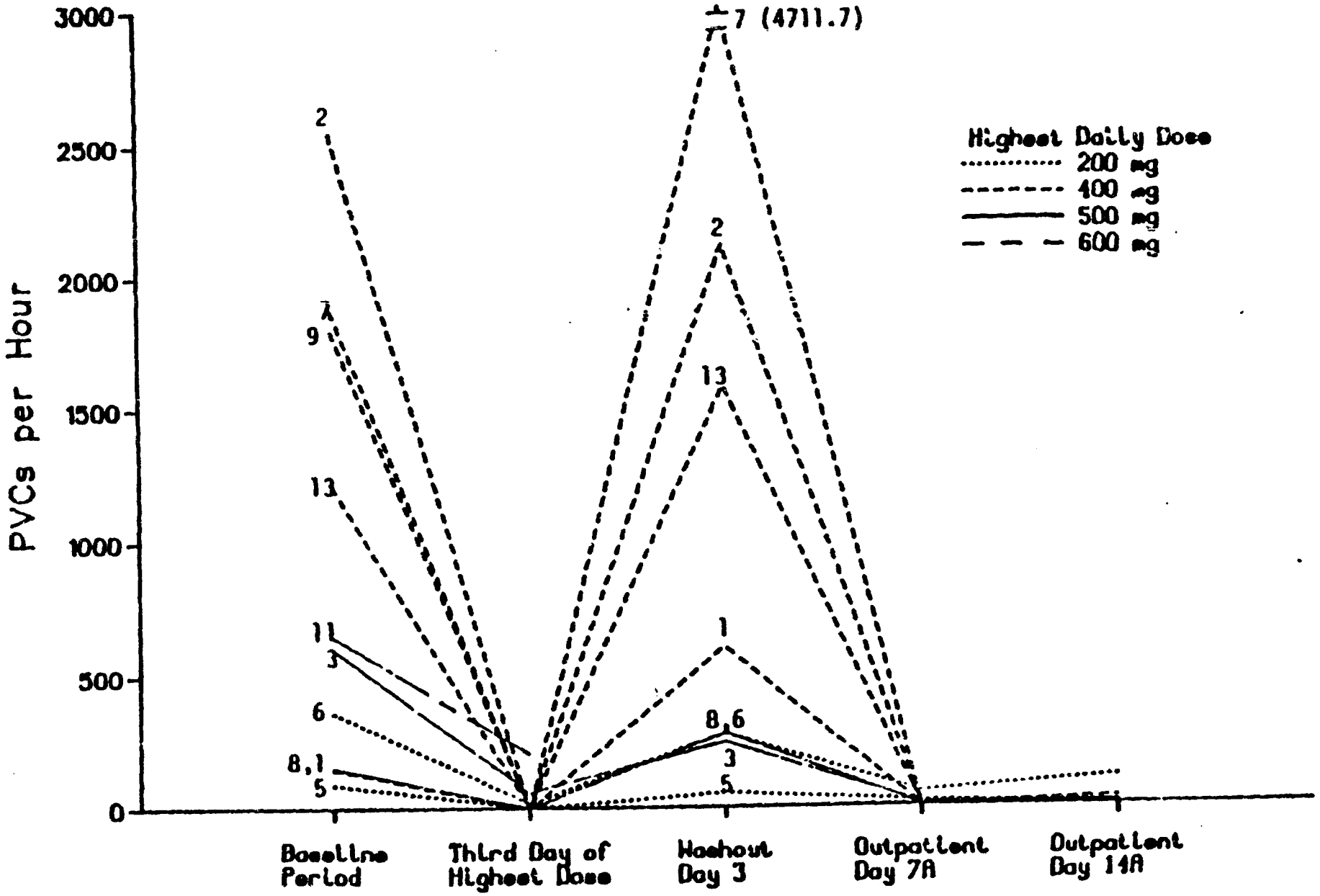
TABLE 27

HOLTER ANALYSIS
PVCs/HOUR - 24-HOUR AVERAGES
(Percent Suppression of Baseline PVCs in Parentheses)

PTNO	Baseline Period	24-Hour Holter From Third Day Of Dose				Washout Day 1	Washout Day 3	Outpatient Day 7A	Outpatient Day 14A
		100 mg bid	200 mg bid	250 mg bid	300 mg bid				
1	147.3	26.1 (82.3%)	1.0 (99.3%)	--	--	239.1 (-62.3%)	602.9 (-309.2%)	0.7 (99.5%)	2.0 (98.6%)
2	2541.2	1060.5 (58.3%)	0.5 (100.0%)	--	--	587.7 (76.9%)	2110.5 (16.9%)	4.5 (99.8%)	0.0 (100.0%)
3	600.4	228.6 (61.9%)	505.1 (15.9%)	58.9 (90.2%)	--	368.0 (38.7%)	246.3 (59.0%)	6.1 (99.0%)	6.2 (99.0%)
4	948.6	447.1 (52.9%)	[a]	--	--	--	--	--	--
5	90.0	2.6 (97.1%)	--	--	--	[illegible] (97.5%)	54.3 (39.7%)	17.2 (80.9%)	6.4 (92.9%)
6	353.4	18.5 (94.9%)	--	--	--	[b]	281.5 (22.5%)	51.6 (85.8%)	109.4 (69.9%)
7	1869.7[c]	504.5 (73.0%)	0.0 (100.0%)	--	--	20.9 (98.9%)	4711.7 (-152.0%)	0.0 (100.0%)	28.4 (98.5%)
8	152.8	371.3 (-143.1%)	[b]	0.3 (99.8%)	--	62.5 (59.1%)	281.4 (-84.2%)	0.1 (99.9%)	1.8 (98.8%)
9	1792.7	1533.3 (14.5%)	0.0 (100.0%)	--	--	930.7 (48.1%)	[b]	0.0 (100.0%)	0.0 (100.0%)
11	644.1	632.9 (1.7%)	520.7 (19.1%)	--	206.4 (68.0%)	[d]	--	--	--
13	1209.8	280.3 (76.8%)	1.0 (99.9%)	--	--	205.4 (83.0%)	1575.6 (-30.2%)	2.9 (99.8%)	3.7 (99.7%)
14	76.0	470.8 (-519.3%)	[a]	--	--	--	--	--	--

[a] Discontinued due to adverse experiences.
[b] No Holter tape available for analysis.
[c] Based on Holter tape from baseline day 2 only. No Holter tape available from baseline day 1.
[d] Discontinued due to lack of response. Holter indicated less than 80% suppression of baseline PVCs at 300 mg bid.

Figure 14
R-818-030-01 HOLTER ANALYSIS
PVCs/Hour - 24-Hour Averages



Purged

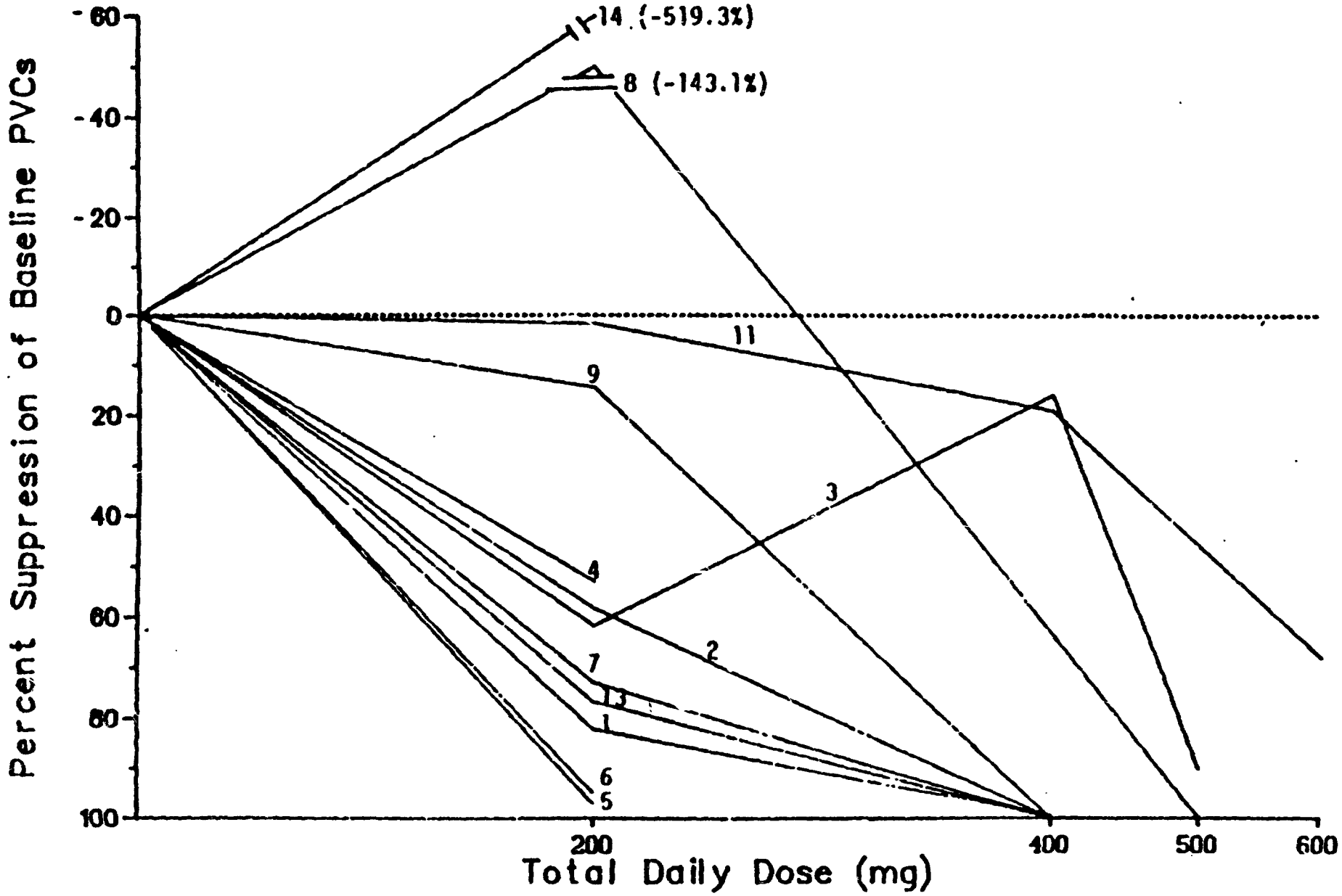
TABLE 28

PVC PERCENT SUPPRESSION AT HIGHEST DOSE[a]

PTNO	HIGHEST DOSE (MG BID)	PERCENT SUPPRESSION of BASELINE PVCs DOSE RANGING: THIRD DAY OF HIGHEST DOSE	OUTPATIENT: DAY 7A	DAY 14A
1	200			
2	200			
3	250			
5	100			
6	100			
7	200			
8	250			
9	200			
11	300			
13	200			
Median	200			
Average		94.9	96.1	95.3

[a]Patients 4 and 14 discontinued study during dose-ranging because of adverse experiences: not included in table.
[b]Patient discontinued due to lack of response. Holter indicated less than 80% suppression of baseline PVCs at 300 mg bid.

Figure 26
R-818-030-01
Relationship Between Dose and Percent Suppression of Baseline PVCs



Purged

TABLE 30

TROUGH PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE
DURING THE DOSE-RANGING PORTION (PART 1) FOLLOWING MULTIPLE ORAL DOSAGE

	Trough Plasma Flecainide Acetate Concentrations (ng/ml)[a]			
Patient Number	Dose-Ranging[b] Day 5	Dose-Ranging[b] Day 8	Dose-Ranging[b] Day 11	Placebo Washout[b] Day 1
1				
2				
3				
5				
6				
7				
8				
9				
13				
Mean	224	539	996	635
Std. Dev.	53	134	528	337
N Patients	9	7	2	9

[a] Trough plasma flecainide level just prior to the morning (9 am) dose and at 12 hours following dosage on the previous evening (9 pm).

[b] Dosage regimens during the dose-ranging portion (part 1) of the study:
Days 3 thru 5 - 100 mg bid.
Days 6 thru 8 - 200 mg bid.
Days 9 thru 11 - 250 mg bid.
Placebo Washout Day 1 - placebo only.

[c] --- indicates that the patient did not require dosage increase to this level.

TABLE 31

APPROXIMATE PEAK PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE DURING THE DOSE-RANGING PORTION (PART 1) FOLLOWING MULTIPLE ORAL DOSAGE

	Approximate Peak Plasma Flecainide Acetate Concentrations (ng/ml)[a]		
Patient Number	Dose-Ranging[b] Day 5	Dose-Ranging[b] Day 8	Dose-Ranging[b] Day 11
1			
2			
3			
5			
6			
7			
8			
9			
13			
Mean	356	875	1191
Std. Dev.	97	192	634
N Patients	9	7	2

[a] Approximate peak plasma flecainide level at three hours following the morning (9 am) dose.

[b] Dosage regimens during the dose-ranging portion (part 1) of the study:
Days 3 thru 5 - 100 mg bid.
Days 6 thru 8 - 200 mg bid.
Days 9 thru 11 - 250 mg bid.

[c] --- indicates that the patient did not require dosage increase to this level.

NDA 18-830
Study: R-818-030-01
Investigator: JEFFREY L. ANDERSON, MD

TABLE 32

TROUGH PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE DURING THE TWO-WEEK OUTPATIENT PORTION (PART 2) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Flecainide Dosage Regimen (mg bid)[b]	Trough Plasma Flecainide Acetate Concentrations (ng/ml)[a] Outpatient Day 7A		Outpatient Day 14A	
		Measured	Normalized[c]	Measured	Normalized[c]
1	200				
2	200				
3	250				
5	100				
6	100				
7	200				
8	250				
9	200				
13	200				
Mean		786	818	844	869
Std. Dev.		357	203	403	213

[a] Trough plasma flecainide level just prior to the morning (9 am) dose and at about 12 hours following dosage on the previous evening (9 pm).
[b] Twice daily oral flecainide dosage regimen on an outpatient basis (at about 9 am and 9 pm).
[c] Plasma level data were normalized to a 200 mg bid dose of flecainide.
[d] Outpatient Day 13A.
[e] Outpatient Day 6A.
[f] Outpatient Day 8A.
[g] Outpatient Day 15A.

TABLE 33

PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE AT THE TIME OF INITIAL REAPPEARANCE OF PREMATURE VENTRICULAR CONTRACTIONS (PVCs) DURING THE PLACEBO WASHOUT PERIOD (PART 1) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Flecainide Dosage Regimen (mg bid)[a]	Baseline Arrhythmia Activity (PVCs/hr)[b]	Initial Reappearance of PVCs During Washout Period: To > 10% of Baseline — Time[c] (hrs)	To > 10% of Baseline — Plasma Level[d] (ng/ml)	To > 30 PVCs per hour — Time[c] (hrs)	To > 30 PVCs per hour — Plasma Level[d] (ng/ml)
1	200					
2	200					
3	250					
5	100					
6	100					
7	200					
8	250					
9	200					
13	200					
Median			22		23	
Mean				438		448
Std. Dev.				259		247

[a]Twice daily oral flecainide dosage regimen prior to the placebo washout period; the last dose was given at about 9 pm on the final dose-ranging day.
[b]Average PVC activity from the two baseline days of 24-hour Holter monitoring; data are from Table 6.
[c]Following the 9 pm dose of flecainide on the final dose-ranging day, the time of initial reappearance of PVCs to the defined degree of PVC activity.
[d]Plasma flecainide level at the time of initial reappearance of PVCs was estimated from the log-linear regression line for the terminal phase of flecainide elimination from plasma of individual patients.
[e]Average PVC activity from 24-hour Holter monitoring on baseline day 2 only; Holter tape from baseline day 1 was not available for analysis.
[f]Holter tape from placebo washout day 2 was not available for analysis.
[g]Plasma flecainide level at 35 hours following the last dose.

TABLE 34

COMPARISON OF TROUGH PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE TO THE PERCENT SUPPRESSION OF PREMATURE VENTRICULAR CONTRACTIONS (PVCs) DURING THE TWO-WEEK OUTPATIENT PORTION (PART 2) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Flecainide Dosage Regimen (mg bid)[a]	Outpatient Day 7A Percent Suppression of PVCs[b]	Outpatient Day 7A Trough Level (ng/ml)[c]	Outpatient Day 14A Percent Suppression of PVCs[b]	Outpatient Day 14A Trough Level (ng/ml)[c]
1	200				
2	200				
3	250				
5	100				
6	100				
7	200				
8	250				
9	200				
13	200	----			
Mean		96.1	786	95.3	844
Std. Dev.		7.3	357	9.8	403

[a] Twice daily oral flecainide dosage regimen on an outpatient basis (at about 9 am and 9 pm).
[b] Percent suppression of baseline PVC activity from 24-hour Holter minitoring; data are from Table 6.
[c] Trough plasma flecainide level just prior to the morning (9 am) dose; data are from Table 23.

Figure 27

R-818-030-02 STUDY DESIGN

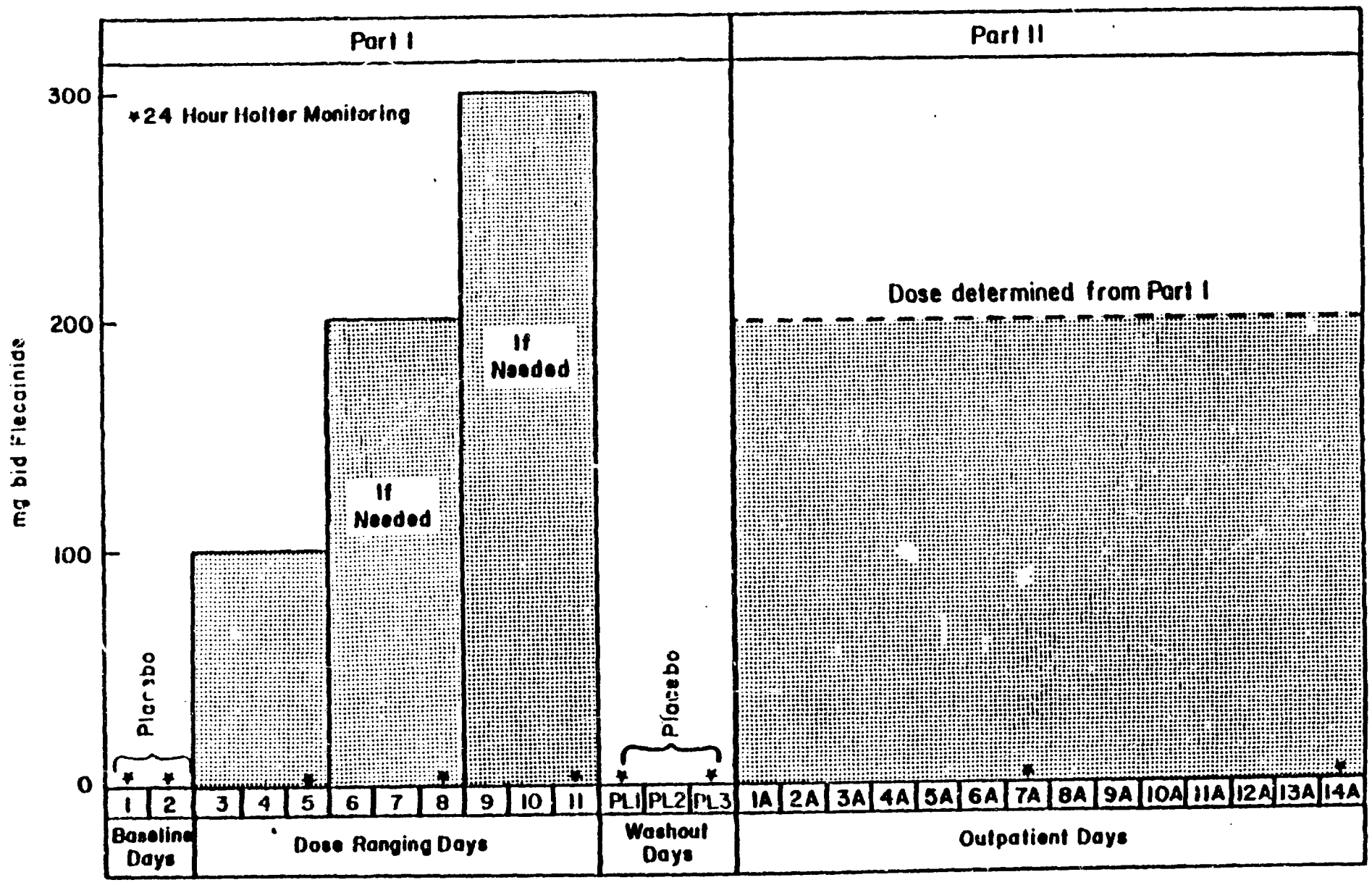


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Figure 31

R-818-030-02 HOLTER ANALYSIS
PVCs/Hour - 24-Hour Averages

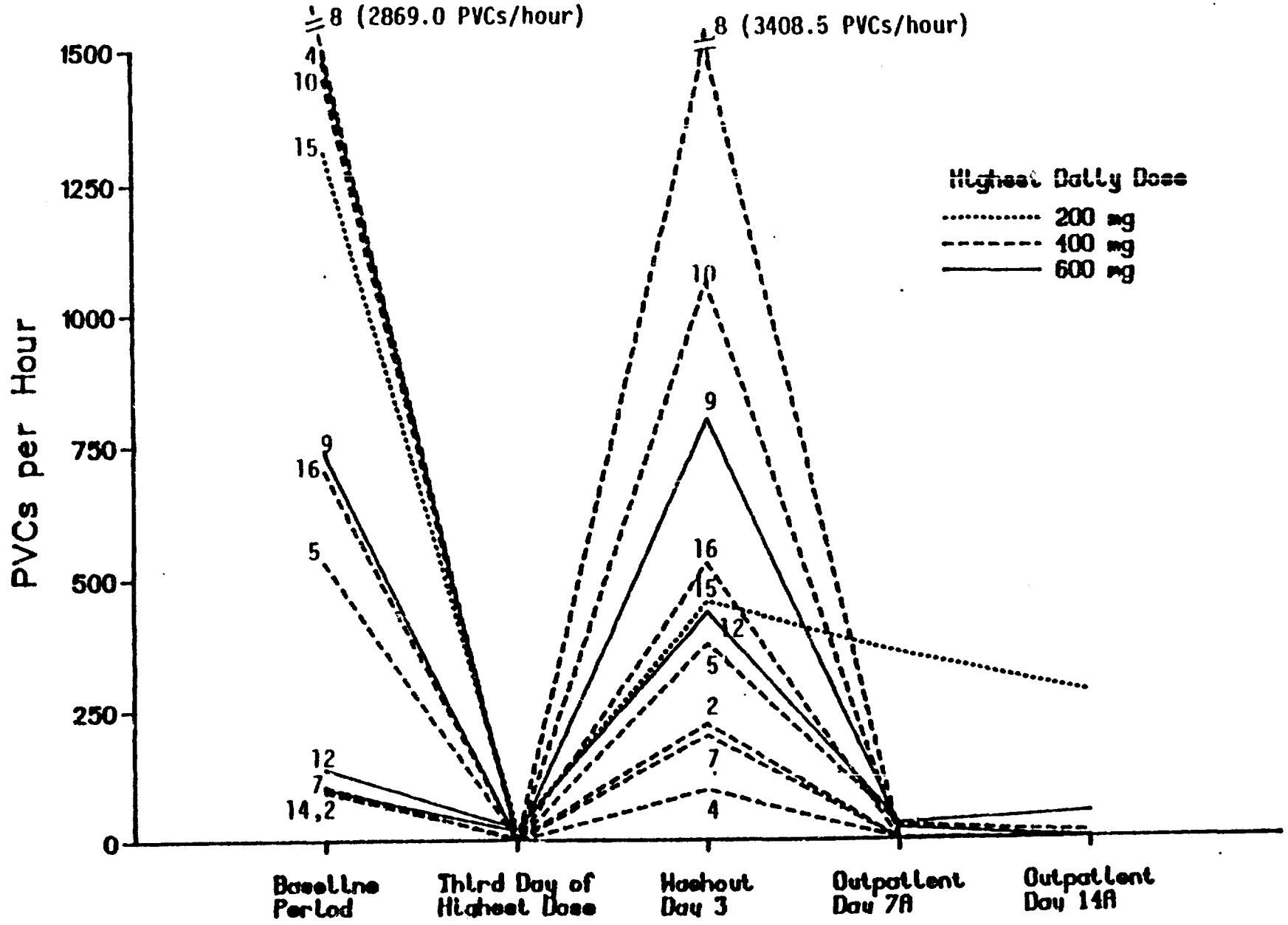


TABLE 36

PVC PERCENT SUPPRESSION AT HIGHEST DOSE

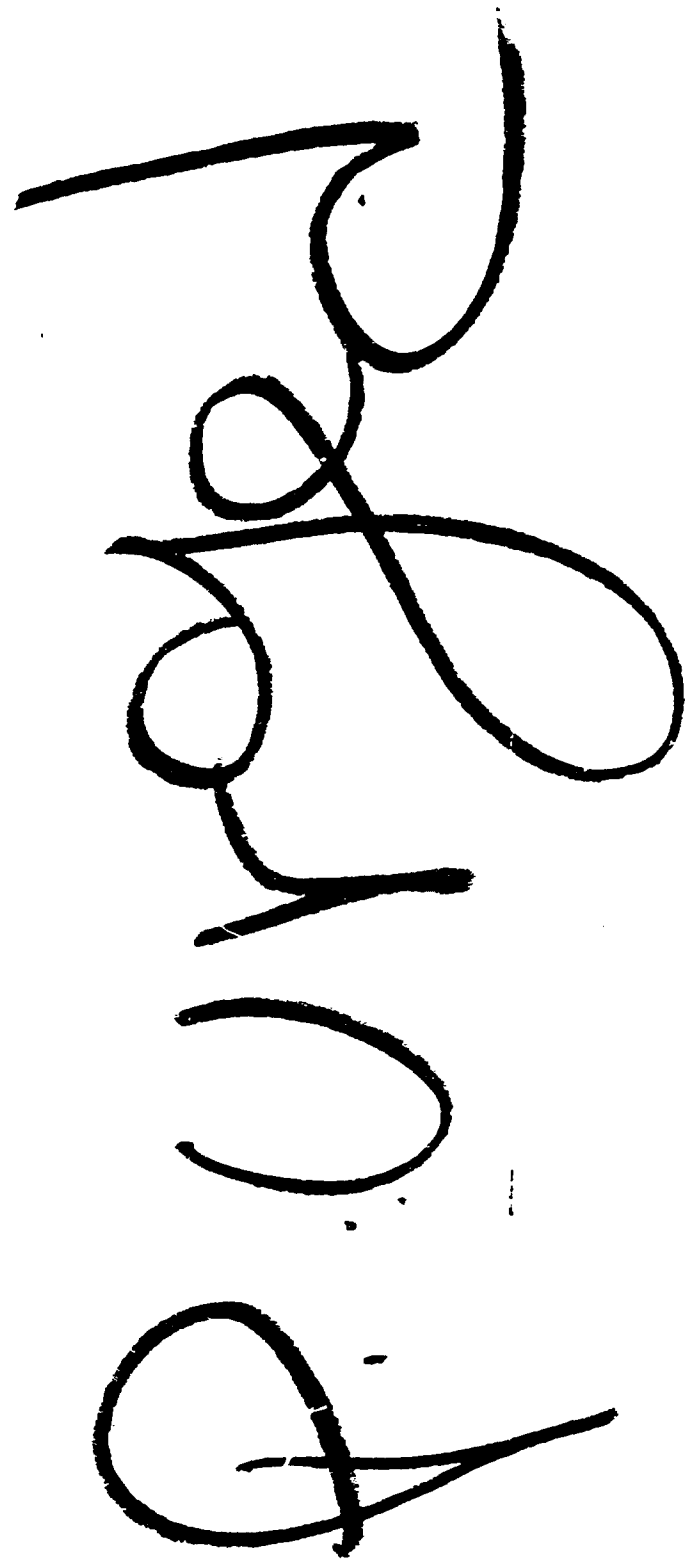
PTNO	HIGHEST DOSE (MG BID)	PERCENT SUPPRESSION OF BASELINE PVCs DOSE RANGING THIRD DAY OF HIGHEST DOSE	OUTPATIENT DAY 7A	OUTPATIENT DAY 14A
2	200			
4	200			
5	200			
7	200			
8	200			
9	300			
10	200			
12	300			
14	300			
15	100			
16	200			
AVERAGE		96.3	94.1	93.2
MEDIAN	200	100.0	99.6	100.0

[a]Holter tape recording technically unsatisfactory.

[b]Patient received 200 mg bid during outpatient phase.

[c]Patient withdrawn, investigator's Trendscriber data indicated less than 80% suppression of PVCs at 300 mg bid.

[d]Patient received 200 mg bid on day 14A.



Study: R-818-030-02
Investigator: M. Hodges, MD
NDA 18-830

TABLE 38

TROUGH PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE DURING THE DOSE-RANGING PORTION (PART 1) FOLLOWING MULTIPLE ORAL DOSAGE

	Trough Plasma Flecainide Acetate Concentrations (ng/ml)[a]			
Patient Number	Dose-Ranging[b] Day 5	Dose-Ranging[b] Day 8	Dose-Ranging[b] Day 11	Placebo Washout[b] Day 1
2				
4				
5				
7				
8				
9				
10				
12				
15				
16				
Mean	233	606	540	691
Std. Dev.	84	204	252	200
N Patients	10	9	2	10

[a] Trough plasma flecainide level just prior to the morning (9 am) dose and at 12 hours following dosage on the previous evening (9 pm).

[b] Dosage regimens during the dose-ranging portion (part 1) of the study:
Days 3 thru 5 - 100 mg bid.
Days 6 thru 8 - 200 mg bid
Days 9 thru 11 - 300 mg bid
Placebo Washout Day 1 - placebo only.

[c] ___ indicates that the patient did not require dosage increase to this level.

Study: R-818-030-02
Investigator: M. Hodges, MD

NDA 18-830

TABLE 39

PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE AT THE TIME OF INITIAL REAPPEARANCE OF PREMATURE VENTRICULAR CONTRACTIONS (PVCs) DURING THE PLACEBO WASHOUT PERIOD (PART 1) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Flecainide Dosage Regimen (mg bid)[a]	Baseline Arrhythmia Activity (PVCs/hr)[b]	Initial Reappearance of PVCs During Washout Perio: To > 10% of Baseline: Time[c] (hrs)	To > 10% of Baseline: Plasma Level[d] (ng/ml)	To > 30 PVCs per hour: Time[c] (hrs)	To > 30 PVCs per hour: Plasma Level[d] (ng/ml)
2	200					
4	200					
5	200					
7	200					
8	200					
9	300					
10	200					
12	300					
15	100					
16	200					
Median						
Mean		461				4
Std. Dev.		216				191

[a] Twice daily oral flecainide dosage regimen prior to the placebo washout perio the last dose was given at about 9 pm on the final dose-ranging day.
[b] Average PVC activity from the two baseline days of 24-hour Holter monitoring; data are from Table 6.
[c] Following the 9 pm dose of flecainide on the final dose-ranging day, the time of initial reappearance of PVCs to the defined degree of PVC activity.
[d] Plasma flecainide level at the time of initial reappearance of PVCs was estimated from the log-linear regression line for the terminal phase of fleca elimination from plasma of individual patients.
[e] Holter tape was not recorded on placebo washout day 2.
[f] Plasma flecainide level at 35 hours following the last dose.
[g] Average PVC activity from 24-hour Holter monitoring on baseline day 1 only; Holter tape from baseline day 2 was not available for analysis.
[h] Average PVC activity from 24-hour Holter monitoring on baseline day 2 only; Holter tape from baseline day 1 was not available for analysis.
[i] Holter tape from placebo washout day 1 was not available for analysis.

TABLE 40

COMPARISON OF TROUGH PLASMA CONCENTRATIONS OF UNCHANGED FLECAINIDE ACETATE TO THE PERCENT SUPPRESSION OF PREMATURE VENTRICULAR CONTRACTIONS (PVCs) DURING THE TWO-WEEK OUTPATIENT PORTION (PART 2) FOLLOWING MULTIPLE ORAL DOSAGE

Patient Number	Flecainide Dosage Regimen (mg bid)[a]	Outpatient Day 7A Percent Suppression of PVCs[b]	Outpatient Day 7A Trough Level (ng/ml)[c]	Outpatient Day 14A Percent Suppression of PVCs[b]	Outpatient Day 14A Trough Level (ng/ml)[c]
2	200				
4	200				
5	200				
7	200				
8	200				
9	300				
10	200				
12	200				
15	100				
16	200				
Mean		94.1	830	93.2	893
Std. Dev.		10.3	311	13.3	335
N Patients		10	10	9	10

[a] Twice daily oral flecainide dosage regimen on an outpatient basis (at about 9 am and 9 pm).
[b] Percent suppression of baseline PVC activity from 24-hour Holter minitoring; data are from Table 6.
[c] Trough plasma flecainide level just prior to the morning (9 am) dose; data are from Table 23.
[d] Holter tape from outpatient day 14A was technically unsatisfactory for analysis.

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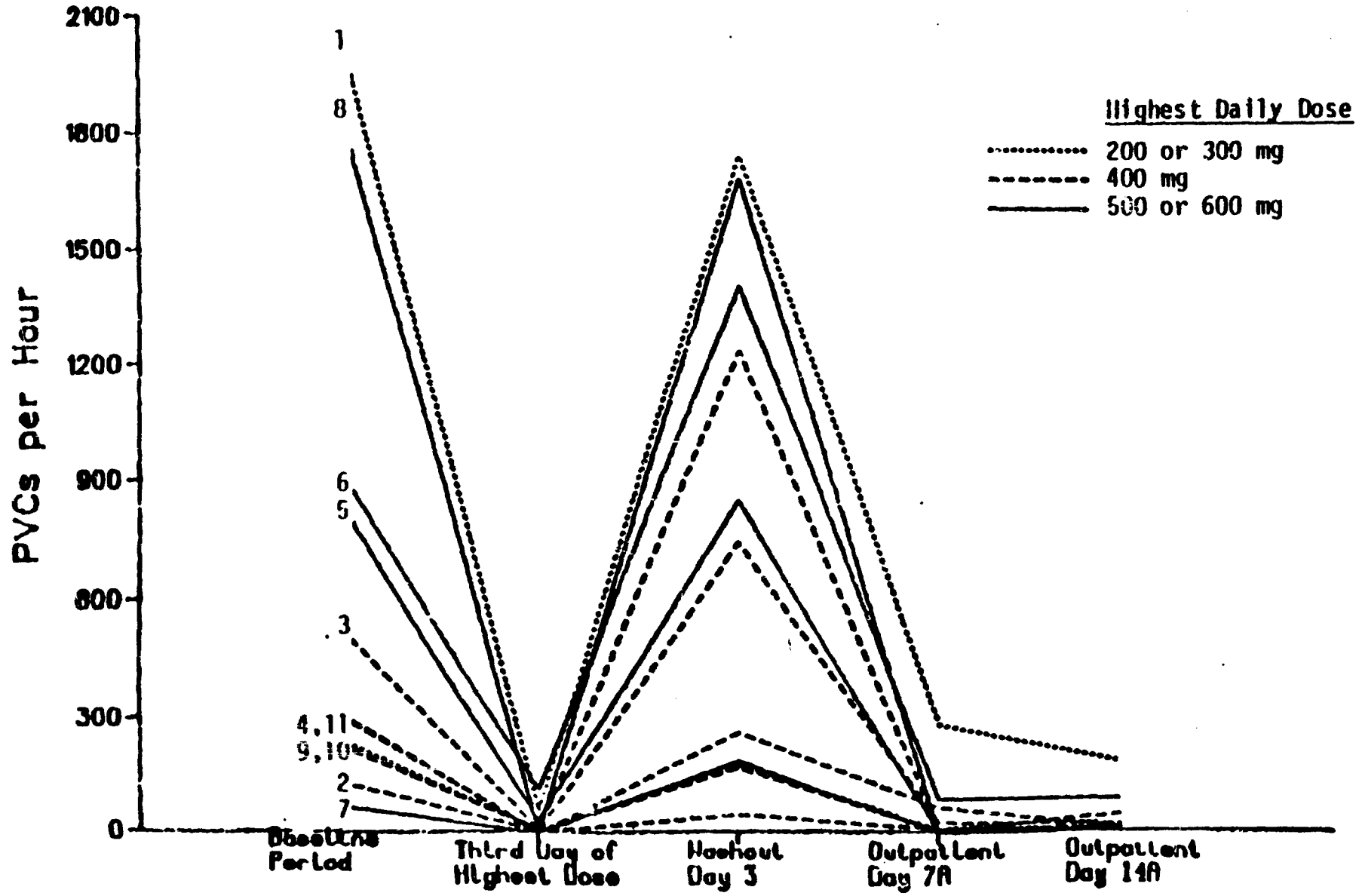
FIGURE 32

R-818-030-03 HOLTER ANALYSIS
PVCs/Hour -- 24-Hour Averages



NDA 18-830

TABLE 42

PVC PERCENT SUPPRESSION AT HIGHEST DOSE

PTNO	HIGHEST DOSE (MG)	PVC PERCENT SUPPRESSION FROM BASELINE DOSE RANGING: THIRD DAY OF HIGHEST DOSE	OUTPATIENT DAY 7A	OUTPATIENT DAY 14A
1	100 BID			
2	200 BID			
3	200 BID			
4	200 BID			
5	300 BID			
6	250 BID			
7	250 BID			
8	250 BID			
9	200 BID			
10	100 Q8H			
11	200 BID	----		
AVERAGE		96.9	92.6	95.8
MEDIAN	200			

FIGURE 33

R-818-030-03
Relationship Between Dose and Percent Suppression from Baseline PVCs

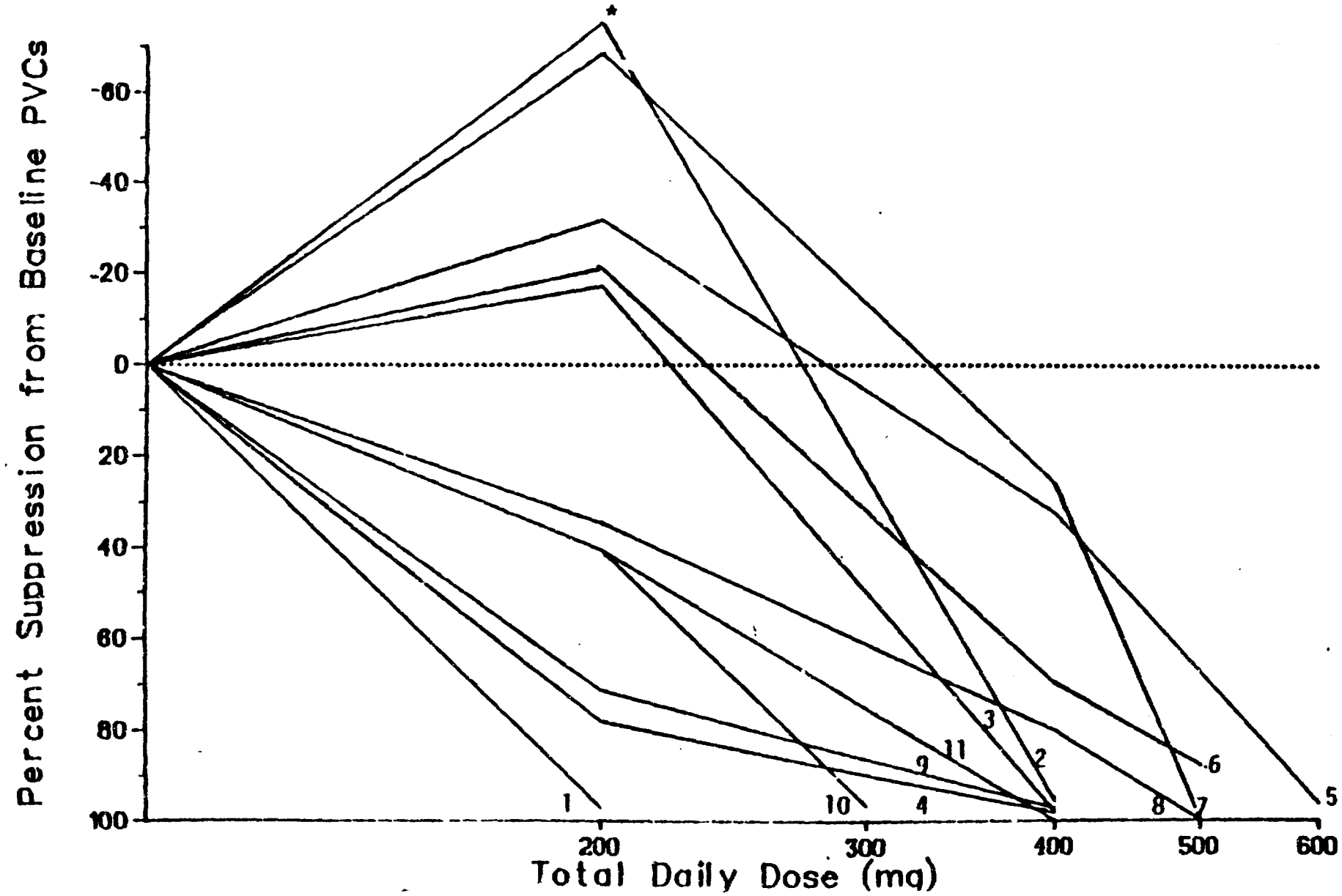


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TABLE 44

Summary of Plasma Pharmacokinetic Data for Flecainide Acetate During Placebo Washout Period Following Multiple Oral Flecainide Dosage to 11 Patients

Patient Number	Last Dose of Flecainide (mg)[a]	Plasma Half-life of Flecainide (hours)[b]	Peak Time (hours)	Peak Level (ng/ml)		Plasma AUC (ng.hours/ml)[d]	
				Measured	Normalized[c]	Measured	Normalized[c]
1	100						
2	200						
3	200						
4	200						
5	250						
6	250						
7	250						
8	250						
9	200						
10	200						
11	200						
Mean		20.3	3.6	916		9286	
Std. Dev.		4.3	1.1	388		3956	

[a] Following multiple oral flecainide dosage, the last dose prior to the placebo washout period was given at about 9 am on placebo washout day 1.

[b] The terminal phase (post-absorptive) plasma half-life of flecainide acetate was estimated from the log plasma concentration versus time graph by calculation of the least squares line.

[c] Peak level and plasma AUC data were normalized to a 200 mg dose of flecainide.

[d] Area under the plasma flecainide level versus time curve (AUC) for one dosage interval (zero to 12 hours after last dose prior to the placebo washout period); plasma AUC values were calculated by the trapezoidal rule.

TABLE 45

NDA 18-830

Trough Plasma Concentrations of Unchanged Flecainide Acetate During the Dose-Ranging Portion (part 1) Following Multiple Oral Flecainide Dosage to 11 Patients

Patient Number	Trough Plasma Flecainide Acetate Concentration (ng/ml)[a]			
	Dose-Ranging[b] Day 5	Dose-Ranging[b] Day 8	Dose-Ranging[b] Day 11	Placebo Washout[b] Day 1
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
Mean	212	563	682	709
Std. Dev.	86	251	359	353
N Patients	11	10	4	10

[a] Trough plasma flecainide level just prior to the morning (9 am) dose and at 12 hours following dosage on the previous evening (9 pm).

[b] Dosage regimens during the dose-ranging portion (part 1) of the study:
Days 3 thru 5 - 100 mg bid.
Days 6 thru 8 - 200 mg bid.
Days 9 thru 11 - 250 mg bid.
Placebo Washout Day 1 - highest dose required by each patient given at 9 am only.

[c] ---indicates that the patient did not require dosage increase to this level.

[d] Blood sample not available for analysis.

[e] Patient No. 10 went directly from dose-ranging day 7 to placebo washout day 1 since the trough level on placebo washout day 1 is from the third day of 200 bid dosage, the value is also shown under dose-ranging day 8.

TABLE 46

NDA 18-830

Trough Plasma Concentrations of Unchanged Flecainide Acetate During the Two-Week Outpatient Portion (part 2) Following Multiple Oral Flecainide Dosage to 11 Patients

Patient Number	Flecainide Dosage Regimen[b] (mg bid)	Trough Plasma Flecainide Acetate Concentration (ng/ml)[a] Outpatient Day 7A		Outpatient Day 14A	
		Measured	Normalized[c]	Measured	Normalized[c]
1	100				
2	200				
3	200				
4	200				
5	300				
6	250				
7	250				
8	250				
9	200				
10	100 tid				
11	200				
Mean		724	713	761	725
Std. Dev.		336	354	361	375
N Patients		10	9	11	10

[a] Trough plasma flecainide level just prior to the morning (9 am) dose and at about 12 hours following dosage on the previous evening (9 pm), except for Patient No. 10.

[b] Twice daily oral flecainide dosage regimen on an outpatient basis at about 9 am and 9 pm, except for patient No. 10 (100 mg tid at about 6 am, 2 pm, and 10 pm).

[c] Plasma level data were normalized to a 200 mg bid dose of flecainide.

[d] Blood sample not available for analysis.

[e] Value not normalized to a 200 mg bid dose of flecainide.

TABLE 47

NDA 18-830

Plasma Concentrations of Unchanged Flecainide Acetate at the Time of Initial Reappearance of Premature Ventricular Contractions (PVCs) During the Placebo Washout Period (part 1 of the study) Following Multiple Oral Flecainide Dosage to 11 Patients

Patient Number	Flecainide Dosage Regimen (mg bid)[a]	Baseline Arrhythmia Activity (PVCs/hr)[b]	Initial Reappearance of PVCs During Washout Perio: To > 10% of Baseline Time[c] (hrs)	To > 10% of Baseline Plasma Level[d] (ng/ml)	To > 30 PVCs per hour Time[c] (hrs)	To > 30 PVCs per hour Plasma Level[d] (ng/ml)
1	100					
2	200					
3	200					
4	200					
5	250					
6	250					
7	250					
8	250					
9	200					
10	200					
11	200					
Median			622		586	
Mean			333		287	
Std. Dev.			10		10	
N Patients						

[a] Twice daily oral flecainide dosage regimen prior to the placebo washout period; the last dose was given at about 9 am on placebo washout day 1.

[b] Average PVC activity from the two baseline days of 24-hour Holter monitoring; data are from Table 6.

[c] Following the 9 am dose of flecainide on placebo washout day 1, the time of initial reappearance of PVCs to the defined degree of PVC activity.

[d] Plasma flecainide level at the time of initial reappearance of PVCs was estimate from the log-linear regression line for the terminal phase of flecainide elimination from plasma of individual patients.

[e] Holter tape from placebo washout day 2 was not available for analysis.

[f] Plasma flecainide level at 24 hours following last dose.

[g] Average PVC activity from 24-hour Holter monitoring on baseline day 2 only; Holter tape from baseline day 1 was not available for analysis.

[h] Holter tapes from placebo washout days 1 and 2 were not available for analysis.

NDA 18-830

TABLE 48

Comparison of Trough Plasma Concentrations of Unchanged Flecainide Acetate to the Percent Suppression of Premature Ventricular Contractions (PVCs) During the Dose-Ranging Portion (part 1) Following Multiple Oral Flecainide Dosage to 11 Patients

Patient Number	Flecainide Dosage Regimen[a] (mg bid)	Dose-Ranging Day	Percent Suppression of PVCs[b]	Trough Plasma Level (ng/ml)[c]
1	100	5		
2	200	8		
3	200	8		
4	200	8		
5	300	[d]		
6	250	11		
7	250	11		
8	250	11		
9	200	8		
10	200	8		
11	200	8		
Mean			96.9	613
Std. Dev.			3.5	283
N Patients			10	10

[a] Twice daily oral flecainide regimen (at about 9 am and 9 pm)

[b] Percent suppression of baseline PVC activity from 24-hour Holter monitoring; data are from Table 6.

[c] Trough plasma flecainide level just prior to the morning (9 am) dose; data are from Table 21.

[d] Data for 300 mg bid dose level in Patient 5 were obtained following the placebo washout period.

[e] Holter tape for dose-ranging day 8 was not available for analysis.

STUDY: R-818-041-01
INVESTIGATOR: Jordan L. Holtzman, MD, PhD

Table 49
Study Flow Chart

Flecainide-Propranolol Interaction Study
Overall Study Plan

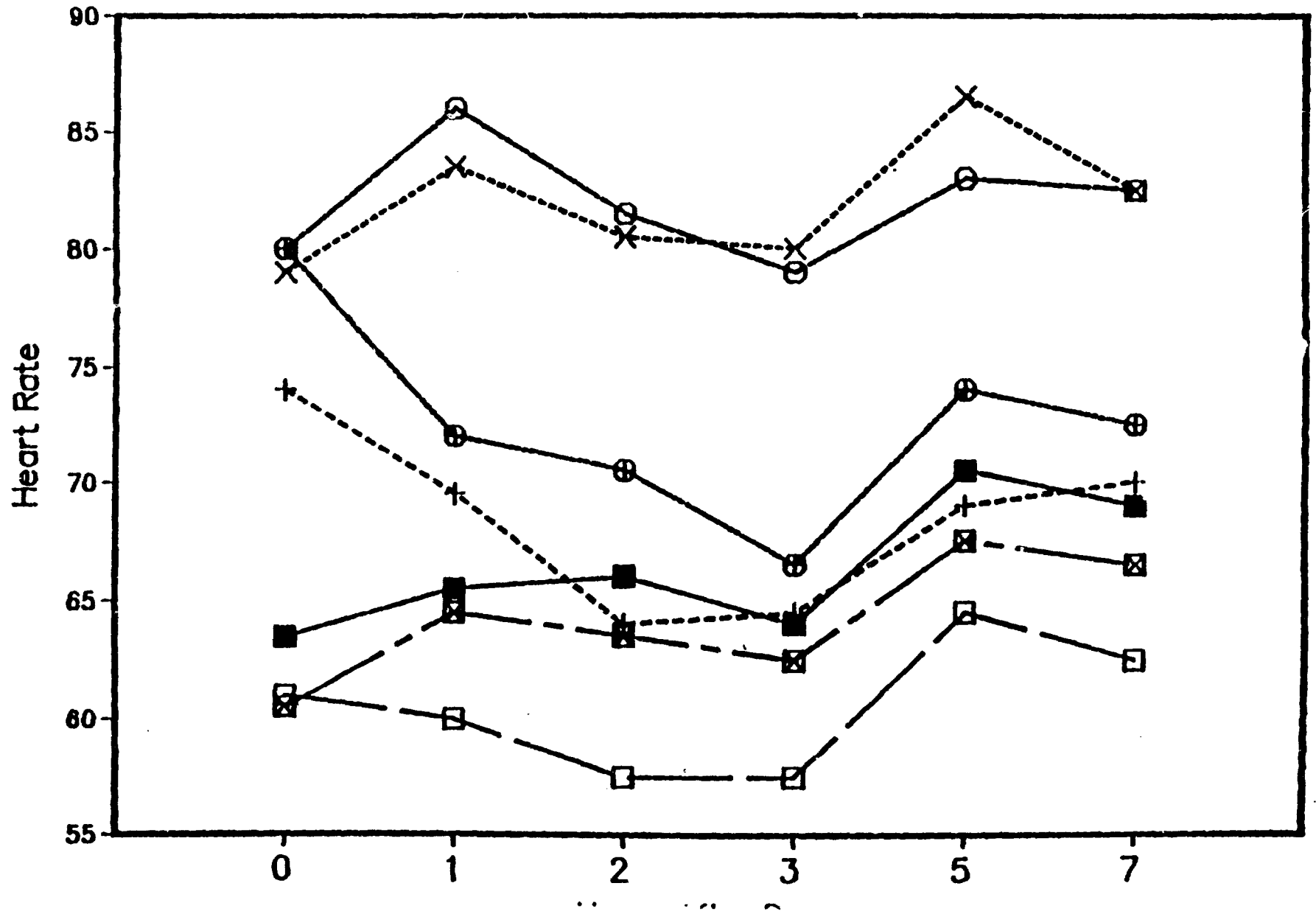
Procedure	Study Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Propranolol, 80 mg, q8h	X	X	X	X	X	X	X	X	X	X	X[a]	Washout Period											X[a]
Flecainide, 200 mg, q12h								X	X	X	X[a]								X	X	X	X	X[a]
Pharmacodynamic Tests[b]	X			X			X			X									X			X	X
Placebo Capsules, q12h	X	X	X	X	X	X	X																
Placebo Tablets, q8h																			X	X	X	X	
Blood Samples for Plasma Drug Level Measurements	X[c]			X[d]			X[c]			X[e]									X[c]			X[c]	X[e]

Day 1 - Effect of propranolol, single dose
Day 5 - Effect of propranolol, multiple doses
Day 8 - Effect of flecainide, single dose, on propranolol, multiple doses
Day 11 - Effects of flecainide and propranolol under steady state conditions
Day 19 - Effect of flecainide, single dose
Day 22 - Effect of flecainide, multiple doses
Day 23 - Effect of propranolol, single dose, on flecainide, multiple doses

[a] AM dose only.
[b] Resting blood pressure, heart rate, respiration, systolic time intervals, echocardiography, exercise heart rate, effect on ECG rhythm strip.
[c] Pre 0900 hours dose.
[d] Pre 0900 hours dose and at 2, 3, 4, 6, and 8 hours postdose.

FIGURE 34

R-818-041-01 HOLTZMAN
Means of Heart Rate



Legend	Study Day
+ F-0, P-S	1
□ F-0, P-M	5
⊠ F-S, P-M	8
■ F-M, P-M	11
X F-S, P-0	19
O F-M, P-0	22
⊕ F-M, P-S	23

F= Flecainide
P= Propranolol
0= No Drug
S= Single Dosing

FIGURE 35

R-818-041-01 HOLTZMAN
Means of Post Exercise–Pre Exercise Heart Rate

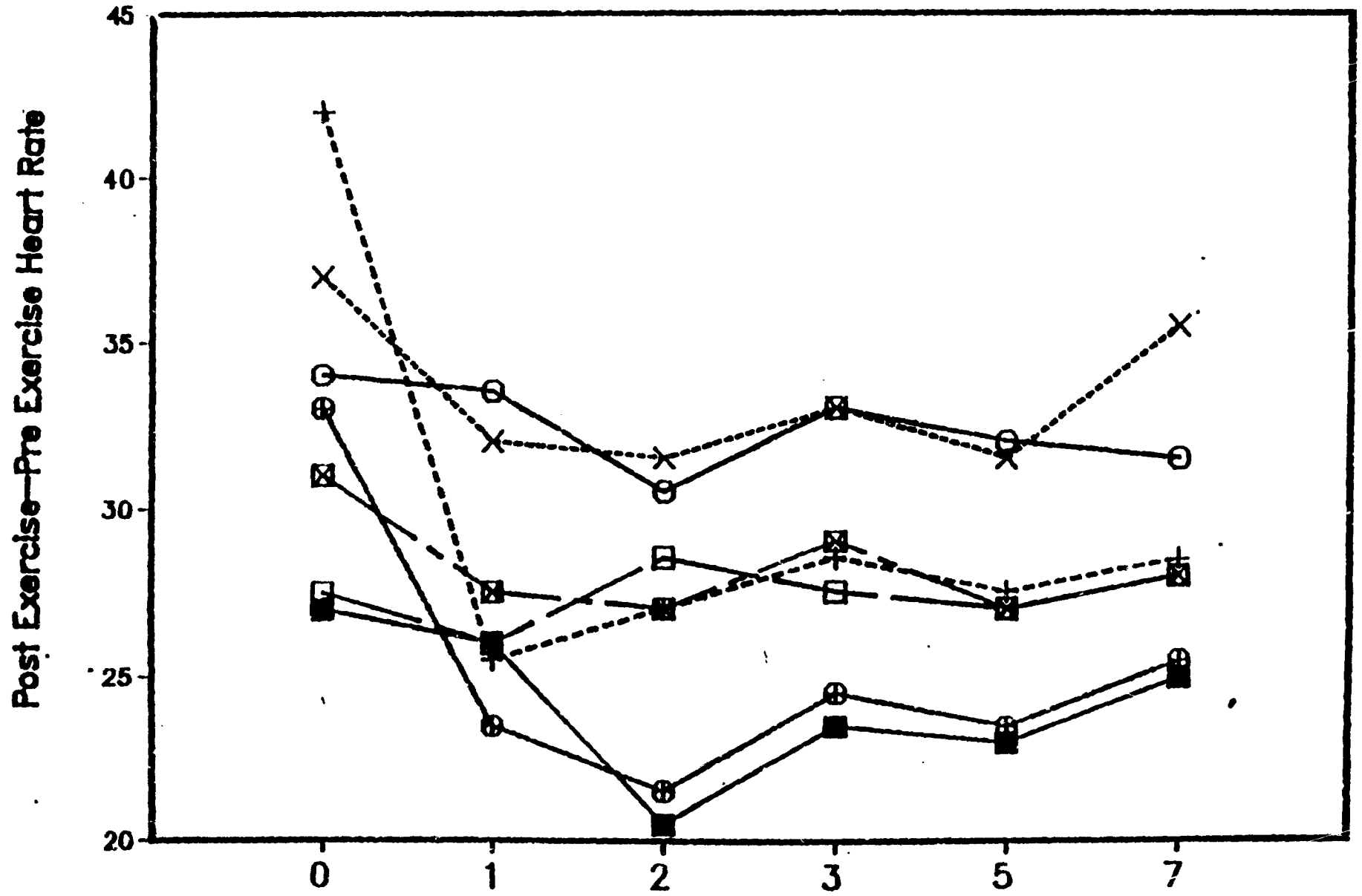


FIGURE 36

R-818-041-01 HOLTZMAN
Means of PR Interval

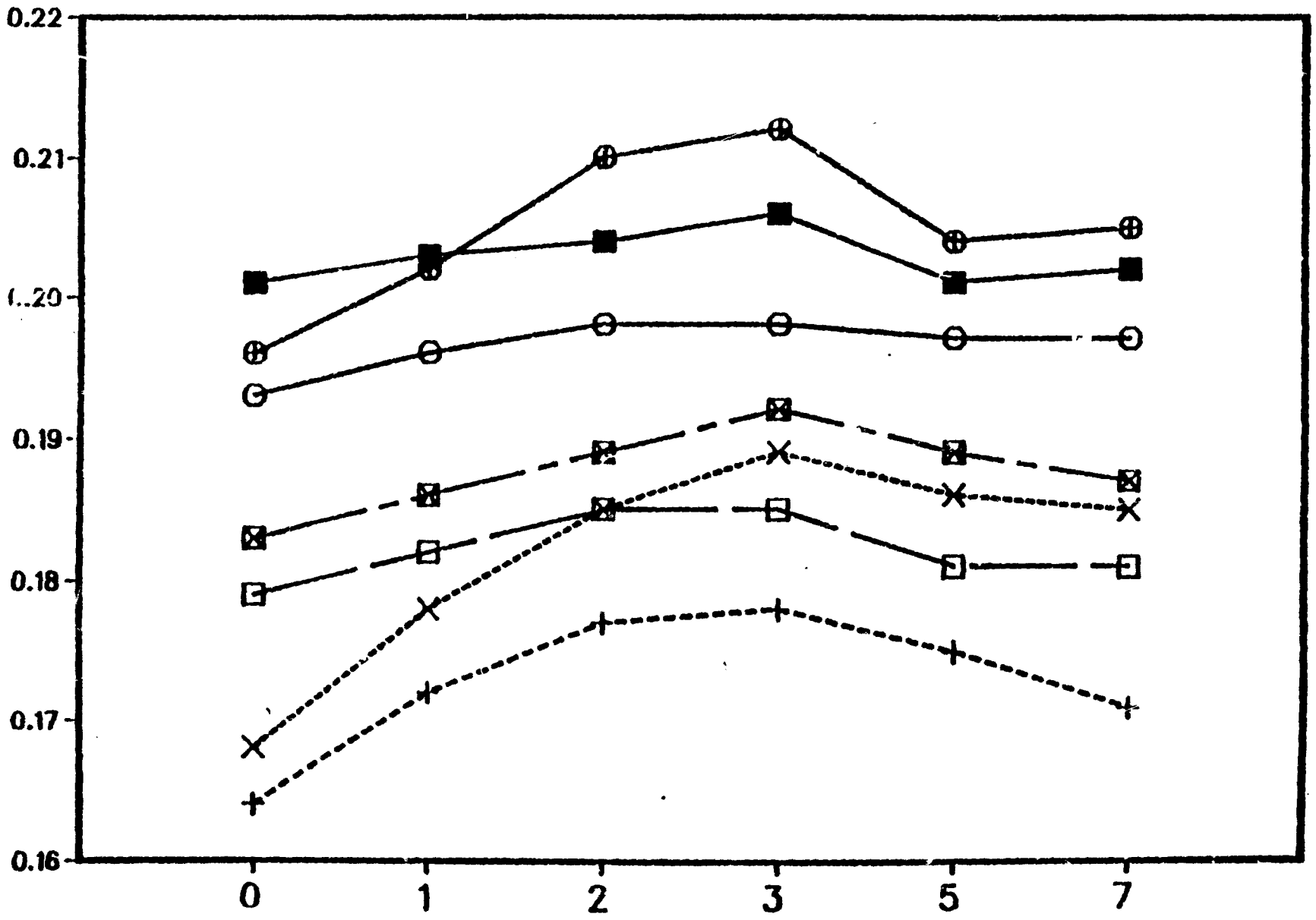


FIGURE 37

R-818-041-01 HOLTZMAN
Means of Corrected QT Interval

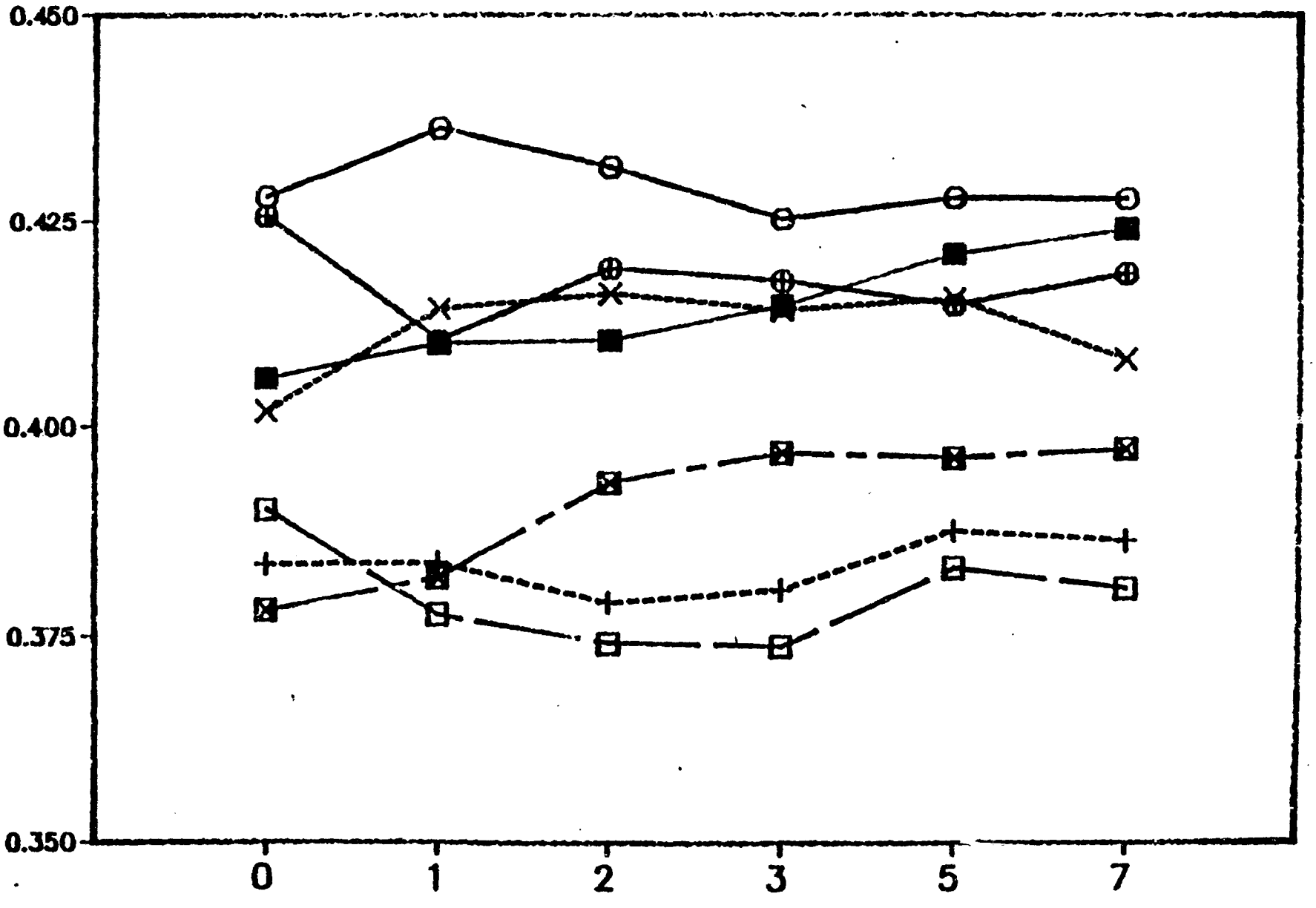


FIGURE 38

R-818-041-01 HOLTZMAN
Means of Systolic Blood Pressure

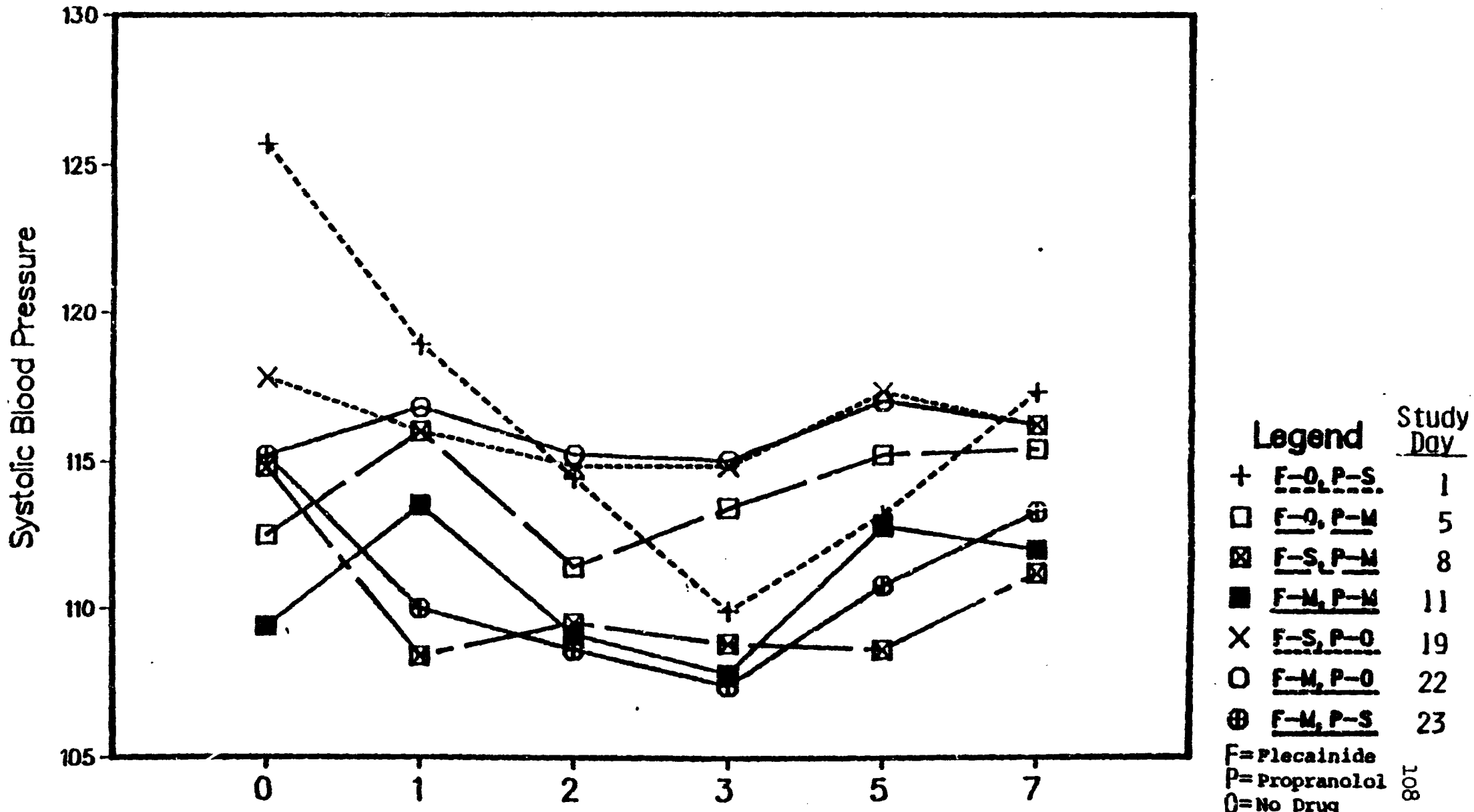


FIGURE 39

R-818-041-01 HOLTZMAN
Means of Diastolic Blood Pressure

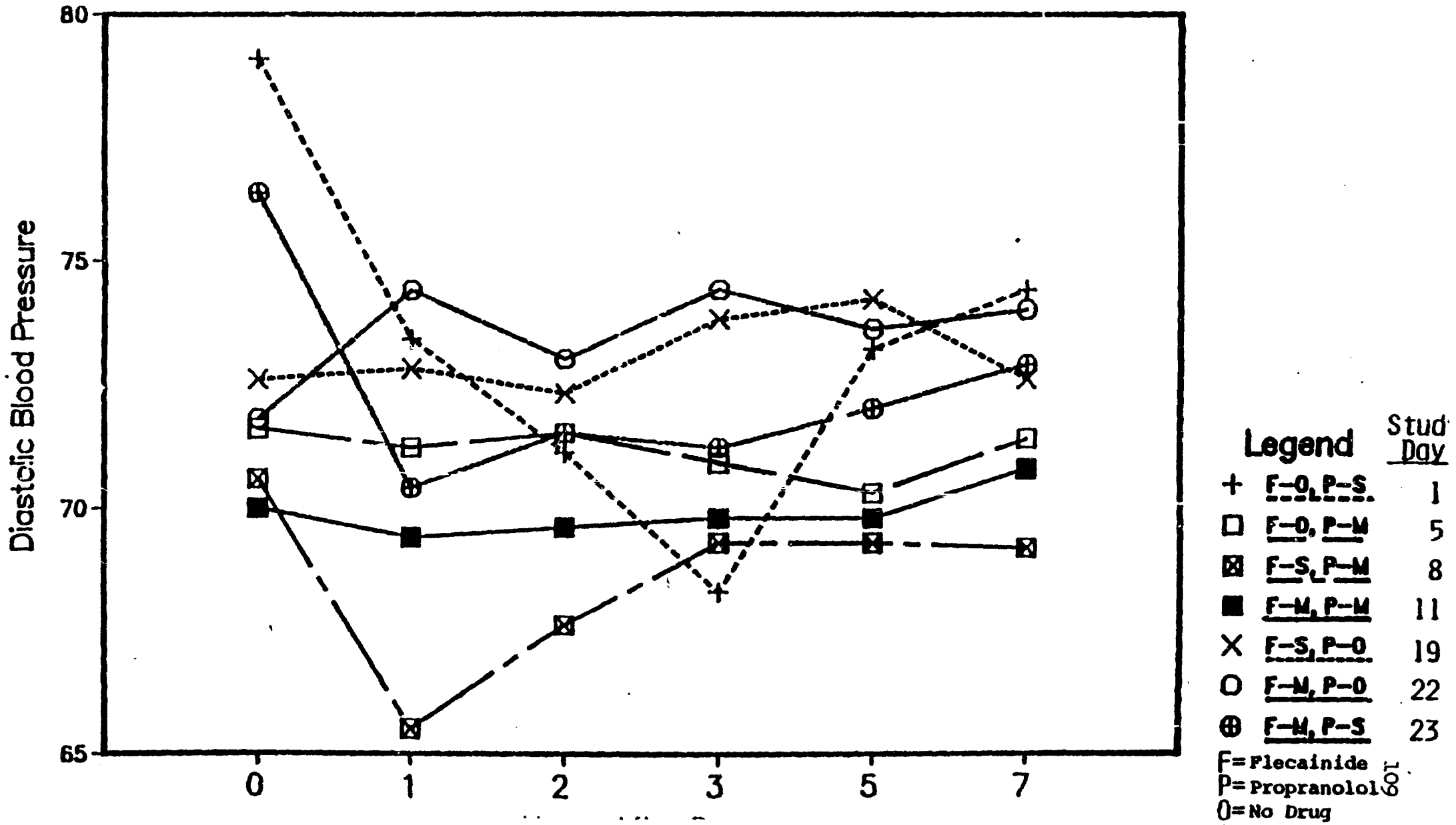
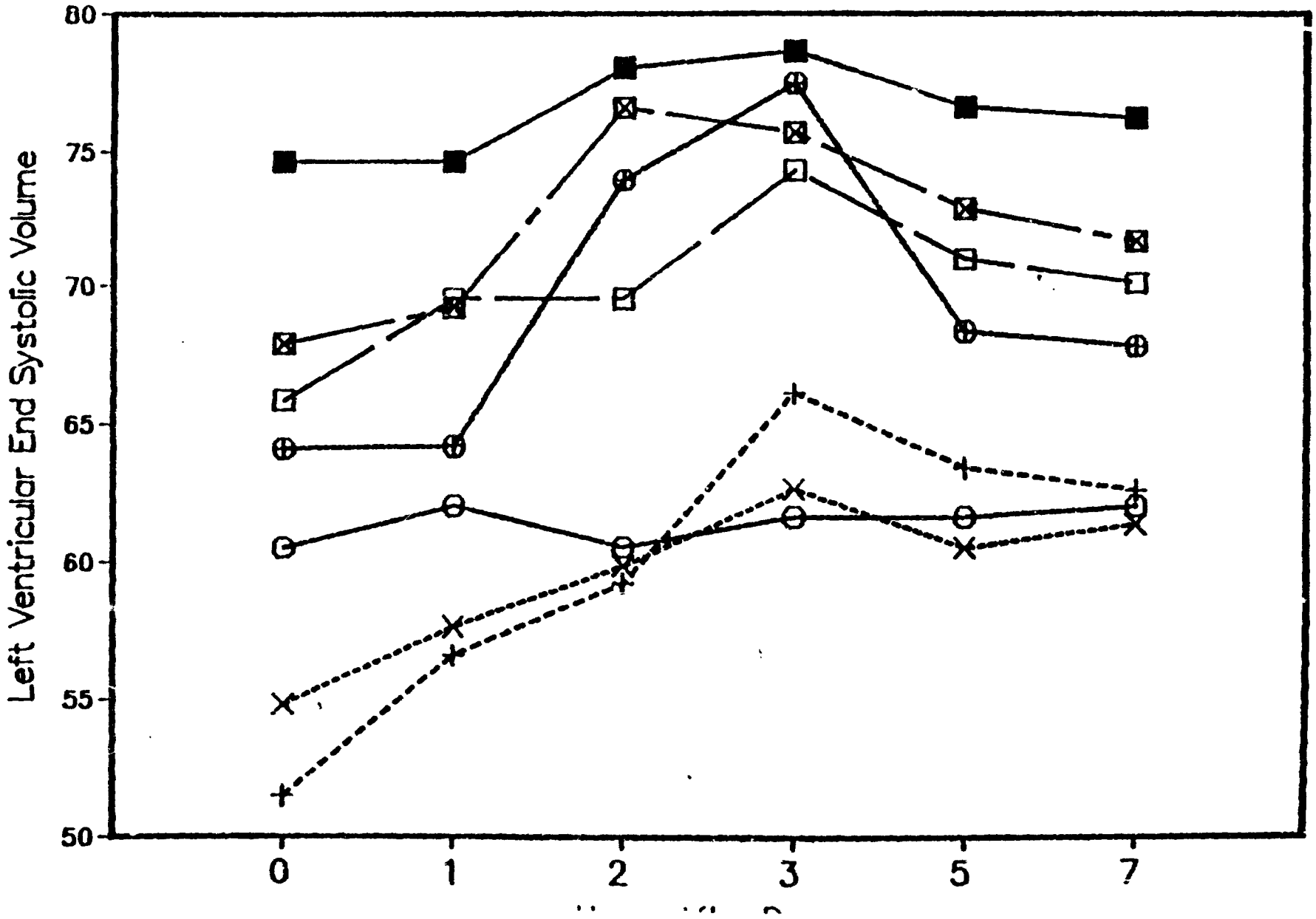


FIGURE 40

R-818-041-01 HOLTZMAN
Means of Left Ventricular End Systolic Volume



Legend	Study Day
+ F-0, P-S	1
□ F-0, P-M	5
⊠ F-S, P-M	8
■ F-M, P-M	11
X F-S, P-0	19
○ F-M, P-0	22
⊕ F-M, P-S	23

F= Flecainide
P= Propranolol
0= No Drug

FIGURE 41

R-818-041-01 HOLTZMAN
Means of Left Ventricular End Diastolic Volume

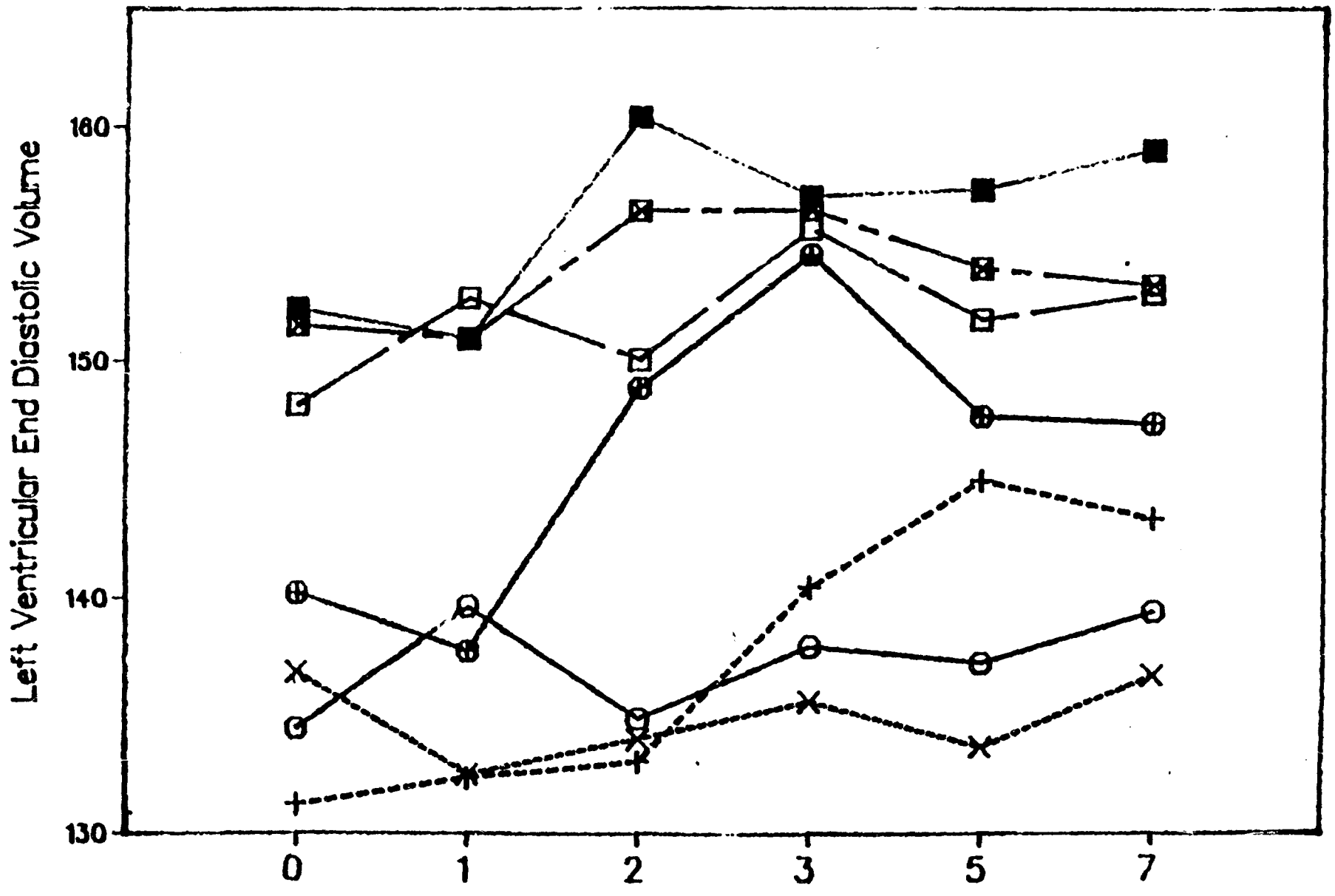


FIGURE 42

R-818-041-01 HOLTZMAN
Means of Mean VCF

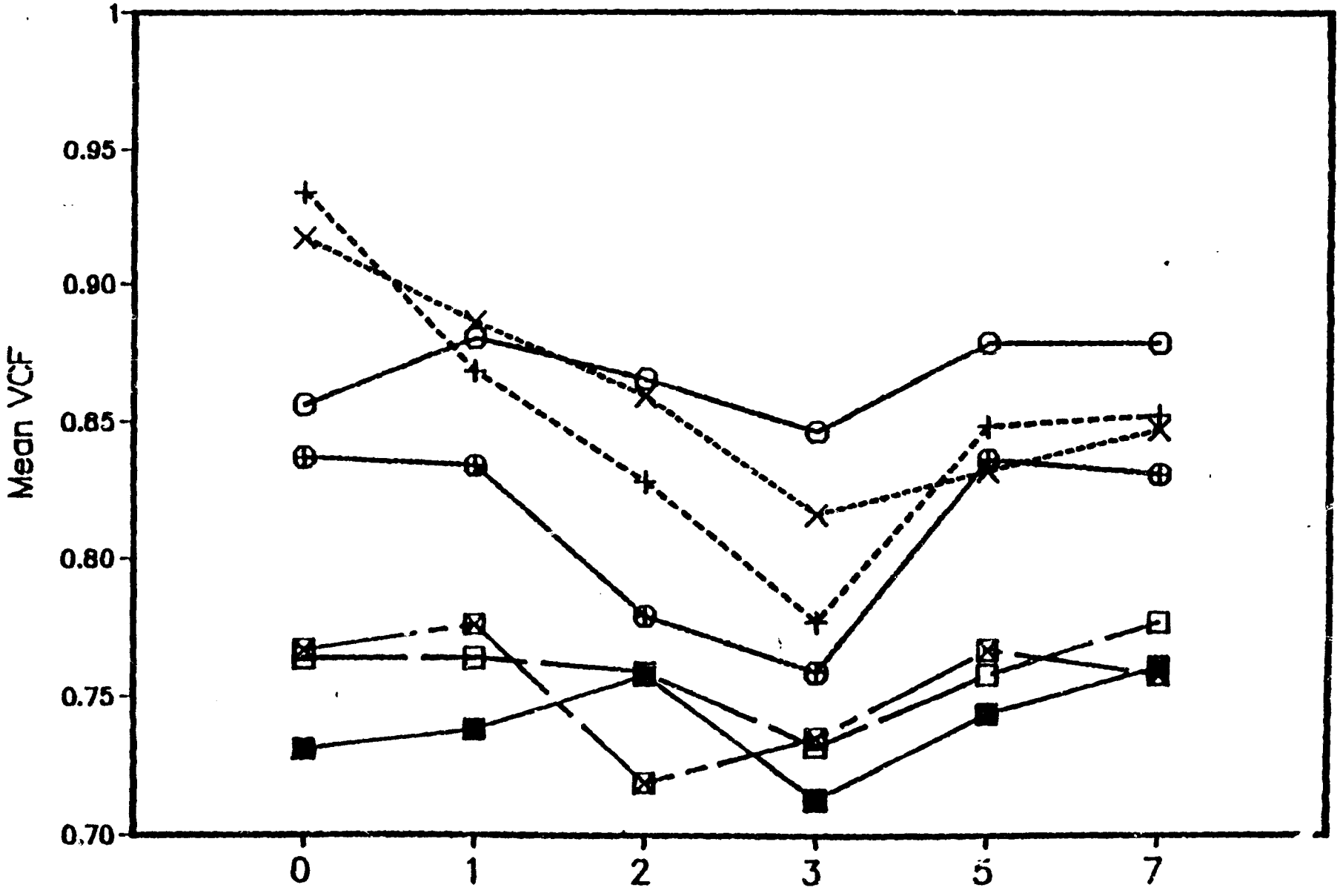
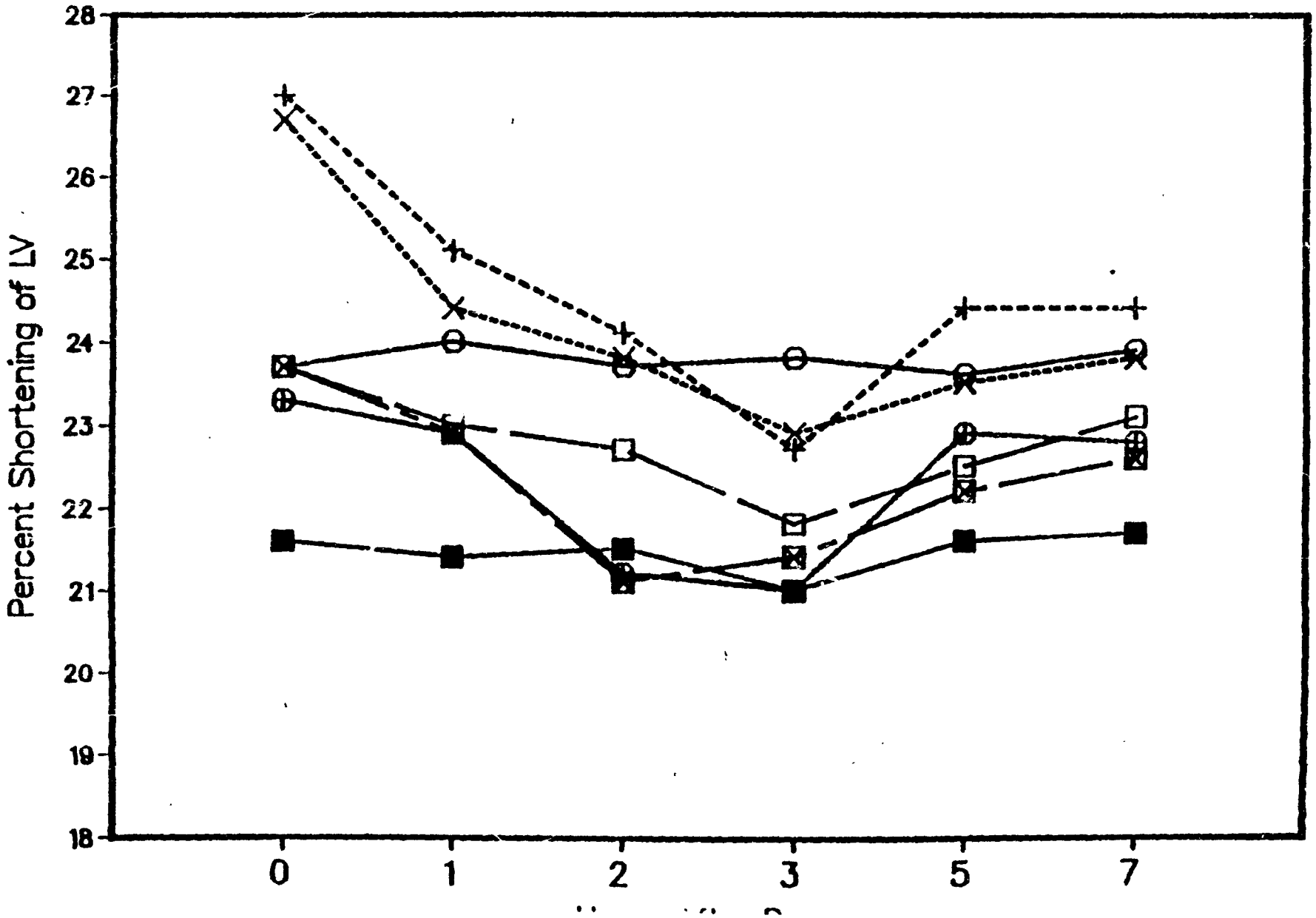


FIGURE 43

R-818-041-01 HOLTZMAN
Means of Percent Shortening of LV



Legend		Study Day
+	F-O, P-S	1
□	F-O, P-M	5
⊠	F-S, P-M	8
■	F-M, P-M	11
X	F-S, P-O	19
O	F-M, P-O	22
⊕	F-M, P-S	23

F= Flecainide
P= Propranolol
O= No Drug
S= Single Dosing

NDA 18-830

FIGURE 44

R-818-041-01 HOLTZMAN
Means of Ejection Fraction

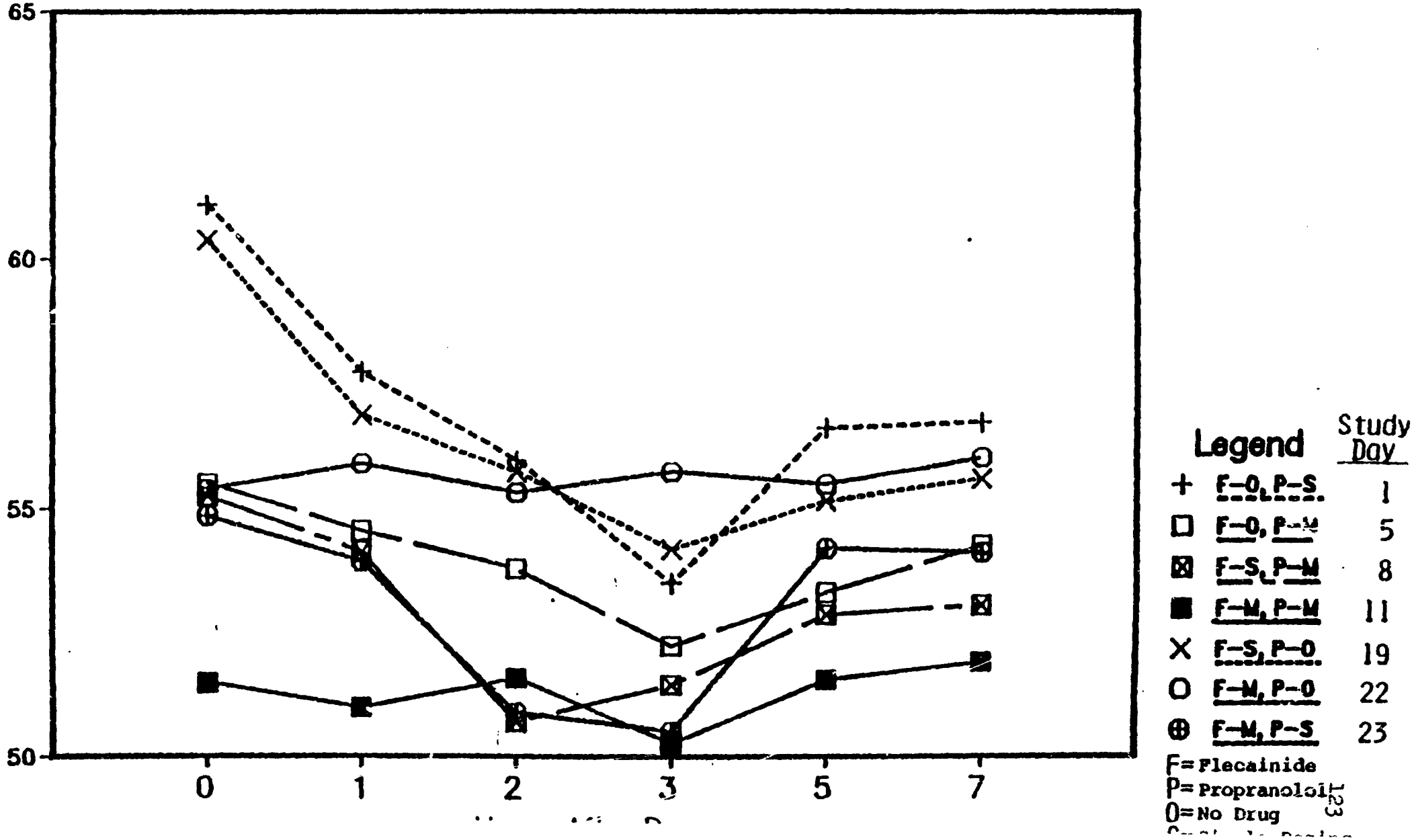
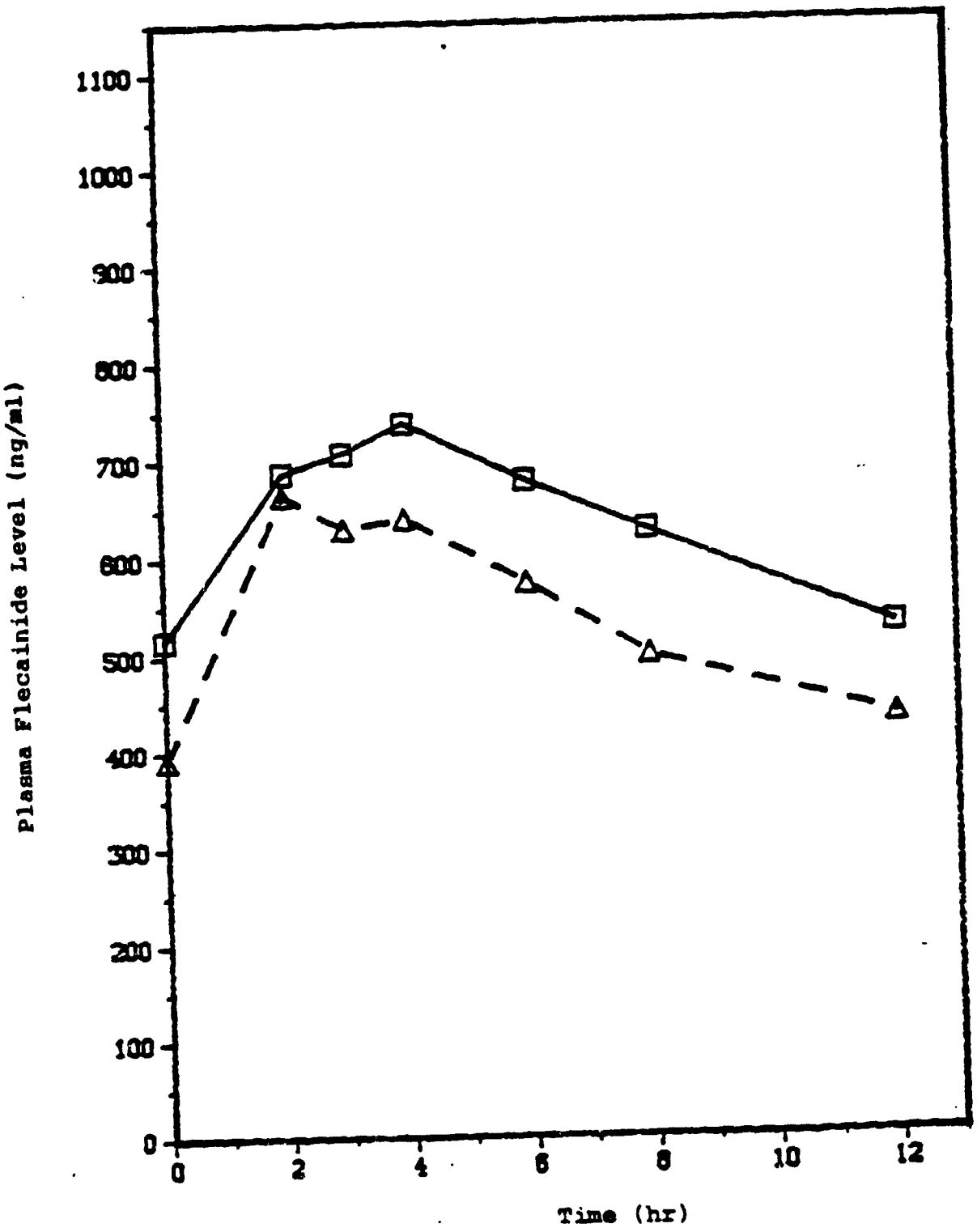


Figure 45: Mean Plasma Flecainide Levels in 10 Subjects on Study Day 23 Following Administration of 200 mg Flecainide Every 12 Hours for Four Days (Days 19-22), Then Coadministration of One 200 mg Flecainide Capsule and a Single 80 mg Propranolol Tablet on Day 23 (△) Compared to Plasma Flecainide Levels on Day 11, the Fourth Day of Coadministration of One 200 mg Flecainide Capsule Every 12 Hours and One 80 mg Propranolol Tablet Every 8 Hours (□).



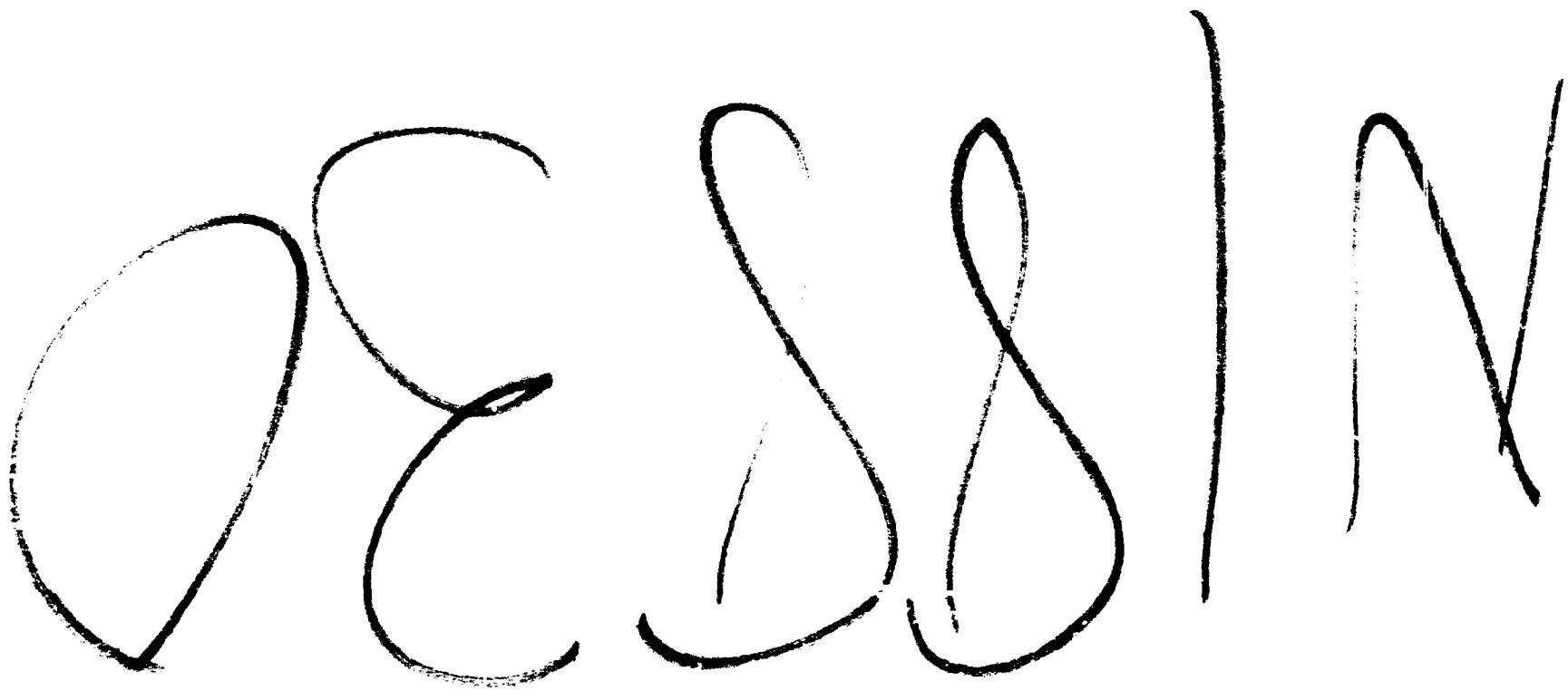
STUDY: R-818-045-01
INVESTIGATOR: GEORGE P. LEWIS,MD
NDA 18-830

TABLE 50

PREDOSE PLASMA DIGOXIN LEVELS FOLLOWING MULTIPLE (ONCE DAILY) ORAL ADMINISTRATION OF 0.25 MG[a]

SUBJECT NUMBER	STUDY DAY:	PLASMA DIGOXIN CONCENTRATION (NG/ML)[b]					
		PRE FLECAINIDE[c]		DURING FLECAINIDE		AFTER FLECAINIDE	
		9	10	13	15	19	22
1							
2							
3							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
16							
17							
MEAN		0.49	0.42	0.57	0.49	0.51	0.39
STD. DEV.		0.28	0.12	0.12	0.11	0.23	0.11

[a] PREDOSE LEVELS WERE DETERMINED ON THE INDICATED DAYS IMMEDIATELY PRIOR TO THE 0800 HOURS DAILY DOSE.
[b] ALL PLASMA DIGOXIN LEVELS ON STUDY DAY 1 (PREDOSE BLANK VALUE) WERE NOT QUANTIFIABLE (<0.15 NG/ML); SEE APPENDIX III.
[c] STUDY BASELINE DAYS.
[d] REPEAT ANALYSES PERFORMED: VALUE GIVEN IS THE MEAN OF ALL DETERMINATIONS EXCEPT WHEN A VALUE WAS ≤0.2 NG/ML (SEE APPENDIX III).



NDA 18-830/S-002
S-003

MAR 6 1987

Riker Laboratories, Inc.
Attention: Florence N. Wong, Pharm.D.
Building 270-3A-01, 3M Center
St. Paul, MN 55144-1000

Dear Dr. Wong:

Please refer to your September 17, 1986 and October 14, 1986 supplemental new drug applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide acetate) Tablets.

We also acknowledge receipt of your amendments dated December 30, 1986 and February 2, 1987.

The supplemental applications as amended provide for the following revisions in the package insert:

S-002

1. A revised paragraph dealing with guidelines for reduced dosage in patients with renal impairment - Dosage and Administration section.

2. A sample "Dear Doctor" letter alerting physicians to the new recommended dosage of flecainide acetate for patients with severe renal impairment.

S-003 added statements providing the following information:

1. Effect of alkaline urine on drug elimination rate - Metabolism section; and a statement that acidification of the urine may promote elimination - Overdosage section.

2. Removal of unabsorbed drug after an overdose - Overdosage section.

3. Effect of age on drug elimination rate - Metabolism section.

4. Excretion of drug in breast milk - Precautions section.

5. Effect of enzyme inducers on drug elimination rate - Drug Interactions, Precautions section.

6. Effect of concomitant use of cimetidine on drug elimination rate - Drug Interactions, Precautions section.

7. Effect of liver disease on drug elimination rate - Precautions section.

8. Interaction with amiodarone - Drug Interactions, Precautions section and Dosage and Administration section.

9. Plasma monitoring - Dosage and Administration section.

We have completed the review of these supplemental applications as amended and they are approved. Our letter of October 31, 1985 detailed the conditions relating to the approval of this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

RL 3/5/87

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-713/GChi
HFN-80/DDIR
HFN-232 (with labeling)
HFN-110/GBuehler/2/20/87;2/27/87
sb/2/26/87;3/4/87/5071s
R/D: CResnick/3/3/87
NRosenthal/3/3/87
THassall for NAM/3/4/87
RWolters/3/3/87

APPROVAL

117

FEB 13 1987

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA #18-830

Name of Drug: TOMBOCOR (Flecainide acetate, R-818)

Sponsor: Riker Lab

Type of Submission: Final Printed Labeling

Date of Submission: February 2, 1987

Date of Review: February 12, 1987

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

The revised package insert FPL (version TR-5, November, 1986) is acceptable.

S. Chun 2/12/87

S. Chun, M.D., HFN-110

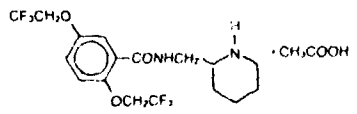
cc:
Orig. NDA 18-830
HFN-83
HFN-110
HFN-110/CSO
HFN-110/SChun/2/2/87
klb/2/12/87/07301

TAMBOCOR®
(flecainide acetate)
Tablets

DESCRIPTION:

TAMBOCOR® (flecainide acetate) is an antiarrhythmic drug available in tablets of 100 mg for oral administration.

Flecainide acetate is benzamide,N-(2-piperidinylmethyl)-2,5-bis (2,2,2-trifluoroethoxy)-, monoacetate. The structural formula is given below:



Flecainide acetate is a white crystalline substance with a pK_a of 9.3. It has an aqueous solubility of 48.4 mg/ml at 37°C.

TAMBOCOR tablets also contain: hydrogenated vegetable oil, magnesium stearate, microcrystalline cellulose and starch.

CLINICAL PHARMACOLOGY:

TAMBOCOR has local anesthetic activity and belongs to the membrane stabilizing (Class I) group of antiarrhythmic agents. It has electrophysiologic effects characteristic of the IC class of antiarrhythmics.

Electrophysiology. In man, TAMBOCOR produces a dose-related decrease in intracardiac conduction in all parts of the heart with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods were observed only in the ventricle. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction (see Warnings).

TAMBOCOR causes a dose-related and plasma-level related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful 30-40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 μg/ml may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 μg/ml. Plasma levels above 0.7 - 1.0 μg/ml are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally.

In animals and isolated myocardium, a negative inotropic effect of flecainide has been demonstrated. Decreases in ejection fraction, consistent with a negative inotropic effect, have been observed after single administration of 200 to 250 mg of the drug in man. Both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses (see Warnings).

Metabolism in Humans. Following oral administration, the absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range, 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life with steady-state levels approached in 3 to 5 days; once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one-fifth as

after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life with steady-state levels approached in 3 to 5 days; once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one-fifth as potent) and the meta-O-dealkylated lactam of flecainide (non-active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found in urine; only 5% of an oral dose is excreted in feces. In patients, free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 μg/ml).

When urinary pH is very alkaline (8 or higher), as may occur in rare conditions (e.g., renal tubular acidosis, strict vegetarian diet), flecainide elimination from plasma is much slower.

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. (See Dosage and Administration.)

In patients with congestive heart failure (NYHA class III), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 14 hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar. (See Dosage and Administration.)

From age 20 to 80, plasma levels are only slightly higher with advancing age. Flecainide elimination from plasma is somewhat slower in elderly subjects than in younger subjects. Patients up to age 80+ have been safely treated with usual dosages.

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 μg/ml. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs (see Precautions, Drug Interactions).

INDICATIONS AND USAGE:

TAMBOCOR is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

TAMBOCOR is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of TAMBOCOR, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, TAMBOCOR, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients depending on their cardiac status and underlying cardiac disease (see Dosage and Administration).

The effects of TAMBOCOR in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including TAMBOCOR, has been shown to have a favorable effect on mortality or sudden death.

CONTRAINDICATIONS:

TAMBOCOR is contraindicated in patients with preexisting second- or third-degree AV block or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Proarrhythmic Effects.

TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias.

In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. Their frequency appears to be related to dose and to the underlying cardiac disease.

Among patients treated for sustained ventricular tachycardia (who frequently also had heart

creased frequency of PVCs or new supraventricular arrhythmias.

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Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule (see Dosage and Administration).

Patients with less serious arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal.

The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).

Heart Failure.
TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of preexisting CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg bid (see Dosage and Administration) and patients should be monitored carefully. Close attention must be given to maintenance of cardiac function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics; others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/ml.

Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose-related increases in PR, QRS, and QT intervals.

PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one-third of patients may develop new first-degree AV heart block (PR interval >0.20 seconds). The QRS complex increases on average about 26% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study, 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur, and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes type arrhythmia associated with TAMBOCOR-induced QT prolongation and bradycardia.

Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block or right bundle branch block associated with a left hemiblock occur, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used

on TAMBOCOR, the degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythmia associated with TAMBOCOR-induced QT prolongation and bradycardia.

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Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally threshold changes are within the range of multiprogrammable pacemakers and, when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture.

Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

PRECAUTIONS:

Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin, a 13% - 19% increase in plasma digoxin levels occurred at six hours postdose.

In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, plasma flecainide levels were increased about 20% and propranolol levels were increased about 30% compared to control values. In this formal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects, when the drugs were administered together, the effects were additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive. In TAMBOCOR clinical trials, patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.

Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction. Limited data in patients receiving known enzyme inducers (phenytoin, phenobarbital, carbamazepine) indicate only a 30% increase in the rate of flecainide elimination. In healthy subjects receiving cimetidine (1 gm daily) for one week, plasma flecainide levels increased by about 30% and half-life increased by about 10%.

When amiodarone is added to flecainide therapy, plasma flecainide levels may increase two-fold or more in some patients. If flecainide dosage is not reduced. (See Dosage and Administration.)

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, the disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgment of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

Pregnancy. Pregnancy Category C. Flecainide has been shown to have teratogenic effects (club paws, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day, respectively; however, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. Limited data suggest that flecainide is excreted in human milk. Because of the drug's potential for serious adverse effects in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.

Hepatic Impairment. Since flecainide elimination from plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma level monitoring is required to guide dosage (see Plasma Level Monitoring); dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days).

ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR, described in detail in Warnings section, were new or exacerbated ventricular arrhythmias which occurred in 7% of patients, and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresponsive ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest, about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these high

TAMBOCOR described in detail in Warnings Section were new or exacerbated ventricular arrhythmias which occurred in 7% of patients and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients TAMBOCOR treatment has been associated with episodes of unacceptable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest in about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/ml.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign post marketing surveillance studies there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects are based on a multicenter efficacy study utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table 1
Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 429 Patients at Any Dose (N = 426)	Incidence by Dose During Upward Titration 200 mg/Day (N = 293)	300 mg/Day (N = 190)	400 mg/Day (N = 100)
Dizziness*	18.9%	11.9%	18.6%	13.0%
Visual Disturbance†	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400-600 mg/day, the incidence of these adverse experiences was similar except for dizziness (32%) and visual disturbances (28%).

The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies. *Body as a Whole* — malaise, fever. *Cardiovascular* — tachycardia, sinus pause or arrest. *Gastrointestinal* — vomiting, diarrhea, dyspepsia, anorexia. *Skin* — rash. *Visual* — diplopia. *Nervous System* — hypesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus. *Psychiatric* — anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients. *Body as a Whole* — swollen lips, tongue and mouth, arthralgia, bronchospasm, myalgia. *Cardiovascular* — angina pectoris, second degree and third-degree AV block, bradycardia, hypertension, hypotension. *Gastrointestinal* — flatulence. *Urinary System* — polyuria, urinary retention. *Hematologic* — leukopenia, thrombocytopenia. *Skin* — urticaria, exfoliative dermatitis, pruritis. *Visual* — eye pain or irritation, photophobia, nystagmus. *Nervous System* — twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor. *Psychiatric* — amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

OVERDOSAGE:

No specific antidote has been established for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the U wave, a reduction in sinus rate and conduction disturbances, hypotension, and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: removal of unabsorbed drug from the gastrointestinal tract, administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol, mechanically assisted respiration, circulation assists such as intra-aortic balloon pumping and transvenous pacing in the event of conduction block. Because of the long plasma half-life of flecainide (12 to 27 hours in patients receiving usual doses) and the possibility of markedly prolonged elimination kinetics at very high doses, these supportive treatments may need to be continued for extended periods of time.

Hemodialysis is not an effective means of removing flecainide acetate rapidly. Since flecainide elimination is much slower when urine is very alkaline (pH 8 or higher), theoretically, acidification of urine to promote drug excretion may be beneficial in overdose cases with very alkaline urine. There is no evidence that acidification from normal urinary pH increases

balloon pumping and transvenous pacing in the event of conduction block. Because of the long plasma half-life of flecainide (12 to 27 hours in patients receiving usual doses) and the possibility of marked, non-linear pharmacokinetics at very high doses, these supportive treatments may need to be continued for extended periods of time.

Hemodialysis is not an effective means of removing flecainide from the blood. Since flecainide is more rapidly eliminated when the urine is very alkaline (pH 8 or higher), therapeutically induced alkalinization of urine (e.g., pre-meal drug ingestion) may be beneficial in overdose cases with very alkaline urine. There is no evidence that acidification from normal urinary secretion

DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels in patients with normal renal and hepatic function may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, **increases in dosage should be made no more frequently than once every four days**, since during the first 2 to 3 days of therapy the optimal effect of a given dose may not be achieved.

For sustained ventricular tachycardia patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most such patients do not require more than 150 mg every 12 hours (300 mg/day), and the maximum dose is 400 mg/day.

For patients with symptomatic nonsustained ventricular tachycardia, couplets, or premature ventricular complexes, the recommended starting dose is also 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day, and the plasma level is below 0.6 μg/ml, the dosage may be cautiously increased to a maximum of 600 mg/day.

Use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and congestive heart failure, particularly during the first few days of dosing (see Warnings). Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients, efficacy at the lower dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction (see Warnings). The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg bid every four days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

In patients with severe renal impairment (creatinine clearance of 35 mL/min/1.73 square meters or less), the initial dosage should be 100 mg once daily (or 50 mg bid). When used in such patients, frequent plasma level monitoring is required to guide dosage adjustments (see Plasma Level Monitoring). In patients with less severe renal disease, the initial dosage should be 100 mg every 12 hours. Plasma level monitoring may also be useful in these patients during dosage adjustment. In both groups of patients, dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days), observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change.

Based on theoretical considerations rather than experimental data, the following suggestion is made when transferring patients from another antiarrhythmic drug to TAMBOCOR: allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting TAMBOCOR at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

When flecainide is given in the presence of amiodarone, reduce the usual flecainide dose by 50% and as usual the patient closely for adverse effects. Plasma level monitoring is strongly recommended to guide dosage with such combination therapy (see below).

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 μg/mL. The probability of adverse experiences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 μg/mL. Periodic monitoring of trough plasma levels may be useful in patient management. Plasma level monitoring is required in patients with severe renal failure or severe hepatic disease. Since plasma level

antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

When flecainide is given to the patient with a myocardial infarction, the usual flecainide dose may be reduced by 50% and therefore the patient's drug regimen after discharge from the hospital should be carefully planned. Plasma level monitoring is strongly recommended to guide dosage adjustments during chronic therapy. (See below)

Plasma Level Monitoring: The large majority of patients studied, treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 µg/ml. The probability of adverse experiences, especially cardiac ones, increases with higher trough plasma levels, especially when these exceed 1.0 µg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Plasma level monitoring is required in patients with severe renal failure or severe hepatic disease. Since elimination of flecainide from plasma may be markedly slower, monitoring of plasma levels is strongly recommended in patients on concurrent amiodarone therapy and may also be helpful in patients with congestive heart failure and in patients with moderate renal disease.

HOW SUPPLIED:

TAMBOCOR is supplied as white round scored tablets containing 100 mg of flecainide acetate and embossed with RIKER on one side and TR 100 on the other side.

Tambocor 100 mg tablet is available in:
Bottles of 100 NDC #0089-0307-10
Boxes of 100 in unit dose blister strips NDC #0089-0307-16

Store at controlled room temperature 15°-30°C (59°-86°F) in a tight, light resistant container.

TR-5 NOVEMBER 1986

Manufactured by
Riker Laboratories, Inc./3M
St. Paul, Minnesota 55144

p.1

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA: 18-830

Name of Drug: Tambocor(flecai· 'e acetate) Tablets

Sponsor: Riker

Type of Submission: Annual Report

Date of Submission: December 30, 1986

Date of Review: January 6, 1987

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

This report covers period from October 85 to 86. There are three supplemental applications to provide for the revision of the package insert which were submitted and approvable. Printed final labeling will be submitted when available.

S-001 Refer to the Chemistry Review.
S-002 & S-003 were reviewed & approved already.

There are a few new references, Electrophysiologic effects of flecainide acetate & its major metabolites in the canine heart [Guehler J. et al. Am J Cardiol 55:807-812, 1985;, Sponsor's clinical report (R-818-061-01) by MA Zinny, Evidence of lack of genetic polymorphic metabolism of flecainide conducted at Riker Lab; sponsor's clinical Report Study R-818-059-01 by JL Holzman; and published Report" Propafenone flecainide and Mexiletine in the treatment of stable ventricular premature beats by HW Klempt published at Kardiale Rhythmusstorungen. 1983, 173. None of these reports are contributing to any change in the labeling.

S C Chun 1/8/86
Sughok K. Chun, M.D.,
HFN-110

cc:
Orig. NDA 18-830
HFN-83
HFN-110
HFN-110/CSO
HFN-110/SChun/12/30/86
klb/1/7/87/07021

9.1

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA #18-830

Name of Drug: Tombocor (flecainide acetate) Tablets

Sponsor: Riker Lab

Type of Submission: ADR

Date of Submission: November 14, 1986

Date of Review: December 9, 1986

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

TT-86-316

RECURRENCE OF HEPATITIS

This 68 year old man had a history of myocardial infarction and coronary artery bypass surgery (December 5, 1985) during which he received blood transfusion. On February 21, 1986 diagnosis of Non-A, Non B hepatitis was made which-- a condition what was considered a result of the earlier transfusions.

Following surgery he had significant problems with PVCs for which neither quinidine nor procainamide proved satisfactory. Flecainide was prescribed April 17, 1986 which was adjusted to a therapeutic dose of 300 mg/day. By mid-July it was apparent that GGT and LDH were increasing along with SGOT, SGPT and alkaline phosphatase. (SGOT, Alk Phos and bilirubin had been elevated as part of the earlier hepatitis). Bilirubin has also increased somewhat. A liver biopsy (July 28, 1986) was reported "to be consistent with toxic hepatitis". Flecainide was discontinued on July 28, 1986. The only laboratory value reported following discontinuation was GGT, drawn on October 14, 1986 which was 172 -- down from it July 23, 1986 value of 316. During flecainide treatment he had been on no other drugs and had no history of amiodarone treatment.

RELEVANT TESTS LABORATORY DATA

	GGT (1.0-30)	SGOT (7-27)	SGPT (8-30)	Alk Phos (8-76)	Bilirubin (0.2-1.2)	LDH (47-140)
02/21/86	ND	475	ND	107	4.2	
03/18/86	ND	14	ND	64	0.5	
04/29/86	121	486	684	212	1.1	
05/20/86	130	9	16	63	0.1	56
07/14/86	272	272				
07/23/86	316	186	284	113	0.7	89
10/14/86	172					

#TT 86-020/Feb. 85-147

POSSIBLE PROPAFENONE INTERACTION, MARKED HYPOTENSION, HEPATIC FUNCTIONS ABNORMAL, POSSIBLE PERICHOLANGIOLITIS

(Although events described here occurred following discontinuation of flecainide and start of propafenone, they began within three half-lives of flecainide and, therefore, presumably while drug was still present.) This 69 year old man had history of alcoholism. With respect to his heart he had LBBB, dilated cardiomyopathy without failure and had presented with syncope associated with VT. His weight was 50kg. Treatment was started with heparin on October 18, 1986 and flecainide (200 mg/day) October 19, 1986. His arrhythmia responded well, but due to QRS widening the dose was reduced to 100 mg/day on October 31, 1986. Lorazepam was added on October 26, 1986 and furosemide on October 31. On November 2, 1987 flecainide was discontinued and propafenone begun. The following day the patient developed hypovolemic shock from which he recovered spontaneously. At this point all drugs were discontinued. The following day he was clinically jaundiced with marked elevations of total bilirubin and transaminases and moderate elevations alk phos, urea and creatinine. By November 18, 1986 all values had returned to within normal limits except prothrombin time which has fallen to 33% on November 3, 1986 was still low at 76%. On November echo exam revealed a small liver, an hepatic biopsy yielded the diagnoses of non-inflammatory portal fibrosis and sclerosing pericholangiolitis (suspected). By November 29, 1986 he was clinically recovered. (Prothrombin time still 80%).

RELEVANT TESTS LABORATORY DATA

	LAB NORM	17OCT PRE-RX	04NOV POST-SHOCK	18NOV	29NOV
Tot. Bilirub.	20	22	105	77	20
SGPT	45	16	2450	45	9
SGOT	30	19	2930	14	12
Alk. Phos.	100	96	129	93	79
Proth Time	100%	91%	33%	76%	89%
Creatinine	115	113	180	93	127
Urea	6.5	7.5	15	5.3	8.8

Flecainide plasm conc. on November 15, 1986 (45 days post dose) = 0.07 microgm/ml (Normal during continual dosing = 0.2-1.0 microgm/ml.

S.C 2/9/87

S. Chun, M.D., HFN-110

cc:
Orig. NDA 18-830
HFN-83
HFN-110
HFN-110/CSO
HFN-110/SChun/12/9/86
klb/2/4/87/07131

9.1

DEC 19

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA # 18-830
NAME OF DRUG: Tombocor (flecainide acetate) Tablets
SPONSOR: Riker
TYPE OF SUBMISSION: ADR
DATE OF SUBMISSION: November 6, 1986
DATE OF REVIEW: November 27, 1986
REVIEWER: Sughok K. Chun, M.D., HFN-110 S.K. Chun 12/17/86

A. Resume:

#RX-86-0070/TT-86-045.
A63Y/M died of lung cancer

#TT-86-417

FEVER, PLEURAL EFFUSION, ARTHRALGIA, ESINOPHILIA, VENTRICULAR FIB.
This 65 years-old woman was being treated with various drugs for atrial fibrillation without results. She was changed to flecainide. The atrial fibrillation was controlled, but ventricular fibrillation required cardioversion (flecainide still ongoing). After one to two weeks of flecainide therapy, she developed intermittent fever and arthralgia, pleural effusion, and eosinophilia. The symptoms soon became intolerable. Flecainide was stopped, and the symptoms resolved. Her ANA titer was not elevated.
WBC normal with a 5-8% eosinophilia; 30% eosinophilia in the pleural effusion.

#TT-86-094
A65 Y/M was hospitalized for CVA.

cc:
Original NDA: 18-830
HFN-110
HFN-110/CSO
HFN-110/SChun/12/1/86
klb/12/15/86/00821

9.1

DEC 30

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA: 18-830

Name of Drug: Tambocor (flecainide acetate) Tablets

Sponsor: Riker Laboratory

Type of Submission: ADR

Date of Submission: October 23, 1986

Date of Review: November 10, 1986

Reviewer: Sughok K. Chun, M.D. (HFN-110)

Resume:

TT-86-257 by:

PURPURA, RENAL FAILURES

This 73-year-old man was admitted to the hospital 5/25/86 for treatment of AMI. He was taking Quinidine, and Lasix . On 5/26/86, he developed VT for which he received two bolus injections of Lidocaine 50 mg and Pronestyl 750 mg by IV drip. In spite of this therapy, VT recurred. On 5/30/86 he was switched to oral Pronestyl, and Solu-Medrol. On 6/2/86, Pronestyl was discontinued and Lidocaine administered for recurring VT. On 6/3/86 Lidocaine was discontinued, a single dose of Tocainide was administered, in spite of which VT persisted. Tambocor 100 mg Q12H was started 6/3/86, and the dose was increased to 150 mg Q12H on 6/4/86, after which time the arrhythmia appeared to be under control. On 6/6/86, Purpura was noted on all four extremities, particularly on palms and soles, and Tambocor was discontinued. The patient's creatinine on admission was 1.4 mg/dl, but was noted to be steadily rising throughout his hospital course. On 6/13/86, his creatinine was 4 mg/dl and Lasix was discontinued. Purpura appears to be subsiding on 6/13/86. Six other drugs have been administered continuously.

S K Chun 12/29/88
Sughok K. Chun, M.D.

cc: Orig. NDA
HFN-110
HFN-110/CSO
HFN-110/SChun
ef:12/29/96:#0767g

NDA 18-830/S-002
S-003

DEC 17 1986

Riker Laboratories, Inc.
Attention: Florence N. Wong, Pharm.D.
Building 270-3A-01, 3M Center
St. Paul, MN 55144-1000

Dear Dr. Wong:

Please refer to your September 17, 1986 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide acetate) Tablets. Also, we acknowledge the receipt on October 16, 1986 of your October 14, 1986 supplemental new drug application submitted for the same drug.

The supplemental applications provide for the following revisions:

S-002

1. A revised paragraph dealing with guidelines for reduced dosage for patients with renal impairment - Dosage and Administration section.

2. A sample "Dear Doctor" letter alerting physicians to the new recommended dosage of flecainide for patients with severe renal impairment.

S-003

1. A statement concerning the effect of alkaline urine on drug elimination rate - Metabolism section; and a statement that acidification of the urine may promote elimination - Overdosage section.

2. A statement regarding removal of unabsorbed drug after an overdose - Overdosage section.

3. A statement regarding the effect of age on drug elimination rate - Metabolism section.

4. A statement regarding excretion of drug in the breast milk - Precautions section.

5. A statement regarding the effect of enzyme inducers on drug elimination rate - Drug Interactions, Precautions section.

6. A statement regarding the effect of concomitant use with cimetidine on drug elimination rate - Drug Interactions, Precautions section.

7. A statement regarding the effect of liver disease on drug elimination rate - Precautions section.

8. A statement regarding interaction with amiodarone - Drug Interactions, Precautions section and Dosage and Administration section.

9. A statement regarding plasma monitoring - Dosage and Administration section.

We have completed the review of these supplemental applications as submitted with draft labeling. Before these supplements may be approved, however, it will be necessary for you to submit final printed labeling. The labeling should incorporate all the proposed changes in both submitted drafts. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Please submit twelve copies of the printed labeling seven of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend these supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw these supplemental applications.

Should you have any questions, please contact:

Mr. Gary Buehler
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

RL 12/17/86

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-83
HFN-110/GBuehler/11/25/86
sb/11/28/86;12/15/86/4565s
R/D: NRosenthal/12/9/86
RWolters/12/9/86
NMorgenstern/12/12/86
SChun/12/1/86
CResnick/12/9/86

APPROVABLE - S-002
ACKNOWLEDGE AND APPROVABLE - S-003

9.1

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA# 18-830/S-003

Name of Drug: Tombocor (flecainide acetate) Tablet

Sponsor: Riker Lab.

Type of Submission: Special Supplement - Changes on Labeling Being Effected

Date of Submission: October 14, 1986 Date of Assignment: Oct 23, 1986

Date of Review: October 23, 1986

Reviewer: Sughok K. Chun, M.D. HFN-110

A. Resume:

This supplement contains changes in labeling to add or strengthen precautions, overdosage, dosage and administration to increase the safe use of the product.

The sponsor plan to start printing this new version in early November. Products packaged in December, 1986 will contain this revised labeling.

B. Conclusion:

All changes in the draft labeling are acceptable. The sponsor may proceed for the final printed labeling.

S. K. Chun 11/23/86

Sughok K. Chun, M.D.

cc:
ORIG
HFN-110
HFN-110/CSO
HFN-110/SChun/10/29/86
cb/10/29/86/1068v

4.1

OCT 6

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA # 18-830

NAME OF DRUG: Tombocor (Flecainide Acetate) Tablets

SPONSOR: Riker Laboratories, INC.

TYPE OF SUBMISSION: Special Supplement - Labeling Change

DATE OF SUBMISSION: September 17, 1986

DATE OF REVIEW: September 19, 1986

REVIEWER: Sughok K. Chun, M.D., HFN-110

A. Resume:

This submission comprises the following documents:

(1) Preliminary Summary, Study R-818-063-01.
The study provides the most direct evidence that an initial dosage of 100 mg b.i.d. of flecainide may be excessive for some patients with severe renal disease and 100 mg daily may provide adequate plasma levels in such patients.

(2) Sponsor's Clinical Report, Study 84-00[illegible]RC-GB-232.
This is a pharmacokinetic study of flecainide acetate in patients with various degrees of chronic renal failure, conducted by Dr. J. Walls in England.

(3) A sample "Dear Doctor" letter alerting physicians to the new recommended dosage of flecainide for patients with severe renal impairment.

(4) A revised, draft package insert with only one paragraph (in Dosage and Administration) changed from the currently approved version. The changed paragraph deals with the use in patients with renal impairment.

*Study #R-818-063-01 by Ralph E. Cutler, M.D., Loma Linda University Medical Center, Loma Linda, CA

This was two-part, open-label study with oral flecainide (F) included an initial single dose and subsequent multiple dosage in patients with chronic renal insufficiency. Patients with varying degrees of renal disease ranging from moderate renal failure (creatinine clearances (CLcr) of less than about 40 ml/min/m^2, but not on routine hemodialysis) to severe renal disease (end-stage and on routine hemodialysis) were selected for the study. Other

than chronic renal disease, patients were free of other complicating clinically significant health problems.

In Part I of the study, all patients received a single, 200 mg oral dose of F. Serial blood samples were obtained predose and periodically during the 96 hours after dosage for plasma F level measurements; complete urine collections were also obtained out to 96 hours postdose from all patients who excreted urine. For patients on hemodialysis, dialysate samples were also collected.

In Part II of the study, patients received multiple oral doses of F for 10 days (either 100 mg every 12 hours or 100 mg once daily). Blood samples for plasma F level determination were collected just before the morning dose (trough levels) on days 1, 3, 5, 7, and 10 and at frequent intervals over the 96 hours after the last dose; total 24-hour urine collections were made for 3 to 4 days after the last dose and selected dialysate samples were collected from patients on hemodialysis.

RESULTS:

A total of 26 patients entered this study. The pharmacokinetic results from the study are based upon data from 21 patients who successfully completed both the single and multiple dosing parts of the study.

The average age of these 21 patients was 57 years (range, 33 to 74 years) and, with the exception of one patient, all were male. Ten patients were on routine hemodialysis (end-stage disease) and had measured or estimated Clcr of less than 5 ml/min/m2; for the 11 patients with moderate renal failure (not on hemodialysis), CLcr ranged from 5.8 to 44 ml/min/m^2 (mean, 20.3 ml/min/m^2).

The data showed that no patient with a CLcr of 15 ml/min/m^2 or greater attained plasma levels of 1.0 ug/ml or greater on a dosage of 100 mg bid (200 mg daily), this regimen continues to be acceptable for this group. However, in patients with CLcr of less than this, 100 mg bid appears to be an unsatisfactory initial dosage, since about one-third attained plasma levels of greater than 1.0 ug/ml on this regimen. Of all the factors examined, CLcr appears to be the only indicator of the risk for any single patient to reach these higher plasma levels. In the interest of maintaining an adequate safety margin, it is therefore recommended that patients with CLcr of 20 ml/min/m^2 or less should receive lower initial doses of 100 mg per day (either 100 mg once daily or 50 mg bid) to avoid plasma levels in excess of 1.0 ug/ml and the potential for adverse effects. In addition, when F is used in such patients with severe renal disease, frequent plasma level monitoring is required as a guide to any dosage adjustment. In patients with less severe renal disease, the initial F dosing regimen should be 100 mg bid and plasma level monitoring should be considered as a guide to dosage adjustments. In both groups of patients, dosage increases should be made cautiously and only after plasma levels have plateaued (more than 4 days).

*Study 84-005-FRC-GB-232
Pharmacokinetics of Flecainide Acetate In Patients With Various Degrees of Chronic Renal Failure by Dr. J. Walls, Area Renal Unit, Leicester General Hospital, England

This open-label, three sequential period study was conducted in patients with renal failure who were not receiving routine hemodialysis treatment.

Patients of either sex, between the ages of 18 and 65 years, whose CLcr were below 12 ml/min/m^2, and who were not receiving hemodialysis treatment were selected for this study. Patients were judged to have moderate renal failure if their CLcr was between 5 and 12 ml/min/m^2 and severe or end-stage renal failure if their CLcr was below 5 ml/min/m^2.

The study was a sequential three-period design with at least a one week washout between study periods. For the intravenous portion (period 1) of the study, patients received 2 mg/kg of F by IV over 15 to 30 minutes; venous blood samples for determination of plasma F levels were taken at 5, 15, 30, and 45 minutes, and at 1, 2, 4, 8, 12, 24, 36, 48, 72, 96, and 120 hours after the end of the infusion. For the single oral dose portion (period 2) of the study, a single 150 mg dose of F was administered orally to each patient; blood samples for determination of plasma F levels were taken at 1, 22, 4, 8, 12, 24, 36, 48, 72, 96, and 120 hours postdose. For the multiple oral dose portion (period 3) of the study, patients who were judged to have moderate renal failure received orally 50 mg of F twice daily for 21 days and patients who were judged to have end-stage renal failure received orally 50 mg of F once daily (morning) for 22 days; on the morning of the 22nd day, all patients received their last dose. For determination of plasma F levels, blood samples were taken just before the morning dose (trough) on days 2, 4, 6, 16, 20, and 22; in addition, blood samples were taken at 1, 2, 4, 8, 12, 24, 36, 48, 72, 96, and 120 hours after the final oral dose on day 22. After the single intravenous and oral doses and after the last dose of the multiple dosing portion of the study, total volumes of urine excreted from 0 to 12, 12 to 24, 24 to 36, 36 to 48, 48 to 72, 72 to 96, and 96 to 120 hours postdose were collected and analyzed for F levels. Selected plasma samples (trough) from the multiple dosing portion of the study were analyzed for levels of free (not conjugated) meta-O-dealkylated flecainide (MODF), a major metabolite of F in humans.

As a measure of safety, ECG rhythm strips were recorded continuously throughout the intravenous administration of F and for 20 minutes thereafter. Further rhythm strips were obtained 4 hours after the single oral dose and weekly during the multiple dose phase.

RESULTS:

Twelve patients (11 male, mean age 49 yrs) with various degrees of renal failure completed this study. Four of the patients (Patients No. 1, 4, 6, and 9) had CLcr below 5.0 ml/min/m^2 during all three phases of the study and Patient No. 12 had a CLcr 6.5 ml/min/m^2 prior to the study but deteriorated

to 2.9 ml/min/m^2 prior to to starting the multiple oral dose phase of the study. Patients No. 1, 4, 6, and 9 were classified as having end-stage renal failure for all phases of the study while patient No. 12 had moderate renal failure for the single oral dose phase but end-stage renal failure for the multiple oral dose phase.

Peak plasma F levels for the eight moderate renal failure patients and for the four end-stage patients after a single, 150 mg oral dose ranged from 198 to 382 ng/ml (mean, 316 ng/ml) and from 274 to 690 ng/ml (mean, 450 ng/ml), respectively. When compared to data from several previous studies in healthy subjects, the peak levels in the moderate group appear to be somewhat higher than in subjects and about twice as high in the end-stage patients as subjects.

The mean times to reach peak plasma F levels after the single, 150 mg oral dose were 3.8 and 3.5 hours for the moderate and end-stage patients, respectively; after 21 days of multiple dosing, these values were approximately the same.

The rate of absorption of F in these renal patients does not appear to be different from healthy subjects, is reasonably prompt, and does not change after multiple dosing.

For the multiple oral dose phase of this study, morning trough plasma F levels. It appears that steady-state or near steady-state plasma levels of F are generally achieved in most patients by the sixth day of dosing although the choice of sampling times makes it impossible to determine precisely when steady-state occurs; thus, prolonged accumulation of F in plasma does not appear to occur in these renal patients.

The plasma half-life of F in the moderate renal failure patients was not appreciably different from plasma clearance in the end-stage patients and did not change appreciably after 21 days of multiple dosing. For the moderate failure patients, the mean plasma clearances after single intravenous (N=5). single oral (N=8), and multiple oral doses (N=5) were 3.76, 3.66, and 2.82 ml/min/kg, respectively; for the end-stage patients, the mean plasma clearances after single intravenous, single oral, and multiple oral doses were 3.47, 2.82, and 3.99 ml/min/kg, respectively. While the mean plasma clearances for these two groups of renal failure patients are clearly lower than the mean plasma clearances of F previously reported for healthy subjects after oral doses. There was some overlap of the plasma clearances for these renal patients with the range of plasma clearances reported for healthy subjects.

In this study with low multiple oral dosage regimens of 50 mg bid (moderate renal patients) and 50 mg daily (end-stage renal patients), steady-state trough plasma levels ranged from about 100 to 400 ng/ml; these levels are below or at the low end of the established range of therapeutic plasma levels (200 to 1000 ng/ml) which are well tolerated (11).

The Volume of distribution (VD) for the moderate failure patients and the end-stage patients did not appear to be appreciably different during any of three dosing periods. The mean VD for the moderate failure patients after single intravenous, single oral and multiple oral doses at steady-state was 7.7, 6.6, and 7.6 l/kg, respectively; the mean VD for the end-stage patients after single intravenous, single oral and multiple oral doses at steady state was 6.2, 5.4, and 7.5 l/kg, respectively. Overall, the VD for F does not appear to be influenced by moderate to severe renal failure and does not change after multiple dosing in patients with chronic renal failure. The range of values for VD in these renal failure patients is well within the range previously reported for healthy adult subjects.

Overall, the comparisons indicate that even in patients with greatly reduced renal clearances, plasma levels of F at steady-state can be reasonably predicted from single dose kinetics. In addition, these comparison results also support the previous conclusion that steady-state plasma levels were generally achieved in most patients prior to estimation of pharmacokinetic data after multiple dosage.

The renal clearance of F was reduced in the end-stage patients when compared to the moderate renal failure patients.

After both single dose periods, the mean renal clearances in the moderate renal failure patients were three to four times greater than in the end-stage patients; the mean renal clearances in the five moderate renal failure patients who received both single intravenous and single oral doses were 74.0 and 52.9 ml/min, respectively about 1/3 of healthy subjects. The renal clearances calculated for patients at steady-state during the multiple dose period were very similar to those values determined for the single dose study periods, and indicate that renal clearance of F does not change with repeated dosing.

Conclusions

In patients with chronic renal failure and not on routine hemodialysis, the rate and extent of oral absorption of F is not altered from that in healthy humans. Although the average plasma half-life is about two-fold longer and the average plasma clearance is clearly reduced in renal failure patients when compared to healthy subjects. These pharmacokinetic parameters tend to be relatively constant in a given patient and do not change appreciably after repeated oral dosing. Apparent Vd for F in renal failure patients is not different from that in healthy volunteers. In patients with severe renal failure (end-stage), the renal clearance of F is considerably reduced; however, the reduction in renal clearance appears to be compensated for by other clearance processes such that the severeity of a patient's renal dysfunction is not necessarily a reliable indicator of total body clearance of F for a given patient. Since F elimination from plasma is slower in renal patients, particularly in more severe renal failure, initial doses should be low and dosage increases should be made cautiously as clinical tolerance permits. In addition, caution should be exercised when F is administered to

renal failure patients concurrently with other drugs that may inhibit nonrenal clearance processes (i.e. biotransformation) or to renal patients who have evidence of cocurrent hepatic dysfunction. The use of plasma level monitoring as a guide for dosage adjustments is recommended for patients with renal failure.

*Dear Doctor letter and proposed addition on package Insert

"In patients with severe renal impairment (creatinine clearance of 35 ml/min/1.73 square meters or less), the initial dosage should be 100 mg once daily (or 50 mg b.i.d.); when used in such patients, frequent plasma level monitoring is required to guide dosage adjustments (see Plasma Level Monitoring). In patients with less severe renal disease, the initial dosage should be 100 mg every 12 hours; plasma level monitoring may also be useful in these patients during dosage adjustment. In both groups of patients, dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days), observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change" and DOSAGE AND ADMINISTRATION is satisfactory.

Dear Doctor letter is acceptable.

S. K. Chun 10/2/86
Sughok K. Chun, M.D.

cc:
~~Orig.~~
HFN-110
HFN-110/CSO
HFN-110/SChun
sh:9/22/86;10/1/86:0645h

-1

NOV 13 1986

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA # 18-830

NOV 13 1986

Name of Drug Tombocor (flecainide)

Sponsor: Riker

Type of Submission: ADR

Date of Submission: 9/3/86

Date of Review: 9/12/86

Reviewer: Sughok K. Chun, M.D. HFN-110

A. Resume:

TT-86-333

PROFOUND HYPOTENSIVE SHOCK
This is a 65-year-old man with history of hypertension and angina of recent onset was treated satisfactorily with nitroglycerin and nifedipine. He had runs of nonsustained ventricular tachycardia. For this latter condition while in the hospital, he was administered 100mg b.i.d. of flecainide. After three days of this regimen, his arrhythmia was we controlled with a 90% reduction of VPCs. About five days into his treatment course, the patient was found unconscious and unresponsive lying on the floor beside his bed in the intensive care unit. Although monitored, nothing had appeared in terms of abnormal EKG nor was it found i. his present condition. His BP was 40/0 and HR of 50. Serum lactate was 23 (this was repeated and confirmed at 23). Cardiac output was determined to have fallen to 2 L/min, internal cardiac chamber pressures incuding PW pressure were normal. Two echocardiograms were WNL. This patient was treated with dobutamine, and 24 hours after the incident his cardiac output was > 4L/min although he remains unresponsive. Flecainide level was drawn shortly after onset of hypotension but results are not yet back.

Concomitant Rx: Nifidipine, NTG.

S K. Chun 10/20/86
Sughok K. Chun, M.D.

cc:
ORIG:
HFN-110
HFN-110/CSO
HFN-110/SChun/10/16/86
cb/10/16/86/1057v

cc: Original NDA
HFN-110
HFN-110/CSO
HFN-83
HFN-232 (with labeling)
HFN-110/CHeald/9/10/86;9/16/86
sb/9/11/86;9/15/86;9/23/86;9/25/86/4180S
R/D: NRosenthal/9/16/86
SChun/9/19/86
CResnick/9/17/86
AThompson/9/16/86
NMorgenstern/9/19/86;9/24/86
SUPPLEMENT APPROVED

NDA 18-830/S-001

OCT 7 1986

Riker Laboratories, Inc.
Attention: Florence N. Wong, Pharm.D.
Building 270-3A, 3M Center
St. Paul, MN 55144-1000

Dear Dr. Wong:

We acknowledge receipt on September 8, 1986 of your September 4, 1986 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide) Tablets.

The supplemental application provides for the voluntary listing of inactive ingredients in your prescription product labeling and the following minor editorial changes to the package insert: rearrangement of the structural formula of the drug substance as requested by Dr. Nathan Rosenthal of this Division, correction of the spelling of hypoesthesia and paresthesia in the Adverse Reactions section, and the addition of the unit dose strips to the How Supplied section.

Most of the labeling changes that you have proposed are permitted by 21 CFR 314.70(c)(2) [formerly 21 CFR 314.8(d)] to be made prior to approval of the supplement. We understand that those changes have been made. The addition of new packaging (such as the unit dose strip) is not permitted to be effected prior to approval of the supplement. You submitted, however, draft labels in the original NDA and they were approvable.

We have completed the review of this supplemental application as submitted with final printed labeling and it is approved. Our letter of October 31, 1985 detailed the conditions relating to the approval of this application.

Please submit twelve copies of the final printed labels for the unit dose strip. Please mount seven of the copies on heavy weight paper or similar materials. Your transmittal letter should refer to this approved supplemental application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

RL 10/7/86

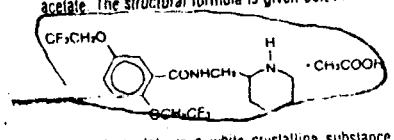
Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

TAMBOCOR®
(flecainide acetate)
Tablets

DESCRIPTION:

TAMBOCOR® (flecainide acetate) is an antiarrhythmic drug available in tablets of 100 mg for oral administration.

Flecainide acetate is benzamide,N-(2-piperidinylmethyl) -2,5-bis (2,2,2-trifluoroethoxy)- ,monoacetate. The structural formula is given below:



Flecainide acetate is a white crystalline substance with a pK_a of 9.3. It has an aqueous solubility of 48.4 mg/ml at 37°C.

TAMBOCOR tablets also contain: hydrogenated vegetable oil, magnesium stearate, microcrystalline cellulose and starch.

CLINICAL PHARMACOLOGY:

TAMBOCOR has local anesthetic activity and belongs to the membrane stabilizing (Class I) group of antiarrhythmic agents; it has electrophysiologic effects characteristic of the IC class of antiarrhythmics.

Electrophysiology. In man, TAMBOCOR produces a dose-related decrease in intracardiac conduction in all parts of the heart with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (AV) nodal conduction time and intraatrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods were observed only in the ventricle. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction (see Warnings).

TAMBOCOR causes a dose-related and plasma-level related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful 30-40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 μg/ml may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 μg/ml. Plasma levels above 0.7 - 1.0 μg/ml are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally.

In animals and isolated myocardium, a negative inotropic effect of flecainide has been demonstrated. Decreases in ejection fraction, consistent with a negative inotropic effect, have been observed after single administration of 200 to 250 mg of the drug in man; both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses (see Warnings).

Metabolism in Humans. Following oral administration, the absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range, 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dos-

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Metabolism in Humans. Following oral administration, the absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range, 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life with steady-state levels approached in 3 to 5 days; once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one-fifth as potent) and the meta-O-dealkylated lactam of flecainide (non-active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found in urine; only 5% of an oral dose is excreted in feces. In patients, free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 μg/ml).

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. (See Dosage and Administration.)

In patients with congestive heart failure (NYHA class III), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 14 hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar. (See Dosage and Administration.)

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 μg/ml. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs (see Precautions, Drug Interactions).

INDICATIONS AND USAGE:

TAMBOCOR is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

TAMBOCOR is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of TAMBOCOR, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, TAMBOCOR, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients depending on their cardiac status and underlying cardiac disease (see Dosage and Administration).

The effects of TAMBOCOR in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including TAMBOCOR, has been shown to have a favorable effect on mortality or sudden death.

CONTRAINDICATIONS:

TAMBOCOR is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Proarrhythmic Effects.

TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias.

In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced

resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias.

In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. Their frequency appears to be related to dose and to the underlying cardiac disease.

Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule (see Dosage and Administration).

Patients with less serious arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal.

The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).

Heart Failure.
TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of preexisting CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg bid (see Dosage and Administration) and patients should be monitored carefully. Close attention must be given to maintenance of cardiac function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics, others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/ml.

Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose related increases in PR, QRS, and QT intervals. PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one-third of patients may develop new first-degree AV heart block (PR interval >0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study, 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur, and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythmia associated with Tambocor-induced QT prolongation and bradycardia

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Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block, or right bundle branch block associated with a left hemiblock occur, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally threshold changes are within the range of multiprogram-

mable pacemakers and, when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture.

Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

PRECAUTIONS:

Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin, a 13% ± 19% increase in plasma digoxin levels occurred at six hours postdose.

In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, plasma flecainide levels were increased about 20% and propranolol levels were increased about 30% compared to control values. In this formal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects; when the drugs were administered together, the effects were additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive. In TAMBOCOR clinical trials, patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.

Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction.

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgment of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

Pregnancy. Pregnancy Category C. Flecainide has been shown to have teratogenic effects (club paws, sternebral and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day, respectively; however, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. It is not known whether flecainide is excreted in human milk. Because many drugs are excreted in human milk and because of the drug's potential for serious adverse effects in infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.

Use in Patients with Hepatic Impairment. Studies to determine the effect of hepatic impairment upon the elimination of TAMBOCOR have not yet been completed. Because the drug undergoes extensive biotransformation (most likely in the liver), patients with significant hepatic impairment should not receive TAMBOCOR unless the potential benefits clearly outweigh the risks.

ADVERSE EFFECTS:

The most serious adverse effects reported for

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.

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ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR, described in detail in Warnings section, were new or exacerbated ventricular arrhythmias which occurred in 7% of patients, and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest, about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/ml.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign post-marketing surveillance studies, there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects are based on a multicenter efficacy study, utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table 1
Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 429 Patients at Any Dose	Incidence by Dose During Upward Titration: 200 mg/Day (N=426)	300 mg/Day (N=293)	400 mg/Day (N=100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance†	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400-600 mg/day, the incidence of these adverse experiences was similar except for dizziness (32%) and visual disturbances (28%).

The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies: *Body as a Whole* – malaise, fever. *Cardiovascular* – tachycardia, sinus pause or arrest. *Gastrointestinal* – vomiting, diarrhea, dyspepsia, anorexia. *Skin* – rash. *Visual* – diplopia. *Nervous System* – hypoesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus. *Psychiatric* – anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients. *Body as a Whole* – swollen lips, tongue and mouth, arthralgia, bronchospasm, myalgia. *Cardiovascular* – angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension. *Gastrointestinal* – flatulence. *Urinary System* – polyuria, urinary retention. *Hematologic* – leukopenia, thrombocytopenia. *Skin* – urticaria, exfoliative dermatitis, pruritis. *Visual* – eye pain or irritation, photophobia, myasthenia. *Nervous System* – twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor. *Psychiatric* – amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the U-wave, a reduction in myocardial rate and contracti

OVERDOSAGE:

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DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels, in patients with normal renal and hepatic function, may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, **increases in dosage should be made no more frequently than once every four days** since during the first 2 to 3 days of therapy the optimal effect of a given dose may not be achieved.

For sustained ventricular tachycardia patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most such patients do not require more than 150 mg every 12 hours (300 mg/day), and the maximum dose is 400 mg/day.

For patients with symptomatic nonsustained ventricular tachycardia, couplets or premature ventricular complexes, the recommended starting dose is also 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day and the plasma level is below 0.6 μg/ml, the dosage may be cautiously increased to a maximum of 600 mg/day.

Use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and congestive heart failure, particularly during the first few days of dosing (see Warnings). Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients, efficacy at the lower dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction (see Warnings). The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg bid every four days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

In patients with renal impairment, the initial dosage should be 100 mg every 12 hours. Dosage increases should be made cautiously at intervals greater than 4 days, observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change. It is recommended that plasma level monitoring be used to guide dosage adjustments (see below).

Based on theoretical considerations, rather than experimental data, the following suggestion is made when transferring patients from another antiarrhythmic drug to TAMBOCOR: allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting TAMBOCOR at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 μg/ml. The probability of adverse experiences

doses are associated with a greater incidence of worsened CHF.

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Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 μg/ml. The probability of adverse experiences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 μg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Because elimination of flecainide from plasma may be slower in patients with severe chronic renal failure or severe congestive heart failure, plasma level monitoring may be especially helpful in these patients.

HOW SUPPLIED:

TAMBOCOR is supplied as white, round, scored tablets containing 100 mg of flecainide acetate and embossed with RIKER on one side and TR 100 on the other side.

Tambocor, 100 mg tablet, is available in:
Bottles of 100 -- NDC #0089-0307-10
Boxes of 100 in unit dose blister strips -- NDC #0089-0307-16

Store at controlled room temperature 15°-30°C (59°-86°F) in a tight, light-resistant container.

TR-3 MARCH 1986

Manufactured by
Riker Laboratories, Inc./3M
St. Paul, Minnesota 55144

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NOV 13 1986

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA# 18-830

Name of Drug: TOMBOCOR (flecainide) Tablets

Sponsor: Riker Lab

Type of Submission: ADR

Date of Submission: 8/28/86

Date of Review: 9/9/86

Reviewer: Sughok K. Chun, M.D. HFN-110

A. Resume:

A case report of "OVERDOSE, GIANT INVERTED T-WAVES, MARKED PROLONGATION OF JT-INTERVAL" by H.J.G.M. Crijns, J.H. Kingma, J.W. Viersma, and K.I. Lie. Accepted for publication about 8/86 in American Heart Journal.

TT-86-304: A 61-year-old woman with a longstanding history of hypertension was treated with flecainide 300 mg t.i.d. at the outpatient department because of Lown IV A arrhytmias causing palpitations. Treatment of hypertension with prazosin 1 mg t.i.d. was left unchanged. The palpitations disappeared rapidly. Two weeks after institution of F the patient was admitted to the hospital with complaints of headaches, blurred vision, photophobia, paraesthesias and general weakness. On admission PE revealed HR 89 beats/min., BP 190/125 mmHg and a fourth heart sound. Full neurologic physical examination was unremarkable. Chest X-ray showed a slight enlargement of the left ventricle and no signs of pulmonary congestion. ECG showed broadening of P-waves, prolongation of PR-interval (0.26 s) and widening of QRS-complexes (0.14 s) with left axis deviation indicating conduction delay in the left anterior fascicle. JTc interval (0.57 s). At that moment the flecainide plasma levels was 2500 ng/ml. Flecainide was discontinued. Hypertension was treated succesfully with captopril. Throughout the whole course of admission serum electrolytes were normal. There was a moderate disturbance of renal function (creat. clearance 40 ml per min) which undoubtfully contributed to the excessively high plasma levels of F. The elimination half life of F appeared to be approximately 80 hours. The most remarkable ECG feature was lengthening of JT-interval to 0.56 s (JTc: 0.60 s), with development of giant inverted T-waves on the third hospital day. These changes persisted from day 3 to day 6, at F plasma levels declining from 1860 to 1125 ng/ml, although at the lower plasma levels the changes were less pronounced. During this period there was a reduction in QRS-width.

No arrhythmia was observed during this period.

At a plasma level of 490 ng/ml the JT-interval normalized and giant inverted T-waves had disappeared, while there was still left axis deviation at a QRS-width of 0.09 s. After complete washout of F ECG normalized completely, however, episodes of VT of probably focal origin appeared. F was resumed at a lower dose of 50 mg b.i.d. resulting in plasma levels around 500 mg/ml. At these plasma levels no ECG-abnormalities were seen apart from the usual QRS-widening.

CONCLUSION:

This patient apart from the known therapeutic effects of F on the surface-ECG also an extreme prolongation of JT-interval with giant inverted T-waves, only occurring in a discrete window of plasma levels between 1860 and 1125 ng/ml. Ideda et.al. reported a modest increase of action potential duration of canine ventricular muscle cells by F. This could explain the increase in JT-interval, expecially at toxic plasma levels in this patient. However, this dose not explain the occurrence of giant negative T-waves. Apart from F intoxication, other possible causes of the reported changes and their transient nature could be concomitant cerebral disorder, or AV-block with a slow escape rhythm, for which no clinical evidence was present.

Primary inhomogeneous depolarization patterns could have provoked these changes in repolarization. Indeed in this patient during washout of F there was a reduction of QRS-width, indicating improvement of intraventricular conduction. However, this was not parallelled by a proportional decrease in the JT-interval, indicating that the observed repolarization disturbances cannot be explained on the basis of slowed intraventricular conduction only.

In view of these considerations the authers concluded that the JT-prolongation with giant inverted T-waves seems to be characteristic of severe F intoxication.

S K Chun 10/20/86

Sughok K. Chun, M.D.

cc:
LORIG
HFN-110
HFN-110/CSO
HFN-110/SChun/10/16/86
cb/10/16/86/1059v

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Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA #: 18-830

Name of Drug: Tombocor (flecainide acetate) Tablets

Sponsor: Riker Lab.

Type of Submission: ADRs

Date of Submission: 6/20/86, 6/18, 6/13/86

Date of Review: July 1, 1986

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

6/20/86 14 ADRs are reported
Sudden cardiac death-3, death due to MI-1, pulmonary edema-4, TIA - 1, Sore throat - 1, Parcytopenia, death* - 1, coma - 1, Neuropathy - 2, recurrent simsitis -1, *Report from France - No detail information

6/18/86 unexpected ADRs are:

#77-86-207 Death, acute renal failure, cholestatic jaundice, elevated liver enzymes, epigastric pain

Patient (72-year-old male) was started on flecainide (100 mg b.i.d.). Patient also had chronic obstructive pulmonary disease and was in CHF. Approximately 4 days after beginning flecainide patient was hospitalized with the chief complaint of epigastric pain and nausea. Lab data revealed an increase bilirubin, serum creatinine, and BUN. Patient showed signs of cholestatic jaundice. A cholesystectomy on 05/04/86 showed no obstruction and was otherwise unremarkable. Patient continued to show evidence of elevated liver enzymes and acute renal failure. Death on 05/09/86.

#77-86-223 Dyspnea, hemoptysis Patient

90-year-old male had been taking F for about one week. Patient suddenly developed dyspnea and began spitting up blood. He was admitted to the hospital for observation and tests. F was discontinued and the patient recovered.

#77-86-230 Hiccups

Patient (65-year-ld male) developed intractable hiccups three days after starting F 100 mg b.i.d. After seven days of intractable hiccups F was discontinued. Prior to discontinuing F, patient was treated with chloral hydrate and phenothiazines for the hiccups with no success.

S K Chun 7/28/86

Sughok K. Chun

cc: ~~Orig.~~
HFN/110
HFN/110/CSO
HFN/110/SChun
keg/7/18/86;7/28/86/0604r

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AUG 19 1986

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA 18-830

Name of Drug: TOMBOCOR (Flecainide) Tab

Sponsor: Riker Laboratories, Inc.

Type of Submission: ADR

Date of Review: 7/29/86

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

TT-86-216: A 67 y/male was hospitalized for surgical removal of a large transitional carcinoma of urinary bladder. He has been taking flecainide for 58 months. Over the years the patient has noted an increase in symptoms and signs of prostatism. At age of two, patient had a benign tomor removed from left inguinal ligament area.

S.K. Chun 8/18/86
Sughok K. Chun, M.D.

cc: Orig. NDA 18-830
HFN/110
HFN/110/CSO
HFN/110/SChun/7/29/86
keg/8/18/86/0665r

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AUG 19 1986

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA 18-830

Name of Drug: TOMBOCOR (Flecainide) Tab

Sponsor: Riker Laboratories, Inc.

Type of Submission: ADR

Date of Review: 7/29/86

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

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S.K. Chun 8/18/86
Sughok K. Chun, M.D.

cc: Orig. NDA 18-830
HFN/110
HFN/110/CSO
HFN/110/SChun/7/29/86
keg/8/18/86/0665r

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA #18-830

NAME OF DRUG: Tombocor (flecainide acetate)

SPONSOR: Riker Laboratories, Inc.

TYPE OF SUBMISSION: ADR

DATE OF SUBMISSION:

DATE OF REVIEW:

REVIEWER: Sughok K. Chun, M.D., HFN-110

A. Resume:

Periodic ADR report December 11, 1985 to March 11, 1986.

Serious labeled:

VT-1, cardiac failure death 1, hypotension 1, arrhythmia/cardiac arrest death 5.

Hepatic function abnormal #1 (TT-86-086): A 48 Y/F with history of severe arteriosclerotic cardiomyopathy, severe CHF and ventricular arrhythmias put on flecainide 100 mg bid. Then, because of fear of the CHF, dose reduced to 50 mg bid which continued to control arrhythmia. Two weeks later she became jaundiced and she was hospitalized where flecainide stopped. Physician felt jaundice was result of severe heart failure and not a drug effect. She later died, but as this was three half-lives beyond D/C of flecainide that death is not considered a drug-related event.

Bronchospasm 1 (TT-86-091): A 65 Y/M developed wheezing asthmatic respiration about 10 days after initiation of Tambocor therapy. Admitted to hospital 3/7/86, for investigation and treatment of bronchospasm, which was becoming more severe, treated with IV aminophyllin and bronchosol (aerosol). Condition was improved, but some bronchospasm still evident.

Serious unlabeled.

Death 24, cardiac failure 7, duodenal ulcer 1, esophaphitis 2, gastroenteritis 1, myocardial infarction 4, suicide attempt 2, infection 4, respiratory disorders 7, rash pustular 1, CVA 3.

NDA 18-830

COMMENTS:

Upon a review of information received this quarter, no information could be incorporated into current labeling on Tombocor.

S. K. Chun 6/17/86
Sughok K. Chun, M.D.

cc: Orig.
HFN-110
HFN-110/CSO
HFN-110/SChun
sh:6/16/86;6/17/86:0559h

N18-830 -002 003, 004

N 10830

NDA 18-830/S-002
S-003

MAR 6

Riker Laboratories, Inc.
Attention: Florence N. Wong, Pharm.D.
Building 270-3A-01, 3M Center
St. Paul, MN 55144-1000

Dear Dr. Wong:

Please refer to your September 17, 1986 and October 14, 1986 supplemental new drug applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide acetate) Tablets.

We also acknowledge receipt of your amendments dated December 30, 1986 and February 2, 1987.

The supplemental applications as amended provide for the following revisions in the package insert:

S-002

1. A revised paragraph dealing with guidelines for reduced dosage in patients with renal impairment - Dosage and Administration section.

2. A sample "Dear Doctor" letter alerting physicians to the new recommended dosage of flecainide acetate for patients with severe renal impairment.

S-003 added statements providing the following information:

1. Effect of alkaline urine on drug elimination rate - Metabolism section; and a statement that acidification of the urine may promote elimination - Overdosage section.

2. Removal of unabsorbed drug after an overdose - Overdosage section.

3. Effect of age on drug elimination rate - Metabolism section.

4. Excretion of drug in breast milk - Precautions section.

5. Effect of enzyme inducers on drug elimination rate - Drug Interactions, Precautions section.

6. Effect of concomitant use of cimetidine on drug elimination rate - Drug Interactions, Precautions section.

7. Effect of liver disease on drug elimination rate - Precautions section.

8. Interaction with amiodarone - Drug Interactions, Precautions section and Dosage and Administration section.

9. Plasma monitoring - Dosage and Administration section.

We have completed the review of these supplemental applications as amended and they are approved. Our letter of October 31, 1985 detailed the conditions relating to the approval of this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

RL 3/5/87

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
~~HFN-110~~
HFN-110/CSO
HFN-713/GChi
HFN-80/DDIR
HFN-232 (with labeling)
HFN-110/GBuehler/2/20/87;2/27/87
sb/2/26/87;3/4/87/507s
R/D: CResnick/3/3/87
NRosenthal/3/3/87
THassall for NAM/3/4/87
RWolters/3/3/87

APPROVAL

NDA 19-830/S-007

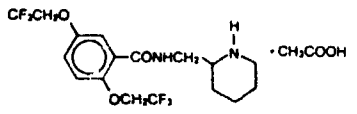
2/20/87

TAMBOCOR®
(flecainide acetate)
Tablets

DESCRIPTION:

TAMBOCOR® (flecainide acetate) is an antiarrhythmic drug available in tablets of 100 mg for oral administration.

Flecainide acetate is benzamide,N-(2-piperidinylmethyl) -2,5-bis (2,2,2-trifluoroethoxy)- ,monoacetate. The structural formula is given below:



Flecainide acetate is a white crystalline substance with a pK_a of 9.3. It has an aqueous solubility of 48.4 mg/ml at 37°C.

TAMBOCOR tablets also contain: hydrogenated vegetable oil, magnesium stearate, microcrystalline cellulose and starch.

CLINICAL PHARMACOLOGY:

TAMBOCOR has local anesthetic activity and belongs to the membrane stabilizing (Class I) group of antiarrhythmic agents; it has electrophysiologic effects characteristic of the IC class of antiarrhythmics.

Electrophysiology. In man, TAMBOCOR produces a dose-related decrease in intracardiac conduction in all parts of the heart with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (AV) nodal conduction time and intraatrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods were observed only in the ventricle. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction (see Warnings).

TAMBOCOR causes a dose-related and plasma-level related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful 30-40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 μg/ml may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 μg/ml. Plasma levels above 0.7 - 1.0 μg/ml are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally.

In animals and isolated myocardium, a negative inotropic effect of flecainide has been demonstrated. Decreases in ejection fraction, consistent with a negative inotropic effect, have been observed after single administration of 200 to 250 mg of the drug in man; both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses (see Warnings)

Metabolism in Humans. Following oral administration, the absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range, 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-

once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 1[illegible] mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one-fifth as potent) and the meta-O-dealkylated lactam of flecainide (non-active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found in urine; only 5% of an oral dose is excreted in feces. In patients, free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 μg/ml).

When urinary pH is very alkaline (8 or higher), as may occur in rare conditions (e.g., renal tubular acidosis, strict vegetarian diet), flecainide elimination from plasma is much slower.

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. (See Dosage and Administration.)

In patients with congestive heart failure (NYHA class III), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 14 hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar. (See Dosage and Administration.)

From age 20 to 80, plasma levels are only slightly higher with advancing age; flecainide elimination from plasma is somewhat slower in elderly subjects than in younger subjects. Patients up to age 80+ have been safely treated with usual dosages.

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 μg/ml. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs (see Precautions, Drug Interactions).

INDICATIONS AND USAGE:

TAMBOCOR is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

TAMBOCOR is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of TAMBOCOR, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, TAMBOCOR, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients depending on their cardiac status and underlying cardiac disease (see Dosage and Administration).

The effects of TAMBOCOR in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including TAMBOCOR, has been shown to have a favorable effect on mortality or sudden death.

CONTRAINDICATIONS:

TAMBOCOR is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Proarrhythmic Effects.

TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias.

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In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. Their frequency appears to be related to dose and to the underlying cardiac disease.

Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 3.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule (see Dosage and Administration).

Patients with less serious arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal.

The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).

Heart Failure.

TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 35%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of pre-

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Heart Failure.
TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of preexisting CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg bid (see Dosage and Administration) and patients should be monitored carefully. Close attention must be given to maintenance of cardiac function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics, others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/ml.

Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose-related increases in PR, QRS, and QT intervals.

PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one-third of patients may develop new first-degree AV heart block (PR interval ≥0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study, 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur, and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythmia associated with TAMBOCOR-induced QT prolongation and bradycardia.

Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block, or right bundle branch block associated with a left hemiblock occur, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally threshold changes are within the range of multiprogrammable pacemakers and, when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture.

Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin, a 13% ±19% increase in plasma digoxin levels occurred at six hours postdose.

In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, plasma flecainide levels were increased about 20% and protocontrol values. In this formal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects; when the drugs were administered together, the effects were additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive. In TAMBOCOR clinical trials, patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.

Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction. Limited data in patients receiving known enzyme inducers (phenytoin, phenobarbital, carbamazepine) indicate only a 30% increase in the rate of flecainide elimination. In healthy subjects receiving cimetidine (1 gm daily) for one week, plasma flecainide levels increased by about 30% and half-life increased by about 10%.

When amiodarone is added to flecainide therapy, plasma flecainide levels may increase two-fold or more in some patients, if flecainide dosage is not reduced. (See Dosage and Administration.)

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgment of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

Pregnancy. Pregnancy Category C. Flecainide has been shown to have teratogenic effects (club paws, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day, respectively; however, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. Limited data suggest that flecainide is excreted in human milk. Because of the drug's potential for serious adverse effects in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.

Hepatic Impairment. Since flecainide elimination from plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma level monitoring is required to guide dosage (see Plasma Level Monitoring); dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days).

ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR, described in detail in Warnings section, were new or exacerbated ventricular arrhythmias which occurred in 7% of patients, and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest, about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/ml.

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There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign post-marketing surveillance studies, there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure, and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice, signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects are based on a multicenter efficacy study, utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table 1
Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 429 Patients at Any Dose	Incidence by Dose During Upward Titration 200 mg/Day (N=426)	300 mg/Day (N=293)	400 mg/Day (N=100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance†	15.5%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400-600 mg/day, the incidence of these adverse experiences was similar, except for dizziness (32%) and visual disturbances (28%).

The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies: *Body as a Whole* – malaise, fever; *Cardiovascular* – tachycardia, sinus pause or arrest; *Gastrointestinal* – vomiting, diarrhea, dyspepsia, anorexia; *Skin* – rash; *Visual* – diplopia; *Nervous System* – hypoesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus; *Psychiatric* – anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients: *Body as a Whole* – swollen lips, tongue and mouth; arthralgia, bronchospasm, myalgia; *Cardiovascular* – angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension; *Gastrointestinal* – flatulence; *Urinary System* – polyuria, urinary retention; *Hematologic* – leukopenia, thrombocytopenia; *Skin* – urticaria, exfoliative dermatitis, pruritis; *Visual* – eye pain or irritation, photophobia, nystagmus; *Nervous System* – twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor; *Psychiatric* – amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the T wave, reduction in myocardial rate and contracti-

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Hemodialysis is not an effective means of removing flecainide from the body. Since flecainide elimination is much slower when urine is very alkaline (pH 8 or higher), theoretically, acidification of urine to promote drug excretion may be beneficial in overdose cases with very alkaline urine. There is no evidence that acidification from normal urinary pH increases excretion.

DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels, in patients with normal renal and hepatic function, may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, **increases in dosage should be made no more frequently than once every four days**, since during the first 2 to 3 days of therapy the optimal effect of a given dose may not be achieved.

For sustained ventricular tachycardia patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg

significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels in patients with normal renal and hepatic function may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, **increases in dosage should be made no more frequently than once every four days**, since during the first 2 to 3 days of therapy the optimal effect of a given dose may not be achieved.

For sustained ventricular tachycardia patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most such patients do not require more than 150 mg every 12 hours (300 mg/day), and the maximum dose is 400 mg/day.

For patients with symptomatic nonsustained ventricular tachycardia, couplets, or premature ventricular complexes the recommended starting dose is also 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day, and the plasma level is below 0.6 μg/ml, the dosage may be cautiously increased to a maximum of 600 mg/day.

Use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and congestive heart failure, particularly during the first few days of dosing (see Warnings). Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients, efficacy at the lower dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction (see Warnings). The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg bid every four days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

In patients with severe renal impairment (creatinine clearance of 35 ml/min/1.73 square meters or less), the initial dosage should be 100 mg once daily (or 50 mg bid), when used in such patients, frequent plasma level monitoring is required to guide dosage adjustments (see Plasma Level Monitoring). In patients with less severe renal disease, the initial dosage should be 100 mg every 12 hours; plasma level monitoring may also be useful in these patients during dosage adjustment. In both groups of patients, dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days), observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change.

Based on theoretical considerations rather than experimental data, the following suggestions are made: when transferring patients from another antiarrhythmic drug to TAMBOCOR allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting TAMBOCOR at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

When flecainide is given in the presence of amiodarone, reduce the usual flecainide dose by 50% and monitor the patient closely for adverse effects. Plasma level monitoring is strongly recommended to guide dosage with such combination therapy (see below).

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 μg/ml. The probability of adverse experiences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 μg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Plasma level monitoring is required in patients with severe renal failure or severe hepatic disease, since elimination of flecainide from plasma may be markedly slower. Monitoring of plasma levels is strongly recommended in patients on concurrent amiodarone therapy and may also be helpful in patients with congestive heart failure and in patients with moderate renal disease.

HOW SUPPLIED:

TAMBOCOR is supplied as white, round, scored tablets containing 100 mg of flecainide acetate and embossed with RIKER on one side and TR 100 on the other side.

Tambocor, 100 mg/tablet, is available in:
Bottles of 100 — NDC #0089-0307-10
Boxes of 100 in unit dose blister strips — NDC #0089-0307-16.

Store at controlled room temperature 15°-30°C (59°-86°F) in a tight, light-resistant container.

TR-5 NOVEMBER 1986

Manufactured by:
Riker Laboratories, Inc./3M
St. Paul, Minnesota 55144

111

FEB 13

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA #18-830

Name of Drug: TOMBOCOR (Flecainide acetate, R-818)

Sponsor: Riker Lab

Type of Submission: Final Printed Labeling

Date of Submission: February 2, 1987

Data of Review: February 12, 1987

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

The revised package insert FPL (version TR-5, November, 1986) is acceptable.

S. Chun 2/12/87
S. Chun, M.D., HFN-110

cc:
Orig. NDA 18-830
HFN-83
HFN-110
HFN-110/CSO
HFN-110/SChun/2/2/87
klb/2/12/87/07301

9.1

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA# 18-830/S-003

Name of Drug: Tombocor (flecainide acetate) Tablet

Sponsor: Riker Lab.

Type of Submission: Special Supplement - Changes on Labeling Being Effected

Date of Submission: October 14, 1986 Date of Assignment: Oct 23, 1986

Date of Review: October 23, 1986

Reviewer: Sughok K. Chun, M.D. HFN-110

A. Resume:

This supplement contains changes in labeling to add or strengthen precautions, overdosage, dosage and administration to increase the safe use of the product.

The sponsor plan to start printing this new version in early November. Products packaged in December, 1986 will contain this revised labeling.

B. Conclusion:

All changes in the draft labeling are acceptable. The sponsor may proceed for the final printed labeling.

S.K. Chun 11/03/86
Sughok K. Chun, M.D.

cc:
ORIG
HFN-110
HFN-110/CSO
HFN-110/SChun/10/29/86
cb/10/29/86/1068v

11.(

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFN-110

2. NDA NUMBER: 18-830

3. NAME AND ADDRESS OF APPLICANT (City and State)
Riker Laboratories/3M
St. Paul, Minnesota 55144-1000

4. AP NUMBER

5. SUPPLEMENT (S)
NUMBER(S) | DATE(S): 1-2-87

6. NAME OF DRUG: TAMBOCOR

7. NONPROPRIETARY NAME: flecainide acetate

8. SUPPLEMENT(S) PROVIDES FOR:

9. AMENDMENTS AND OTHER (Reports, etc.) DATES

10. PHARMACOLOGICAL CATEGORY

11. HOW DISPENSED: XX Rx ___ OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S): tablet

14. POTENCY (Ibs.): 100 mg or 200 mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS
CURRENT: ___ YES ___ NO
REVIEWED: ___ YES ___ NO

17. COMMENTS

The revised package insert in final print dated November 1986 was submitted February 2, 1987 and received in HFN-110 February 6, 1987. This labeling is technically correct from the standpoint of the reviewing chemist.

18. CONCLUSIONS AND RECOMMENDATIONS

Approved

2/27/87

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Nathan R. Rosenthal, Ph.D.	Nathan R. Rosenthal	Feb. 27, 1987

DISTRIBUTION: ☑ ORIGINAL JACKET ☐ REVIEWER ___ DIVISION FILE

FORM FDA 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

NDA 18-830/S-002
S-003

DEC 17 1986

Riker Laboratories, Inc.
Attention: Florence N. Wong, Pharm.D.
Building 270-3A-01, 3M Center
St. Paul, MN 55144-1000

Dear Dr. Wong:

Please refer to your September 17, 1986 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide acetate) Tablets. Also, we acknowledge the receipt on October 16, 1986 of your October 14, 1986 supplemental new drug application submitted for the same drug.

The supplemental applications provide for the following revisions:

S-002

1. A revised paragraph dealing with guidelines for reduced dosage for patients with renal impairment - Dosage and Administration section.

2. A sample "Dear Doctor" letter alerting physicians to the new recommended dosage of flecainide for patients with severe renal impairment.

S-003

1. A statement concerning the effect of alkaline urine on drug elimination rate - Metabolism section; and a statement that acidification of the urine may promote elimination - Overdosage section.

2. A statement regarding removal of unabsorbed drug after an overdose - Overdosage section.

3. A statement regarding the effect of age on drug elimination rate - Metabolism section.

4. A statement regarding excretion of drug in the breast milk - Precautions section.

5. A statement regarding the effect of enzyme inducers on drug elimination rate - Drug Interactions, Precautions section.

6. A statement regarding the effect of concomitant use with cimetidine on drug elimination rate - Drug Interactions, Precautions section.

7. A statement regarding the effect of liver disease on drug elimination rate - Precautions section.

8. A statement regarding interaction with amiodarone - Drug Interactions, Precautions section and Dosage and Administration section.

9. A statement regarding plasma monitoring - Dosage and Administration section.

We have completed the review of these supplemental applications as submitted with draft labeling. Before these supplements may be approved, however, it will be necessary for you to submit final printed labeling. The labeling should incorporate all the proposed changes in both submitted drafts. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Please submit twelve copies of the printed labeling seven of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend these supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw these supplemental applications.

Should you have any questions, please contact:

Mr. Gary Buehler
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

RZ 12/17/86

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-83
HFN-110/GBuehler/11/25/86
sb/11/28/86;12/15/86/4565s
R/D: NRosenthal/12/9/86
RWolters/12/9/86
NMorgenstern/12/12/86
SChun/12/1/86
CResnick/12/9/86

APPROVABLE - S-002
ACKNOWLEDGE AND APPROVABLE - S-003

NDA 18-830/S-004 OCT 5 1987

Riker Laboratories, Inc.
Attention: Florence N. Wong, Pharm. D.
Bldg. 270-3A, 3M Center
St. Paul, Minnesota 55144-1000

Dear Dr. Wong:

Please refer to your December 30, 1986 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor Tablets (flecainide acetate) 100 mg or 200 mg strength.

The supplemental application provides for revision of the formulation to include croscarmellose sodium as an inert ingredient.

We have completed the review of this supplemental application and it is approved. Our letter of October 31, 1985 detailed the conditions relating to the approval of this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

RJW 10/2/87

Robert J. Wolters, Ph.D.
Supervisory Chemist
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-713/GChi
HFN-80/DDIR
HFN-232 (with labeling)
HFN-110/NRosenthal/6/23/87;10/1/87 N.R. Rosenthal 10/1/87
clb/10/1/87/1796k

APPROVAL

NOV 10 1987

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION
HFN-110

2. NDA NUMBER
18-830

3. NAME AND ADDRESS OF APPLICANT (City and State)
Riker Laboratories
St. Paul, Minnesota

4. AF NUMBER

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-004	12/30/86
S-005	12/30/86
S-006	12/30/86

6. NAME OF DRUG
TAMBOCOR

7. NONPROPRIETARY NAME
flecainide acetate

8. SUPPLEMENT(S) PROVIDES FOR:
S-004 croscarmellose sodium new ingredient
S-005 new drug product 150 mg strength
S-006 new manufacturing facility in U.K., EIR pending

9. AMENDMENTS AND OTHER (Reports, etc.) DATES
S-005 6/8/87
S-006 6/10/87

10. PHARMACOLOGICAL CATEGORY
cardiac depressant

11. HOW DISPENSED
☒ RX ☐ OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S)
tablet

14. POTENCY (Use)
100 mg. ; 200 mg.
150 mg. (new)

15. CHEMICAL NAME AND STRUCTURE
Please refer to Chemist Review No. 1.

16. RECORDS AND REPORTS
CURRENT ☐ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS
Bio review completed; waiver granted.

18. CONCLUSIONS AND RECOMMENDATIONS

S-004 Satisfactory; draft letter attached: approved for formulation revision.
S-005 Satisfactory; draft letter attached: approvable pending submission of FPL.
S-006 No action until completion of a satisfactory EIR-expected within 2 months - per telecon with Dr. Florence Wong 6/23/87.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Nathan R. Rosenthal, Ph.D.		6/23/87

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FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

1

N 18830 CAST S-010

A1880
CAST

AUG 30 1989

NDA 18-830/S-010

Riker Laboratories, Inc.
Attention: Mr. Gene L. Harris
Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000

Dear Mr. Harris:

Please refer to your May 10, 1989 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide acetate).

We also acknowledge receipt of your amendment dated August 10, 1989.

The supplemental application, as amended, provides for final printed labeling revised to include the Agency's requested changes as a result of the announcement of the Cardiac Arrhythmia Suppression Trial (CAST) results and modified according to my telephone discussions and agreements with Dr. Florence Wong of Riker. As we have agreed, you have made the following changes from your May 10 draft:

Indications and Usage

1. The first sentence has been reworded from ". . . treatment of documented life-threatening . . ." to ". . . that in the judgment of the physician, are life-threatening."

2. The following statements have also been added:

(a) "Because of the proarrhythmic effects of Tambocor, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks."

(b) "The effect of Tambocor in patients with recent myocardial infarction (except as described in the Warnings section) . . ."

(c) "As is the case of other antiarrhythmic agents, there is no evidence from controlled trials that the use of Tambocor favorably affects survival or the incidence of sudden death."

Warnings

1. The statement, "The average duration of treatment with Tambocor in this study was 10 months," was added to the end of the first paragraph of the Mortality subsection of the Warnings section and the entire paragraph was included in a black box.

2. The following second paragraph was added to the same subsection:

> The applicability of these results to other populations (e.g., those without recent infarction) is uncertain, but at present it is prudent to consider the risks of Class IC agents, coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

We have completed the review of this supplemental application and it is approved. Our letter of October 31, 1989 detailed the conditions relating to the approval of this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

We request that at the next printing you make some additional changes for the sake of consistency. The following statement in the last paragraph of the Proarrhythmia subsection of the Warnings section should be deleted:

> Hospitalization should also be considered for other patients with underlying structural heart disease (See Dosage and Administration).

It does not agree with the first sentence in the Dosage and Administration section:

> For patients with sustained ventricular tachycardia, no matter what their cardiac status, Tambocor, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring (see Warnings).

That sentence should be retained, however, the "(see Warnings)" phrase should be deleted. Throughout the labeling you use the trade name, Tambocor, to refer to your product except in the Effects on Pacemaker Thresholds subsection of the Warnings section in which you refer to "flecainide." It would be more consistent to switch that reference to "Tambocor."

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-80/ODIR
HFD-100
HFD-232 (with labeling)
HFD-730
HFD-110/MO'Hagan/3/22/90
sb/3/20/90;3/31/90/2691S
R/D: MMorgenstern/3/30/90

APPROVAL

Labeling: HFD-110
NDA No: 18-830 Rc'd. Aug 21, 1989
Reviewed by: [redacted] 8/21/89

TAMBOCOR®

FINAL PRINTED PACKAGE INSERT

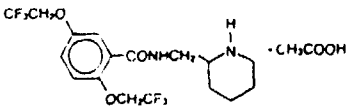
APPROVED

TAMBOCOR®
(flecainide acetate)
TABLETS
AUG 30 1989

DESCRIPTION:

TAMBOCOR® (flecainide acetate) is an antiarrhythmic drug available in tablets of 50, 100 or 150 mg for oral administration.

Flecainide acetate is benzamide, N-(2-piperidinyl methyl)-2,5-bis (2,2,2-trifluoroethoxy)-, monoacetate. The structural formula is given below.



Flecainide acetate is a white crystalline substance with a pK_a of 9.3. It has an aqueous solubility of 48.4 mg/ml at 37°C.

TAMBOCOR tablets also contain: croscarmellose sodium, hydrogenated vegetable oil, magnesium stearate, microcrystalline cellulose and starch.

CLINICAL PHARMACOLOGY:

TAMBOCOR has local anesthetic activity and belongs to the membrane stabilizing (Class I) group of antiarrhythmic agents. It has electrophysiologic effects characteristic of the IC class of antiarrhythmics.

Electrophysiology. In man, TAMBOCOR produces a dose-related decrease in intracardiac conduction in all parts of the heart with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods were observed only in the ventricle. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction. (See Warnings.)

TAMBOCOR causes a dose-related and plasma-level related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful 30-40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 μg/ml may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 μg/ml. Plasma levels above 0.7 - 1.0 μg/ml are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate

[redacted] stearate, microcrystalline cellulose and starch

CLINICAL PHARMACOLOGY:

TAMBOCOR has local anesthetic activity and belongs to the membrane stabilizing (Class I) group of antiarrhythmic agents; it has electrophysiologic effects characteristic of the IC class of antiarrhythmics.

Electrophysiology. In man, TAMBOCOR produces a dose-related decrease in intracardiac conduction in all parts of the heart with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods were observed only in the ventricle. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction. (See Warnings.)

TAMBOCOR causes a dose-related and plasma-level related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful 30-40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 μg/ml may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 μg/ml. Plasma levels above 0.7 - 1.0 μg/ml are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally.

In animals and isolated myocardium, a negative inotropic effect of flecainide has been demonstrated. Decreases in ejection fraction, consistent with a negative inotropic effect, have been observed after single administration of 200 to 250 mg of the drug in man; both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses. (See Warnings.)

Metabolism in Humans. Following oral administration, the absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range, 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life with steady-state levels approached in 3 to 5 days, once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one-fifth as potent) and the meta-O-dealkylated lactam of flecainide (non active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found in urine; only 5% of an oral dose is excreted in feces. In patients, free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 μg/ml).

When urinary pH is very alkaline (8 or higher), as may occur in rare conditions (e.g., renal tubular acidosis, strict vegetarian diet), flecainide elimination from plasma is much slower.

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. (See Dosage and Administration.)

In patients with congestive heart failure (NYHA class III), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 14 hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar. (See Dosage and Administration.)

From age 20 to 80, plasma levels are only slightly higher with advancing age. Flecainide elimination from plasma is somewhat slower in elderly subjects than in younger subjects. Patients up to age 89+ have been safely treated with usual dosages.

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 μg/ml. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs. (See Precautions, Drug Interactions.)

INDICATIONS AND USAGE:

TAMBOCOR is indicated for the treatment of docu-[redacted]

[redacted] slower than for healthy subjects (mean half-life, 1[illegible] hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar. (See Dosage and Administration.)

From age 20 to 80, plasma levels are only slightly higher with advancing age. Flecainide elimination from plasma is somewhat slower in elderly subjects than in younger subjects. Patients up to age 80+ have been safely treated with usual dosages.

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 μg/ml. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs. (See Precautions, Drug Interactions.)

INDICATIONS AND USAGE:

TAMBOCOR is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgment of the physician, are life-threatening. Because of the proarrhythmic effects of TAMBOCOR, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks. The use of TAMBOCOR is not recommended in patients with less severe ventricular arrhythmias even if the patients are symptomatic.

Use of TAMBOCOR for the treatment of sustained ventricular tachycardia, like other antiarrhythmics, should be initiated in the hospital.

The effects of TAMBOCOR in patients with recent myocardial infarction (except as described in the WARNINGS section) and in patients with supraventricular tachycardia have not been adequately studied. As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of TAMBOCOR favorably affects survival or the incidence of sudden death.

CONTRAINDICATIONS:

3 TAMBOCOR is contraindicated in patients with pre-existing second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Mortality.

TAMBOCOR was included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-center, randomized, double-blind study in patients with asymptomatic non-life-threatening arrhythmias who had a myocardial infarction more than six days, but less than two years previously. An excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with TAMBOCOR compared with that seen in a carefully matched placebo-treated group. This rate was 16/315 (5.1%) for TAMBOCOR and 7/309 (2.3%) for its matched placebo. The average duration of treatment with TAMBOCOR in this study was 10 months.

The applicability of these results to other populations (e.g., those without recent infarction) is uncertain, but at present it is prudent to consider the risks of Class IC agents, coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

Proarrhythmic Effects.

TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of ventricular arrhythmia patients treated with TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias. It is uncertain if TAMBOCOR's risk of proarrhythmia is exaggerated in patients with chronic atrial fibrillation (CAF), high ventricular rate, and/or exercise. Wide complex tachycardia and ventricular fibrillation have been reported in two of 12 CAF patients undergoing maximal exercise tolerance testing.

In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Their frequency appears to be related to dose and to the underlying cardiac disease.

Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a

considered approximations. Their frequency appears to be related to dose and to the underlying cardiac disease.

Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule. (See Dosage and Administration.)

The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease. (See Dosage and Administration.)

Heart Failure.

TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). CHF developed rarely (1%) in patients who had no previous history of CHF. In ventricular arrhythmia patients with preexisting heart failure, 15% developed worsening of CHF at some time during TAMBOCOR treatment. Exacerbation of preexisting CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg bid (see Dosage and Administration) and patients should be monitored carefully. Close attention must be given to maintenance of cardiac function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics, others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/ml.

Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose-related increases in PR, QRS, and QT intervals.

PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one-third of patients may develop new first-degree AV heart block (PR interval ≥0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study, 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur, and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There have been rare cases of Torsade de Pointes-type arrhythmia associated with TAMBOCOR therapy.

Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects. (See Dosage and Administration.) If second- or third-degree AV block, or right bundle branch block associated with a left hemiblock occur, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and

propranolol levels were increased about 30% compared to control values. In this formal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects. When the drugs were administered together, the effects were additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive. In TAMBOCOR clinical trials, patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.

Flecainide is not extensively bound to plasma proteins. *In vitro* studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction. Limited data in patients receiving known enzyme inducers (phenytoin, phenobarbital, carbamazepine) indicate only a 30% increase in the rate of flecainide elimination. In healthy subjects receiving cimetidine (1 gm daily) for one week, plasma flecainide levels increased by about 30% and half-life increased by about 10%.

When amiodarone is added to flecainide therapy, plasma flecainide levels may increase two-fold or more in some patients, if flecainide dosage is not reduced. (See Dosage and Administration.)

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgment of the physician, the benefits of this combination outweigh the risks. There has been little experience with the coadministration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg kg day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any teratogenic effects. A fertility reduction study at doses up to 50 mg kg day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

Pregnancy. Pregnancy Category C. *Flecainide* has been shown to have teratogenic effects (cleft palate, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (by mg/kg basis) the usual human dose

should not be administered to patients with existing poor myocardial reserve or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally threshold changes are within the range of multiprogrammable pacemakers and, when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture

Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR

PRECAUTIONS:

Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin, a 13% ± 19% increase in plasma digoxin levels occurred at six hours postdose. In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, plasma flecainide levels were increased about 20% and pro-

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When amiodarone is added to flecainide therapy, plasma flecainide levels may increase two-fold or more in some patients. If flecainide dosage is not reduced. (See Dosage and Administration.)

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgment of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity tests (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A fertility and reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

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Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. Limited data suggest that flecainide is excreted in human milk. Because of the drug's potential for serious adverse effects in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.

Hepatic Impairment. Since flecainide elimination from plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma level monitoring is required to guide dosage (see Plasma Level Monitoring); dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days).

ADVERSE REACTIONS:

In post myocardial infarction patients with asymptomatic PVCs and non-sustained ventricular tachycardia, TAMBOCOR therapy was found to be associated with a 5.1% rate of death and non-fatal cardiac arrest, compared with a 2.3% rate in a matched placebo group. (See Warnings.)

Adverse effects reported for TAMBOCOR, described in detail in the Warnings section, were new or exacerbated ventricular arrhythmias which occurred in 7% of 1330 patients with PVCs, non-sustained or sustained ventricular tachycardia. 198 patients with sustained ventricular tachycardia experienced a 13% incidence of new or exacerbated ventricular arrhythmias when dosage was initiated at 200 mg/day with slow upward titration and did not exceed 300 mg/day in most patients, in some patients TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. (See Warnings.) New or worsened congestive heart failure occurred in 6.3% of 1046 patients with PVCs, non-sustained or sustained ventricular tachycardia. Of 297 patients with sustained ventricular tachycardia, 9.1% experienced new or worsened CHF. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause or sinus arrest in about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/ml.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have [illegible]

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Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. Limited data suggest that flecainide is excreted in human milk. Because of the drug's potential for serious adverse effects in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 16 years of age have not been established.

Hepatic Impairment. Since flecainide elimination from plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma level monitoring is required to guide dosage (see Plasma Level Monitoring); dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days).

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In post-myocardial infarction patients with asymptomatic PVCs and non-sustained ventricular tachycardia, TAMBOCOR therapy was found to be associated with a 5.1% rate of death and non-fatal cardiac arrest, compared with a 2.3% rate in a matched placebo group. (See Warnings.)

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There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign post-marketing surveillance studies, there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure, and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects are based on a multicenter efficacy study, utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table I

Most Common Non-Cardiac Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 429 Patients at Any Dose	Incidence by Dose During Upward Titration: 200 mg/Day (N=436)	300 mg/Day (N=293)	400 mg/Day (N=100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance†	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.8%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.3%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.1%	1.0%

*Dizziness includes reports of true dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.

†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies. *Body as a Whole* - malaise, fever. *Cardiovascular* - tachycardia, sinus pause or arrest. *Gastrointestinal* - vomiting, diarrhea, dyspepsia, anorexia. *Skin* - rash. *Visual* - diplopia. *Nervous System* - paresthesia, dysesthesia, paresthesia, paresis, ataxia, [illegible] increased sweating, [illegible] *Psychiatric*

third-degree (0.4%) AV block, 2% with new-onset sinus bradycardia, sinus pause or sinus arrest, about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/ml.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and a cause and effect relationship with TAMBOCOR has been established. In foreign post-marketing surveillance studies there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

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Visual Disturbance†	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.1%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
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*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
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The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies. *Body as a Whole* - malaise, fever. *Cardiovascular* - tachycardia, sinus pause or arrest. *Gastrointestinal* - vomiting, diarrhea, dyspepsia, anorexia. *Skin* - rash. *Visual* - diplopia. *Nervous System* - hypoesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus. *Psychiatric* - anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients. *Body as a Whole* - swollen lips, tongue and mouth, arthralgia, bronchospasm, myalgia. *Cardiovascular* - angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension. *Gastrointestinal* - flatulence. *Urinary System* - polyuria, urinary retention. *Hematologic* - leukopenia, thrombocytopenia. *Skin* - urticaria, exfoliative dermatitis, pruritis. *Visual* - eye pain or irritation, photophobia, nystagmus. *Nervous System* - twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor. *Psychiatric* - amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the T-wave, a reduction in myocardial rate and contractility, conduction disturbances, hypotension, and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: removal of unabsorbed drug from the gastrointestinal tract, administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol, mechanically assisted respiration, circulatory assists such as intra-aortic balloon pumping, and transvenous pacing in the event of conduction block. Because of the long plasma half-life of flecainide (12 to 27 hours in patients receiving usual doses) and the possibility of marked, non-linear elimination kinetics at very high doses, these supportive measures may need to be continued for extended periods of time.

Hemodialysis is not an effective means of removing flecainide from the body. Since flecainide elimination is much slower when urine pH is 6.5 or less, pH 8 or higher; theoretically, bicarbonate should be more to promote drug excretion in the rare event of an overdose cases with very alkaline urine. There is no evidence that acidification from normal urinary pH increases excretion.

DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady state plasma levels in patients with normal renal and hepatic function may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, **increases in dosage should be made no more frequently than once every four days** [illegible] during the first

monitoring (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels in patients with normal renal and hepatic function may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore **increases in dosage should be made no more frequently than once every four days** since during the first 3 to 5 days of therapy the optimal effect of a given dose may not be achieved.

The recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most patients with sustained ventricular tachycardia do not require more than 150 mg every 12 hours (300 mg/day) and the maximum dose is 400 mg/day.

Use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and congestive heart failure, particularly during the first few days of dosing (see Warnings). Therefore a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12 hour intervals may be dosed at eight hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients efficacy at the lower dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction (see Warnings).

In patients with severe renal impairment (creatinine clearance of 35 ml/min/1.73 square meters or less) the initial dosage should be 100 mg once daily (or 50 mg bid), when used in such patients frequent plasma level monitoring is required to guide dosage adjustments (see Plasma Level Monitoring). In patients with less severe renal disease the initial dosage should be 100 mg every 12 hours; plasma level monitoring may also be useful in these patients during dosage adjustment. In both groups of patients dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days), observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady state plasma level is reached following a dosage change.

[illegible] theoretical considerations, rather than experimental data, the following suggestion is made [illegible] starting patients from another antiarrhythmic to TAMBOCOR allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting TAMBOCOR at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

When flecainide is given in the presence of amiodarone, reduce the usual flecainide dose by 50% and monitor the patient closely for adverse effects. Plasma level monitoring is strongly recommended to guide dosage with such combination therapy (see below).

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 μg/ml. The probability of adverse experiences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 μg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Plasma level monitoring is required in patients with severe renal failure or [illegible] hepatic disease, since elimination of flecainide from plasma may be markedly slower. Monitoring of plasma levels is strongly recommended in patients on concurrent amiodarone therapy and may also be helpful in patients with congestive heart failure and in patients with moderate renal disease.

HOW SUPPLIED.

All tablets are embossed with RIKER on one side and TR 50, TR 100 or TR 150 on the other side.

Tambocor, 50 mg per white, round tablet, is available in:
Bottles of 100 -- NDC #0089-0305-10
Boxes of 100 in unit dose blister strips
NDC #0089-0305-16

Tambocor, 100 mg per white, round, scored tablet, is available in:
Bottles of 100 -- NDC #0089-0307-10
Boxes of 100 in unit dose blister strips --
NDC #0089-0307-16

Tambocor, 150 mg per white, oval, scored tablet, is available in:
Bottles of 100 -- NDC #0089-0314-10

Store at controlled room temperature, 15°-30°C (59°-86°F) in a tight, light-resistant container.

CAUTION: Federal law prohibits dispensing without prescription.

TR-10 JULY 1989

Manufactured by
3M Riker
3M Health Care
Northridge, CA 91324

3M

CSO Review of Labeling

NDA 18-830/S-010 AUG 2 2 '989
Applicant: Riker Laboratories, Inc.
Drug Name: Tambocor (flecainide acetate)
Date of supplement: May 10, 19
Date of amendments: August 18, 989
Date of review: August 21, 1989

This supplement, as amended, consists of FPL revised at FDA's request to include the rewording of the Indications and Warnings sections as previously FAX'd to the firm (see attachment). The black box was added to the Warnings section at the company's own discretion, but only after prior telephone discussion with Dr. Lipicky. (Eristol-Myers has also added a black box to the Warnings section of encainide labeling.)

In addition, the following editorial changes were made to the Warnings section:

Under the Proarrhythmic Effects subsection, the beginning of the third sentence "In studies of Tambocor" was changed to "In studies of ventricular arrhythmia patients treated with Tambocor". **Acceptable.** The following statements were added after the third sentence:

> It is uncertain if Tambocor's risk of proarrhythmia is exaggerated in patients with chronic atrial fibrillation (CAF), high ventricular rate, and/or exercise. Wide complex tachycardia and ventricular fibrillation have been reported in two of 12 CAF patients undergoing maximal exercise tolerance testing. **Accepted by Dr. Lipicky in 7/27/89 telephone conversation.**

The following sentences were deleted from the same subsection:

> Proarrhythmic effects were reported in 7% of patients treated with Tambocor.
>
> Patients with less serious arrhythmias (chronic PVC's and nonsustained ventricular tachcardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal. **Acceptable.**

The following sentence should be deleted:

> Hospitalization should also be considered for other patients with

Under the Heart Failure subsection, the following sentences:

> New or worsened CHF which might be attributed to Tambocor therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF.

were revised to:

> CHF developed rarely (1%) in patients who had no previous history of CHF. In ventricular arrhythmia patients with preexisting heart failure, 15% developed worsening of CHF at some time during Tambocor treatment. **Acceptable.**

Under the Effects on Cardiac Conduction subsection the following sentence

> There has been one case of Torsade de Pointes-type arrhythmia associated with Tambocor-induced QT prolongation and bradycardia.

to read:

> There have been rare cases of Torsade de Pointes-type arrhythmia associated with Tambocor therapy. **Acceptable.**

In the second sentence of the Effects on Pacemaker Thresholds subsection, "flecainide" should be changed to "Tambocor" for the sake of consistency.

The following sentence was added to the beginning of the Adverse Reactions section:

> In post-myocardial infarction patients with asymptomatic PVCs and non-sustained ventricular tachycardia, Tambocor therapy was found to be associated with a 5.1% rate of death and non-fatal cardiac arrest, compared with a 2.3% rate in a matched placebo group (See Warnings.) **Acceptable.**

The sentences immediately after the preceding, formerly read:

> The most serious adverse effects reported for Tambocor, described in detail in Warnings section, were new or exacerbated ventricular arrhythmias which occurred in 7% of patients, and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, Tambocor treatment has been associated with episodes

of unresuscitatable ventricular tachycardia or ventricular fibrillation.

and have been changed to:

> Adverse effects reported for Tambocor, described in detail in the Warnings section, were new or exacerbated ventricular arrhythmias which occurred in 7% of 1330 patients with PVCs, non-sustained or sustained ventricular tachycardia. 198 patients with sustained ventricular tachycardia experienced a 13% incidence of new or exacerbated ventricular arrhythmias when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300mg/day in most patients. In some patients, Tambocor treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation (See Warnings.) New or worsened congestive heart failure occurred in 6.3% of 1046 patients with PVCs, non-sustained or sustained ventricular tachycardia. Of 297 patients with sustained ventricular tachycardia, 9.1% experienced new or worsened CHF.

The following sentence has been deleted:

> In a trial of ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400-600 mg/day, the incidence of these adverse experiences was similar, except for dizziness (32%) and visual disturbances (28%).

The following sentence has been deleted:

> Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

"For sustained ventricular tachycardia patients" was deleted from the first sentence of the third paragraph. The following fourth paragraph was also deleted:

> For patients with symptomatic nonsustained ventricular tachycardia, couplets, or premature ventricular complexes the recommended starting dose is also 100 mg every 12 hours. This dose may be increased in increments of 50 mg every four days until efficacy is achieved. Most of these patients do no require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day, and the plasma level is below 0.6 ug/ml, the dosage may be cautiously increased to a maximum of 600 mg/day.

The following sentence, because of its redundancy, was also deleted:

> The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg bid every four

days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

RECOMMENDATION: If MO finds the added statements in the Proarrhthmic subsection of the Warnings section acceptable, the labeling should be approved. Suggestions for editorial changes to be made at the time of the next printing as noted above can be added to the AP letter.

Virginia B. O'Hagan

cc:
Orig. NDA/IND
HFD-110
HFD-110/CSO
HFD-111/Benton
HFD/111/O'Hagan

INDICATIONS AND USAGE

Insert A

TAMBOCOR is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgment of the physician, are life-threatening. Because of the proarrhythmic effects of TAMBOCOR, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks. The use of TAMBOCOR is not recommended in patients with less severe ventricular arrhythmias, even if the patients are symptomatic.

Use of TAMBOCOR for the treatment of sustained ventricular tachycardia, like other antiarrhythmics, should be initiated in the hospital.

The effects of TAMBOCOR in patients with recent myocardial infarction and in patients with supraventricular tachycardia has not been adequately studied. As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of TAMBOCOR favorably affects survival or the incidence of sudden death.

Concept a
discuss
in the
WARNING
section)

INSERT
A

WARNINGS

Mortality

Insert B

TAMBOCOR was included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-center, randomized, double-blind study in patients with aymptomatic non-life-threatening arrhythmias who had a myocardial infarction more than six days, but less than two years previously. An excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with TAMBOCOR compared with that seen in a carefully matched placebo-treated group. This rate was 16/315 (5.1%) for TAMBOCOR and 7/309 (2.3%) for its matched placebo. The average duration of treatment with TAMBOCOR in this study was 10 months.

The applicability of these results to other populations (e.g., those without recent infarction) is uncertain, but at present it is prudent to consider the risks of Class IC agents, coupled with the lack of any evicence of improved survival, generally unacceptable in patients without life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

Proarrhythmia

AUG 2 2 1989

DIVISION OF CARDIO-renal drug products
MEDICAL OFFICER'S REVIEW

NDA #18-830/SR-010

Name of Drug: TAMBOCOR (flecainide acetate)

Sponsor: 3M Riker Labs, Inc.

Type of Submission: Final print of labeling

Date of Submission: 8/18/89

Date of Review: 8/21/89

Reviewer: Sughok K. Chun, M.D.

Submitted final printed package insert (TR-10, July 1989) for Tambocor Tablets is acceptable.

S.K. Chun 8/22/89
Sugnok K. Chun, M.D. 8/22/89

cc:
ORIGINAL NDA 18-830/SR-010
HFD-110
HFD-110/CSO
HFD-110/SKC
mn/#0251R

NDA 18-830/S-010

Riker Laboratories, Inc.
Attention: Ms. Jeanne M. Fox
Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000

Dear Ms. Fox:

We acknowledge the receipt on May 4, 1989 of your May 3, 1989 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide hydrochloride) Tablets.

We also acknowledge receipt of your amendment dated May 10, 1989.

The supplemental application provides for draft labeling revised according to our agreement reached at the April 25, 1989 meeting. As agreed, included in the submission was the "Dear Doctor" letter sent to the nation's physicians informing them of the interim findings of the CAST trial and the resultant change in the indications for Tambocor. We note that all promotion of Tambocor has halted.

We have completed the review of this supplemental application as submitted with draft labeling. Before the supplement may be approved, however, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the draft copy. If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Please submit twelve copies of the printed labeling, seven of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the supplemental application.

Should you have any questions, please contact:

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-110/VO'Hagan/5/3/89
sb/5/9/89;5/15/89/2301S
R/D: Milorgenstern/5/12/89

Ms. Virginia O'Hagan
Consumer Safety Officer
Telephone: (301) 443-4720

Sincerely yours,

APPROVABLE

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA #18-830

Name of Drug: Tambocor (flecainide acetate) Tablets

Sponsor: Riker

Type of Submission: Suppl. Amendment for labeling

Date of Submission: 5/10/89

Date of Review: 5/15/89

Reviewer: Sughok K. Chun, M.D. HFD-110

A. Resume:

This amendment was additional proposed changes to the prescribing information based on the sponsor's review/reanalysis of the adverse experience information, with the focus on the restricted indication of life-threatening ventricular arrhythmias.

The proposed section of Adverse Reactions contains proarrhythmia information based on the previously reviewed data, but broken out to highlight sustained VT information. The CHF information has been revised based on a reanalysis of the data base which was done for the Canadian HPB just prior to approval in that country. As proposed, information on new and worsened CHF are presented separately for the entire data base analyzed, and the incidence in the sustained VT population overall is presented. The supporting information from the analysis done for HPB concerning these changes is also included.

B. Comments:

The proposed additional changes in ADR to the labeling are satisfactory. Additional comments made on May 3, 1989 submission still hold.

C. Recommendations:

Refer to the MO review of May 3, 1989 submission.

S K Chun 5/16/89
Sughok K. Chun, M.D.

cc:
Orig NDA
HFD-110
HFD-110/CSO
HFD-110/SChun
clb/5/15/89;5/16/89/1515C

CSO Review of Labeling MAY 11 1989

NDA 18-830/S-010

Date of submission: May 4, 1989
Applicant: Riker Laboratories, Inc.
Drug Name: Tambocor (flecainide hydrochloride) Tablets
Date of review: May 8, 1989

At the April 25, 1989 meeting between Riker and Bristol-Myers representatives and those of FDA, the following agreements were reached: (1) a "Dear Doctor" letter drafted by FDA would immediately be issued by each company (in the interest of time, allowed to go out without revised labeling), and (2) all advertisement and promotion of both products would be immediately halted. The May 4 submission contains a chronology of Riker's actions to fulfill the April 25 agreement and draft labeling revised to delete all references to use of Tambocor in any population but those with a life-threatening arrhythmia, such a sustained ventricular tachycardia. The following sections of the labeling required revision:

Indications and Usage: The second paragraph beginning, "Tambocor is also indicated for..." and the statement, "No antiarrhythmic agent, including Tambocor, has been shown to have a favorable effect on mortality or sudden death" were deleted. **The "No antiarrhythmic..." statement should be put back in.**

Contraindications: Unchanged. **The phrase "frank congestive heart failure" should be added after "in the presence of..." in last sentence.**

Warnings: The following paragraph was added at the beginning of the section:

> Mortality. Tambocor was included in the Cardiac Arrhythmia Suppression Trial (CAST), designed to determine whether antiarrhythmic therapy reduced sudden cardiac death in post-myocardial infaction patients with asymptomatic premature ventricular complexes and non-sustained ventricular tachycardia. Tambocor was found to be associated with a higher (2.2 fold) rate of mortality and non-fatal carrdiac arrest than was its matching placebo. This rate was 16/315 (5.1%) for Tambocor and 7/309 (2.3%) for its matched placebo.

The following deletions have been made from the Proarrhythmia subection:

"In studies of Tambocor," from the beginning of the third sentence.

"Proarrhythmic effects were reported in 7% of patients treated with Tambocor" from the second paragraph.

"Patients with less serious arrhythmias (chronic PVC's and non-sustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal" from the third paragraph.

Adverse Effects: The heading was previously "Adverse Reactions". The following sentence has been added as the first statement after the heading:

In post-myocardial infarction patients, Tambocor was found to be associated with a 5.1% rate of mortality and non-fatal cardiac arrest.

The new or exacerbated ventricular arrhythmia rate in the next sentence was changed from "7%" to "13%". **The source of the 13% figure should be given, i.e., only sustained ventricular tachycardia patients in the controlled clinical trials, pooled data including CAST, etc.**

The noncardiac adverse experience table with data from the sustained ventricular tachycardia study population only is not included with this submission but will be submitted ASAP.

Dosage and Administration: The following deletions were made:

"Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings)" from the first paragraph.

"For sustained ventricular tachycardia patients..." and "Most such patients..." from the first and second sentences, respectively, in the the third paragraph.

The fourth paragraph beginning "For patients with symptomatic nonsustained...".

The sentence beginning "The initial dose..." for CHF and myocardial dysfunction patients because it repeats the same dosing information already given.

RECOMMENDATION: The labeling is Approvable with the following charges: (1) Restoration of the "No antiarrhythmic agent..." sentence to

the Indications section, (2) the addition of "frank congestive heart failure" to the Contraindications section (per review by Medical Officer, Sughok Chun, M.D.), and (3) reference to the databases on which the adverse effect rates are based.

Virginia B. O'Hagan

cc:
Orig. NDA/IND
HFD-110
HFD-110/CSO
HFD-111/Morgenstern
HFD/111/O'Hagan

MAY 10 1989

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA #18-830
Name of Drug: TAMBOCOR (flecainide acetate) Tablets
Sponsor: 3M Riker
Type of Submission: New CORRESPONDENCE
Date of Submission: May 03, 1989
Date of Review: May 08, 1989
Reviewer: Sugnok K. Chun, M.D. HFD-110

A. RESUME: The sponsor informed us the steps 3M Riker has taken following the recently released results of the NHLBI NIH Cardiac Arrhythmia Suppression Trail (CAST), and subsequent to 3M Riker's meeting with FDA on April 25, 1989.

1. A "Dear Doctor" letter was sent out informing physicians throughout the United States of the results of the recently released CAST data, and the change in indications for Tambocor.

2. All promotional activity for Tambocor has been suspended.

3. The sales representatives have been instructed not to answer any questions while in a physician's office pertaining to an alternate therapy for symptomatic PVCs and NSVT.

4. A "Dear Pharmacist" letter has been sent which explains the procedure for pt reimbursement for unused Tambocor, and is accompanied by a copy of the "Dear Doctor" letter.

5. All scheduled convention/hospital displays and speaker's bureau programs have been cancelled.

6. All journal advertising for Tambocor, scheduled to occur has been cancelled until further notice.

7. The 2 ongoing supraventricular arrhythmia clinical studies with Tambocor have been immediately discontinued. The study investigators were notified telephone, followed by written communication confirming decision.

8. Similar letters were sent to investigators doing independent studies with Tambocor.

9. Discussions concerning the 2 ongoing pediatric studies are underway with the investigators. The investigators are anxious to continue the studies and 3M Riker is working with them to re-define appropriate use of Tambocor in these trials. Documentation concerning protocol amendments, IRB re-approval, etc., will be submitted to IND 12,404 as soon as it becomes available.

10. A draft of the revised Tambocor package insert is included herein. The changes have been made in light of Dr. Lipicky's discussion with Jeanne Fox during the meeting on April 25, 1989.

B. COMMENTS and RECOMMENDATIONS:

The sponsor's actions ref to CAST are satisfactory. Referencte to the draft of revised package insert the labeling should specify the premarketing clinical trial data vs CAST results in order to avoid the confusion.

1. INDICATIONS AND USAGE.
   put back the last sentence -
   "No antiarrhythmic agent, including TAMBOCOR, has been shown to have a favorable effect on mortality of sudden death".

2. CONTRAINDICATIONS.
   insert frank congestive heart failure in the last sentence -
   TAMBOCOR is also contraindicated in the presence of cardiogenic shock, frank congestive heart failure or known hypersensitivity to the drug.

3. ADVERSE REACTIONS.
   Table 1-Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study.
   add additional column for the patient's population with sustained VT.

S K Chun 5/11/89
Sugnok K. Chun, M.D. 5/9/89

cc: Original NDA 18-830
HFD-110
HFD-110/CSO
HFD-110/SKC/09may89
mn/0192R

N1830

5012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-830/S-012

OCT 23 1991

3M Pharmaceuticals
Attention: Mr. Gene L. Harris
3M Center Building, 270-3A-01
St. Paul, MN 55144-1000

Dear Mr. Harris:

Please refer to your July 26, 1989 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide acetate) Tablets.

We also acknowledge receipt of your amendments dated September 6, October 1 and 14, 1991.

The supplemental application provides for a new use of Tambocor for the treatment of supraventricular arrhythmias.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

TAMBOCOR®

(flecainide acetate)

TABLETS

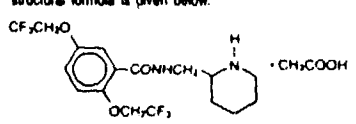
APPROVED

10-234

DESCRIPTION:

TAMBOCOR® (flecainide acetate) is an antiarrhythmic drug available in tablets of 50, 100 or 150 mg for oral administration.

Flecainide acetate is benzamide, N-(2-piperidinylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)-, monoacetate. The structural formula is given below.



Flecainide acetate is a white crystalline substance with a pK_a of 9.3. It has an aqueous solubility of 48.4 mg/mL at 37°C.

TAMBOCOR tablets also contain: croscarmellose sodium, hydrogenated vegetable oil, magnesium stearate, microcrystalline cellulose and starch.

CLINICAL PHARMACOLOGY:

TAMBOCOR has local anesthetic activity and belongs to the membrane stabilizing (Class 1) group of antiarrhythmic agents; it has electrophysiologic effects characteristic of the IC class of antiarrhythmics.

Electrophysiology. In man, TAMBOCOR produces a dose-related decrease in intracardiac conduction in all parts of the heart with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods were observed only in the ventricle. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction. (See Warnings.)

TAMBOCOR causes a dose-related and plasma-level related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful 30-40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 µg/mL may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 µg/mL. Plasma levels above 0.7-1.0 µg/mL are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally.

In animals and isolated myocardium, a negative inotropic effect of flecainide has been demonstrated. Decreases in ejection fraction, consistent with a negative inotropic effect, have been observed after single administration of 200 to 250 mg of the drug in man; both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses. (See Warnings.)

Metabolism in Humans. Following oral administration, absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range, 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life with steady-state levels approached in 3 to 5 days; once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one fifth as potent) and the meta-O-dealkylated lactam of flecainide (non-active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also

[illegible] any contraindicated [illegible] (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life with steady-state levels approached in 3 to 5 days; once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one fifth as potent) and the meta-O-dealkylated lactam of flecainide (non-active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found in urine; only 5% of an oral dose is excreted in feces. In patients, free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 µg/mL).

When urinary pH is very alkaline (8 or higher), as may occur in rare conditions (e.g., renal tubular acidosis, strict vegetarian diet), flecainide elimination from plasma is much slower.

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. (See Dosage and Administration.)

In patients with NYHA class III congestive heart failure (CHF), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 14 hours), but similar to the rate for patients with PVCs without CHF. The extent of excretion of unchanged drug in urine is also similar. (See Dosage and Administration.)

From age 20 to 80, plasma levels are only slightly higher with advancing age, flecainide elimination from plasma is somewhat slower in elderly subjects than in younger subjects. Patients up to age 80+ have been safely treated with usual dosages.

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 µg/mL. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs. (See Precautions, Drug Interactions.)

Clinical Trials. In two randomized, crossover, placebo-controlled clinical trials of 16 weeks double-blind duration, 79% of patients with paroxysmal supraventricular tachycardia (PSVT) receiving flecainide were attack free, whereas 15% of patients receiving placebo remained attack free. The median time before recurrence of PSVT in patients receiving placebo was 11 to 12 days, whereas over 85% of patients receiving flecainide had no recurrence at 60 days.

In two randomized, crossover, placebo-controlled clinical trials of 16 weeks double-blind duration, 31% of patients with paroxysmal atrial fibrillation/flutter (PAF) receiving flecainide were attack free, whereas 8% receiving placebo remained attack free. The median time before recurrence of PAF in patients receiving placebo was about 2 to 3 days, whereas for those receiving flecainide the median time before recurrence was 15 days.

INDICATIONS AND USAGE:

In patients without structural heart disease, TAMBOCOR is indicated for the prevention of

- paroxysmal supraventricular tachycardias (PSVT), including atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia and other supraventricular tachycardias of unspecified mechanism associated with disabling symptoms
- paroxysmal atrial fibrillation/flutter (PAF) associated with disabling symptoms

TAMBOCOR is also indicated for the prevention of

- documented ventricular arrhythmias, such as sustained ventricular tachycardia (sustained VT), that in the judgment of the physician, are life-threatening.

Use of TAMBOCOR for the treatment of sustained VT, like other antiarrhythmics, should be initiated in the hospital. The use of TAMBOCOR is not recommended in patients with less severe ventricular arrhythmias even if the patients are symptomatic.

Because of the proarrhythmic effects of TAMBOCOR, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

TAMBOCOR should not be used in patients with recent myocardial infarction (See Boxed Warnings).

Use of TAMBOCOR in chronic atrial fibrillation has not been adequately studied and is not recommended. (See Boxed Warnings)

As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of TAMBOCOR favorably affects survival or the incidence of sudden death.

CONTRAINDICATIONS:

TAMBOCOR is contraindicated in patients with pre-existing second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Mortality. TAMBOCOR was included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days, but less than two years previously. An excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with TAMBOCOR compared with that seen in a carefully matched placebo-treated group. This rate was 18/315 (5.1%) for TAMBOCOR and 7/309 (2.3%) for its matched placebo. The average duration of treatment with TAMBOCOR in this study was 10 months.

[illegible] Patients with

TAMBOCOR should not be used in patients with recent myocardial infarction. (See Boxed Warnings).

Use of TAMBOCOR in chronic atrial fibrillation has not been adequately studied and is not recommended. (See Boxed Warnings).

As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of TAMBOCOR temporarily affects survival or the incidence of sudden death.

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Ventricular Pro-arrhythmic Effects in Patients with Atrial Fibrillation/Flutter. A review of the world literature revealed reports of 568 patients treated with oral TAMBOCOR for paroxysmal atrial fibrillation/flutter (PAF). Ventricular tachycardia was experienced in 0.4% (2/568) of these patients. Of 19 patients in the literature with chronic atrial fibrillation (CAF), 10.5% (2) experienced VT or VF. FLECAINIDE IS NOT RECOMMENDED FOR USE IN PATIENTS WITH CHRONIC ATRIAL FIBRILLATION. Case reports of ventricular proarrhythmic effects in patients treated with TAMBOCOR for atrial fibrillation/flutter have included increased PVCs, VT, ventricular fibrillation (VF), and death.

As with other class I agents, patients treated with TAMBOCOR for atrial flutter have been reported with 1:1 atrioventricular conduction due to slowing the atrial rate. A paradoxical increase in the ventricular rate also may occur in patients with atrial fibrillation who receive TAMBOCOR. Concomitant negative chronotropic therapy such as digoxin or beta-blockers may lower the risk of this complication.

The applicability of the CAST results to other populations (e.g., those without recent infarction) is uncertain, but at present it is prudent to consider the risks of Class IC agents, coupled with the lack of any evidence of improved survival, generally unacceptable in patients whose ventricular arrhythmias are not life-threatening, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

PROARRHYTHMIC EFFECTS

TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened supraventricular or ventricular arrhythmias. Ventricular proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of ventricular arrhythmia patients treated with TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias. In patients treated with flecainide for sustained ventricular tachycardia, 80% (51/64) of proarrhythmic events occurred within 14 days of the onset of therapy. In studies of 225 patients with supraventricular arrhythmia (108 with paroxysmal supraventricular tachycardia and 117 with paroxysmal atrial fibrillation), there were 9 (4%) pro-arrhythmic events, 8 of them in patients with paroxysmal atrial fibrillation. Of the 9, 7 (including the one in a PSVT patient) were exacerbations of supraventricular arrhythmias (longer duration, more rapid rate, harder to reverse) while 2 were ventricular arrhythmias, including one fatal case of VT/VF and one wide complex VT (the patient showed inducible VT, however, after withdrawal of flecainide), both in patients with paroxysmal atrial fibrillation and known coronary artery disease.

It is uncertain if TAMBOCOR's risk of proarrhythmia is exaggerated in patients with chronic atrial fibrillation (CAF), high ventricular rate, and/or exercise. Wide complex tachycardia and ventricular fibrillation have been reported in two of 12 CAF patients undergoing maximal exercise tolerance testing.

In patients with complex ventricular arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Their frequency appears to be related to dose and to the underlying cardiac disease.

Among patients treated for sustained VT (who frequently also had CHF, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained VT utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule. (See Dosage and Administration.)

The relatively high frequency of proarrhythmic events in patients with sustained VT and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained VT be started in the hospital. (See Dosage and Administration.)

HEART FAILURE

TAMBOCOR has a negative inotropic effect and may cause or worsen CHF, particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). In patients with supraventricular arrhythmias new or worsened CHF developed in 0.4% (1/225) of patients. In patients with sustained ventricu-

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HEART FAILURE

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Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose-related increases in PR, QRS, and QT intervals.

PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one-third of patients may develop new first-degree AV heart block (PR interval ≥ 0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study, 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur, and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There have been rare cases of Torsade de Pointes-type arrhythmia associated with TAMBOCOR therapy.

Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second degree AV block (0.5%) and third degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects. (See Dosage and Administration.) If second- or third-degree AV block, or right bundle branch block associated with a left hemiblock occur, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally threshold changes are within the range of multiprogrammable pacemakers and, when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture.

Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Pre-existing hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

PRECAUTIONS:

Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin, a 13% - 19% increase in plasma digoxin levels occurred at six hours postdose.

In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, plasma flecainide levels were increased about 20% and propranolol levels were increased about 30% compared to control values. In this formal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects; when the drugs were administered together, the effects were additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive. In TAMBOCOR clinical trials, patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.

Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction. Limited data in patients receiving known enzyme inducers (phenytoin, phenobarbital, carbamazepine) indicate only a 30% increase in the rate of flecainide elimination. In healthy subjects receiving cimetidine (1 gm daily) for one week, plasma flecainide levels increased by about 30% and half-life increased by about 10%.

When amiodarone is added to flecainide therapy, plasma flecainide levels may increase two-fold or more in some patients, if flecainide dosage is not reduced. (See Dosage and Administration.)

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgement of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to 60 mg/kg/day have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

Pregnancy. Pregnancy Category C. Flecainide has been shown to have teratogenic effects (club paws, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) when given doses of 30 and 35 mg/kg/day, but not in another breed of rabbit (Dutch Belted) when given doses up to 30 mg/kg/day. No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day, respectively; however, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. Results from a multiple dose study conducted in mothers soon after delivery indicates that flecainide is excreted in human breast milk in concentrations as high as 4 times (with average levels about 2.5 times) corresponding plasma levels, assuming a maternal plasma level at the top of the therapeutic range (1 µg/mL), the calculated daily dose to a nursing infant (assuming about 700 mL breast milk over 24 hours) would be less than 3 mg. Because of the drug's potential for serious adverse effects in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.

Hepatic Impairment. Since flecainide elimination from plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma level monitoring is required

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Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.

Hepatic Impairment. Since flecainide elimination from plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma level monitoring is required to guide dosage (see Plasma Level Monitoring); dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days).

ADVERSE REACTIONS:

In post-myocardial infarction patients with asymptomatic PVCs and non-sustained ventricular tachycardia, TAMBOCOR therapy was found to be associated with a 5.1% rate of death and non-fatal cardiac arrest, compared with a 2.3% rate in a matched placebo group. (See Warnings.)

Adverse effects reported for TAMBOCOR, described in detail in the Warnings section, were new or worsened arrhythmias which occurred in 1% of 108 patients with PSVT and in 7% of 117 patients with PAF, and new or exacerbated ventricular arrhythmias which occurred in 7% of 1330 patients with PVCs, non-sustained or sustained VT. In patients treated with flecainide for sustained VT, 80% (51/64) of proarrhythmic events occurred within 14 days of the onset of therapy. 198 patients with sustained VT experienced a 13% incidence of new or exacerbated ventricular arrhythmias when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresusctatable VT or ventricular fibrillation (cardiac arrest). (See Warnings.) New or worsened CHF occurred in 6.3% of 1046 patients with PVCs, non-sustained or sustained VT. Of 297 patients with sustained VT, 9.1% experienced new or worsened CHF. New or worsened CHF was reported in 0.4% of 225 patients with supraventricular arrhythmias. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest, about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 µg/mL.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign postmarketing surveillance studies, there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure, and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects in patients with ventricular arrhythmias are based on a multicenter efficacy study utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table 1

Incidence of Common Non-Cardiac Adverse Effects in Ventricular Arrhythmia Patients Treated with TAMBOCOR in the Multicenter Study

	Incidence in All 429 Patients at Any Dose	Incidence by Dose During Upward Titration		
		200 mg/Day (N=426)	300 mg/Day (N=293)	400 mg/Day (N=100)

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Table I

Most Common Non-Cardiac Adverse Effects in Ventricular Arrhythmia Patients Treated with TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 428 Patients at Any Dose		Incidence by Dose During Upward Titration		
			200 mg/Day (N=428)	300 mg/Day (N=285)	400 mg/Day (N=100)
Dizziness*	16.9%		11.0%	16.8%	13.0%
Visual Disturbance+	15.9%		5.4%	12.3%	16.0%
Dyspnea	10.3%	§	5.2%	7.5%	4.0%
Headache	9.6%		4.5%	6.1%	8.0%
Nausea	9.3%		4.9%	4.9%	8.0%
Fatigue	7.7%		4.5%	4.4%	2.0%
Palpitation	6.1%		3.5%	2.4%	7.0%
Chest Pain	4.7%		2.1%	3.5%	1.1%
Asthenia	[illegible]%		2.6%	2.0%	4.0%
Tremor	[illegible]		2.6%	3.4%	2.5%
Constipation	4.4%	§	2.6%	2.1%	1.0%
Edema	2.8%		1.9%	1.4%	2.0%
Abdominal Pain	2.3%		1.9%	2.4%	1.0%

* Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.

+ Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies: *Body as a Whole* - malaise, fever; *Cardiovascular* - tachycardia, sinus pause or arrest; *Gastrointestinal* - vomiting, diarrhea, dyspepsia, anorexia; *Skin* - rash; *Visual* - diplopia; *Nervous System* - hypoesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, drowsiness, tinnitus; *Psychiatric* - anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients: *Body as a Whole* - swollen lips, tongue and mouth, arthralgia, bronchospasm, myalgia; *Cardiovascular* - angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension; *Gastrointestinal* - flatulence; *Urinary System* - polyuria, urinary retention; *Hematologic* - leukopenia, thrombocytopenia; *Skin* - urticaria, exfoliative dermatitis, pruritus, alopecia; *Visual* - eye pain or irritation, photophobia, nystagmus; *Nervous System* - twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor, neuropathy; *Psychiatric* - amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

For patients with supraventricular arrhythmias, the most commonly reported noncardiac adverse experiences remain consistent with those known for patients treated with TAMBOCOR for ventricular arrhythmias. Dizziness is possibly more frequent in PAF patients.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage, lengthening of the PR interval; increase in the QRS duration, QT interval and amplitude of the T wave; a reduction in myocardial rate and contractility; conduction disturbances, hypotension, and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: removal of unabsorbed drug from the gastrointestinal tract; administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol; mechanically assisted respiration; circulatory assists such as intra-aortic balloon pumping; and transvenous pacing in the event of conduction block. Because of the long plasma half-life of flecainide (12 to 27 hours in patients receiving usual doses), and the possibility of markedly non-linear elimination kinetics at very high doses, these supportive treatments may need to be continued for extended periods of time.

Hemodialysis is not an effective means of removing flecainide from the body. Since flecainide elimination is much slower when urine is very alkaline (pH 8 or higher), theoretically, acidification of urine to promote drug excretion may be beneficial in overdose cases with very alkaline urine. There is no evidence that acidification from normal urinary pH increases excretion.

DOSAGE AND ADMINISTRATION:

For patients with sustained VT, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring.

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels, in patients with normal renal and hepatic function, may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, *increases in dosage* should be made no more frequently than *once every four days*, since during the first 2 to 3 days of therapy the optimal effect of a given dose may not be achieved.

For patients with PSVT and patients with PAF the recommended starting dose is 50 mg every 12 hours. TAMBOCOR doses may be increased in increments of 50 mg bid every four days until efficacy is achieved. For PAF patients, a substantial increase in efficacy without a substantial increase in discontinuations for adverse experiences may be achieved by increasing the TAMBOCOR dose from 50 to 100 mg bid. The maximum recommended dose for patients with paroxysmal supraventricular arrhythmias is 300 mg/day.

For sustained VT the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most patients with sustained VT do not require more than 150 mg every 12 hours (300 mg/day) and the maximum dose recommended is 400 mg/day.

In patients with sustained VT, use of higher initial doses

may not be achieved.

For patients with PSVT and patients with PAF the recommended starting dose is 50 mg every 12 hours. TAMBOCOR doses may be increased in increments of 50 mg bid every four days until efficacy is achieved. For PAF patients, a substantial increase in efficacy without a substantial increase in discontinuations for adverse experiences may be achieved by increasing the TAMBOCOR dose from 50 to 100 mg bid. The maximum recommended dose for patients with paroxysmal supraventricular arrhythmias is 300 mg/day.

For sustained VT the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most patients with sustained VT do not require more than 150 mg every 12 hours (300 mg/day) and the maximum dose recommended is 400 mg/day.

In patients with sustained VT, use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and CHF, particularly during the first few days of dosing (see Warnings). Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients, efficacy at the lower dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of CHF or myocardial dysfunction (see Warnings).

In patients with severe renal impairment (creatinine clearance of 35 mL/min/1.73 square meters or less), the initial dosage should be 100 mg once daily (or 50 mg bid); when used in such patients, frequent plasma level monitoring is required to guide dosage adjustments (see Plasma Level Monitoring). In patients with less severe renal disease, the initial dosage should be 100 mg every 12 hours; plasma level monitoring may also be useful in these patients during dosage adjustment. In both groups of patients, dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days), observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady state plasma level is reached following a dosage change.

Based on theoretical considerations, rather than experimental data, the following suggestion is made: when transferring patients from another antiarrhythmic drug to TAMBOCOR allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting TAMBOCOR at its usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

When flecainide is given in the presence of amiodarone, reduce the usual flecainide dose by 50% and monitor the patient closely for adverse effects. Plasma level monitoring is strongly recommended to guide dosage with such combination therapy (see below).

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 µg/mL. The probability of adverse experiences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 µg/mL. Periodic monitoring of trough plasma levels may be useful in patient management. Plasma level monitoring is required in patients with severe renal failure or severe hepatic disease, since elimination of flecainide from plasma may be markedly slower. Monitoring of plasma levels is strongly recommended in patients on concurrent amiodarone therapy and may also be helpful in patients with CHF and in patients with moderate renal disease.

HOW SUPPLIED:

All tablets are embossed with Riker on one side and TR 50, TR 100 or TR 150, on the other side.

Tambocor, 50 mg per white, round tablet, is available in
Bottles of 100 - NDC #0089 0305 10
Boxes of 100 in unit dose blister strips -
NDC #0089 0305 16
Tambocor, 100 mg per white, round, scored tablet, is available in
Bottles of 100 - NDC #0089 0307 10
Boxes of 100 in unit dose blister strips -
NDC #0089 0307 16
Tambocor, 150 mg per white, oval, scored tablet, is available in
Bottles of 100 - NDC #0089 0314 10

Store at controlled room temperature 15°-30°C (59°-86°F) in a tight, light-resistant container.

CAUTION: Federal law prohibits dispensing without prescription.

TR-10GH October 1991

Printed in USA

Manufactured by
3M Riker
3M Health Care
Northridge, CA 91324

3M

TC

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

SEP 17 1991

NDA: #18-830

Name of Drug: TAMBOCOR (flecainide acetate) tablets

Sponsor: 3M Pharmaceuticals

Type of Submission: Revised Draft Package Insert

Date of Submission: 9/06/91

Date of Review: Sughok K. Chun, M.D. HFD-110

A. RESUME:

The sponsor made revisions of Draft Package Insert for Tambocor requested in the approvable ltr dated 7/31/91 and a few minor modifications and additions.

The following my comments are discussed with the sponsor Gene Harris, Sr. Regulatory Coordiantor, (612) 736-.016 on 9/16/91.

1) INDICATIONS AND USAGE:

"Use of TAMBOCOR in chronic atrial fibrillation has not been adequately studied and is not recommended."

Insert (CAF) after chronic atrial fibrillation that abbreviation CAF appears in mid of 2nd para. WARNINGS be understood.

2) OVERDOSAGE:

There are a few overdose cases reported in ADR Report. It is better to utilize human data than animal data.

S K. Chun 9/17/91
Sughok K. Chun, M.D., 9/17/91

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-110/[illegible]
HFD-110[illegible]
mm:#18-

DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION — Public Health Service

Memorandum

DATE : JUN 12 1991

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approvable status of NDA 18-830/S-012, Flecainide for Supraventricular Arrhythmias, 3M-Riker

TO : Director, Office of Drug Evaluation I, HFD-100

This memorandum responds to your June 5, 1991 memorandum and attempts to answer your questions. Some can be answered straightforwardly, others in a slightly contorted fashion.

I have read all of your comments and instructions in your editing of the SBA. All are appropriate and I have no comments with respect to any of them.

1) Description of pro-arrhythmic events.

Reports of pro-arrhythmic events vary from snap shot to snap shot and specific numbers written in one document or another vary depending upon the instant in time the document is written. The SBA, the most recently written document is a reasonable source to pick numbers from. Your modifications of the package insert are appropriate with one exception. The two patients with ventricular "pro-arrhythmia" in addition to known coronary artery disease, also had paroxysmal atrial fibrillation; this identity is important, I think. I have edited the last sentence a little bit to add the identity of the initial rhythm abnormality.

The explicit nature of this part of labeling is a little bothersome. When we get a revised safety update, the numbers will once again change and after marketing (with each month and/or year) it will once again change, particularly when individual investigators may conduct more studies.

So, I am not too concerned over the exact numbers. The point is made that pro-arrhythmic events occur. That in PSVT it is more exacerbation of PSVT

type stuff and in PAF it is more likely to be ventricular. I do not know what else to say and the point estimate (based on 275 patients) has very wide .

2) Sure a description of the findings of the studies would be appropriate. I suggest the following:

In two randomized, parallel group, placebo-controlled clinical trials of 8 weeks double-blind duration, 79% of patients with PAT receiving flecainide were attack free, whereas 15% of patients receiving placebo remained attack free. The median time-before-recurrence of PAT in patients receiving placebo was 11 to 12 days, whereas over 85% of patients receiving flecainide had no recurrence at 60 days.

In two randomized, parallel group, placebo-controlled clinical trials of 8 weeks double-blind duration, 31% patients with PAF receiving flecainide were attack free, whereas 8% receiving placebo remaining attack free. The median time-before-recurrence of PAF in patients receiving placebo was about 2 to 3 days, whereas for those receiving flecainide the median time-before-recurrence was 15 days.

3) You are correct. The labeling with respect to patients with chronic atrial fibrillation is not adequately written. It is clear the paroxysmal atrial fibrillation carries with it a ventricular pro-arrhythmia risk and that results (now that there will be a description of the trials) in PAF are less spectacular than in PSVT. So the PAF/PSVT distinctions are clear.

It is clearly not wise to use flecainide in the treatment of patients with chronic atrial fibrillation, pending further study. So it should be a warning as opposed to a bland statement about insufficient study.

I suggest that the ventricular pro-arrhythmia in both PAF and chronic AF be placed in the WARNINGS Black Box. I suggest the sponsor review the pertinent literature and draft the paragraph.

4) Upper limit on dose of 400 mg/day.

Considering the difficulties of studying paroxysmal supraventricular, arrhythmias the existing dose-response information is superb. However, it needs to be appreciated, I think, that the point estimates have wide confidence limits.

Nonetheless, it seems reasonably conservative to conclude that doses below 50 mg bid (100 mg/day) are not very worth trying (even though I might in the

right circumstance). So 50 mg bid (100 mg/day) seems the most reasonable recommended starting dose; and that is what labeling says. Clearly, side effects begin to increase as dose increases from 100 mg/day and above. Also the concentration-response for block of voltage dependent sodium and potassium conductances goes from a just detectable effect at about 3×10^{-7} M to 100% block at 3×10^{-3} M (4 orders of magnitude). In a biological sense, discussing whether the dose range from minimally effective to maximum usable dose is a factor of 2, 3, or 4 (as opposed to 10, 100, 1000, or 10,000 fold) is a quible. However, the limiting factor in the upper end of dose is something other than the effects of flecainide on electrically-excitable membranes. I am not sure what that limiting factor is.

The labeling as it exists says, that one can increase efficacy without substantially increasing adverse effects by varying dose between 50 and 100 mg bid. That is a true statement.

The existing prose says, by implication that going above 100 mg bid, one may buy increased adverse effects and that doses above 200 mg bid is the absolute maximum (because it has not been studied; the labeling does not say that). That seems a fair enough statement of facts to me.

However, were you to elect to use 300 mg/day, that is 150 mg bid, (instead of 400) I would have no objection. I would not elect to do that.

5 and a little bit of 3) The approvable letter now contains a request for another safety update and a discussion of recent literature on ventricular pro-arrhythmias being treated with flecainide.

Attached is a recent article from the *Amer. J. of Cardiol.*,67:889-891, 1991. It is germaine to the issue of PAF and ventricular arrhythmia problems. It strikes me that the author's statement that "patients with multiple accessory pathways are more likely to be present with both atrial fibrillation and ventricular fibrillation" is consistent not only with their data in WPW but with what we have ssen in this NDA supplement and previously with lidoflazine. Having atrial fibrillation (the diagnosis not being mechanistic) means that there is a higher probability of the patient having a ventricular problem, especially when one begins to mess around with electrically-excitable membranes.

Also attached is a copy of another article from the *Am. J. Cardiol.*, 67:976-980, 1991. It is Dr. Pritchett's expression of his findings on mortality; a better job of expression than you found in my memorandum of February 20, 1991, although the conclusions are the same.

The reason for including this copy is that for 1C agents (encainide and flecainide) there now exists a mortality analysis of 579 patients. The limitations of the study are delineated in the article. It is not clear to me that adding another 1000, 2000, 3000, or 10,000 patients can substantively add to our knowledge. It is clear that a randomized, controlled trial could, but as I detailed in my February 20, 1991 memorandum, such a study is preposterous to even suggest (moral, ethical, and human behavior problems simply make it not feasible).

So, I do not know that there is any post-marketing study that is reasonable. Simply because there is uncertainty about the bottom line (and I readily admit there is) does not dictate putting the sponsor of a treatment that has historical significance on-the-spot with a request that is impossible. That is a penalty, not a reward.

Thus, I have not added any specific post-marketing study speculation to the approvable letter. I am open to suggestions.

Raymond J. Lipicky, M.D.

cc: Orig. NDA
HFD-110
HFD-110/CSO ✓
HFD-110/RLipicky
ef:6/11/91

HFD-110/CSO

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: JUN 5 1991

FROM: Director, Office of Drug Evaluation I, HFD-100

SUBJECT: Flecainide SVT Supplement, NDA 18-830/S-012

TO: Raymond Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products, HFD-110

I agree that the claimed use for supraventricular arrhythmias is approvable. I have just a few questions, most about labeling.

1. Description of pro-arrhythmic events

   Proposed labeling cites 9/225, 6 SV and 3 ventricular. The SBA seems to record 7 SV and 2 ventricular. I have modified and expanded the last sentence of the first paragraph on p 7:

   "In studies of 225 patients with supraventricular arrhythmias (108 with paroxysmal supraventricular tachycardia and 117 with paroxysmal atrial fibrillation), there were 9 (4%) pro-arrhythmic events, 8 of them in patients with paroxysmal atrial fibrillation. Of the 9, 7 (including the one in a PSVT patient, were exacerbations of supraventricular arrhythmias (longer duration, more rapid rate, harder to reverse) while 2 were ventricular arrhythmias, including one fatal case of VT/VF and one wide complex VT (the patient showed inducible VT, however, after withdrawal of flecainide), both in patients with known coronary artery disease."

2. Shouldn't there be a brief presentation of the clinical trial results in PSVT and PAF (e.g., of attack-free rates over the 8 week studies), or at least a description in words of what the findings were (significant increase in the number of patients with no attacks, etc.)

3. On p 6 it is stated that the effects of flecainide in patients with chronic AF have not been adequately studied. Dr. Ruskin suggested noting in labeling that fatal VT/VF has been reported in such patients. Shouldn't we add that? Also, the SBA (p 150) is, as Dr. Chun points out, over-reassuring re chronic AF, ignoring on p 150, the Falk case(s) on p 143-4. It also does not mention isolated case reports in the literature. Consider also an addition to the letter inviting the sponsor to discuss possible post-marketing studies (see Ruskin suggestion).

4. Why suggest doses of 400 mg? There seemed little gain even from 300?

5. They should safety update the supplement with respect to pro-arrhythmic events, both from formal studies, if any and isolated reports.

Robert Temple, M.D.

cc:
Orig. NDA 18-830/S-012
HFD-100/Chron File
HFD-100/NDA File
HFD-100/Carter
HFD-101/Botstein
HFD-110
HFD-110/CSO
RT:jp:6/4/91
Revised:RT:jp:6/5/91(2)

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE : FEB 26 1991

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approval of NDA 18-830/S-012, Flecainide for Supraventricular Arrhythmias, 3M-Riker

TO : Director, Office of Drug Evaluation I, HFD-100

This is a much belated Division recommendation that flecainide be approved for the treatment of supraventricular arrhythmias. Although the the Cardio-Renal Advisory Committee recommended approval of flecainide for this indication on October 5, 1989, the press of other work in the Division has delayed forwarding this supplement to you for your consideration. I apologize to both you and the sponsor for this delay. The delay should not be taken as representing any doubt.

In summary, flecainide can be viewed as the first drug in the history of medicine that unequivocally has been demonstrated to have a major clinical benefit in patients with recurrent supraventricular arrhythmias (verapamil, the one other approval in the last 20 years, although unquestionably more effective than placebo, pales in relationship to the effects of flecainide; granted, this statement is made absent a randomized head-to-head comparison). For sure, and without qualification, flecainide is only the second drug in the last 20 years that has been shown to have unequivocal benefit in patients with supraventricular arrhythmias.

Patients with supraventricular arrhythmias, treated with the "best" available therapies have a death rate (from the only estimate available) that is greater than that of an age and sex-matched general population (so patients with supraventricular arrhythmias, managed with approved available therapy, cannot be assumed to be mortality risk free). The mortality rate in patients with supraventricular arrhythmias treated with encainide or flecainide (the 1C antiarrhythmic agents that produced excess mortality in CAST) is not distinguishable from the mortality rate in patients with supraventricular arrhythmias not treated with these agents. These rates are much less than the mortality rate found in CAST for 1C treated patients who survived a myocardial infarction but had asymptomatic ventricular premature contractions.

Thus, although the contemplated use of a 1C agent in today's climate is inevitably dominated by discussions of risk, the outstanding efficacy of flecainide in supraventricular arrhythmias and the available data with respect to mortality in this therapeutic setting definitely tilt the risk/benefit evaluation toward the benefit side. Consequently, flecainide is approvable and, when judiciously used, will be a significant addition to the therapeutic armamentarium.

HISTORICAL PERSPECTIVE

At present, except for a variety of drugs (i.e., digitalis glycosides, beta blockers) that simply control ventricular rate without modifying the supraventricular arrhythmia or the frequency of recurrence of the arrhythmia, there are only two drugs approved for the treatment of supraventricular arrhythmias where the expectation is to alter the frequency of recurrence of arrhythmia. Quinidine, known since the mid-1800s, approved years ago, and not well studied (by current standards), is one of them. The other, verapamil, was approved in 1983, on the basis of the results of three trials (total of only 41 patients) that showed it to be superior to placebo for increasing the interval between recurrence of the supraventricular arrhythmias. Other therapies (e.g., adenosine, recently approved) abort acute arrhythmias and play no role in preventing recurrence.

The therapeutic armamentarium is not rich. It is clear that quinidine, in addition to significant organ system toxicity, has the ability to produce Torsades de Pointes as well as other serious ventricular arrhythmias. Verapamil lowers blood pressure (one of its major uses is as an antihypertensive agent), has organ system toxicity, can produce heart block, and has a variety of lesser side effects, such as constipation. Thus, the treatment of patients with supraventricular arrhythmias represents difficult risk/benefit assessments and the known benefits of currently approved drugs, at the moment, are well defined only for verapamil and that was based on the results of sufficient, but rather small trials.

CURRENT STUDIES SUPPORTING FLECAINIDE'S APPROVAL

The major sources of supportive data are three double-blind, randomized, cross-over or parallel group, placebo-controlled trials that enrolled a total of 115 patients with recurrent supraventricular tachycardia. A fourth study enrolled 73 patients who received flecainide long-term. Thus, a total of 188 patients were enrolled in controlled trials for supraventricular tachycardia; this is a very large database.

Although supraventricular tachycardias can be classified into a relatively long list of specific arrhythmias, each patient enrolled in 3M-Riker's trials was categorized for analysis purposes as belonging to a Paroxysmal Atrial Tachycardia (PAT) group or a Paroxysmal Atrial Fibrillation (PAF) group by reasonably defined criteria. This is somewhat confusing terminology since PAT really means paroxysmal supraventricular tachycardia (PSVT) that includes

paroxysmal atrial tachycardia but not atrial flutter/fib. Most, but not all, patients entered had the specific mechanisms of their arrhythmias characterized by electrophysiological testing. In fact, each arrhythmia in the lengthy mechanistic classification is represented in the patients studied, but, in spite of a large sample size, the results in patients with specific mechanisms cannot be analyzed separately.

All major results (arrhythmia attack or its absence) were determined by Trans-Telephonic Monitoring (TTM). Wherever and whenever a patient experienced symptoms, the patient was able (by telephone) to transmit a rhythm strip that could be recorded. The absence of a transmitted rhythm strip can therefore be taken as absence of symptoms and if TTM was used, the patient was symptomatic. A TTM record is a symptom event and the rhythm strip, after evaluation by the investigator, is the documentation of cardiac rhythm associated with the symptoms. Patients could have had symptoms and not have been close to a telephone, but this is not known to have happened and is not perceived to be a meaningful problem. Thus, the trial results should be taken as a measure of direct clinical benefit, being based essentially on symptoms. The rhythm present at the time of symptoms is irrelevant, except for mechanistic documentation and conceptual framework of reference.

The studies were analyzed in a variety of ways. Two placebo controlled studies of identical design were conducted (R-818-065 and R-818-066). Each was multicenter and each was analyzed separately. Each found statistically significant results favoring flecainide. For purposes of this memorandum, only the combined results will be cited. Patients received flecainide in studies R-818-065/066 for eight weeks. For PAT the most impressive result was that 79% of patients, while receiving flecainide, had no recurrence during the studies (compared to 15% while receiving placebo, p less than 0.001), and 3% had only one recurrence while receiving flecainide (compared to 24% who had only one recurrence while receiving placebo, p less than 0.001).

In patients with PAF, 31% of patients, while receiving flecainide, had no recurrence during the studies (compared to 8% while receiving placebo, $p = 0.013$). Not as impressive as in PAT but clearly a clinically meaningful and statistically significant finding.

It is clear that supraventricular tachycardia is a recurrent arrhythmia and that life-table analysis is the most appropriate way to analyze such data (time between attacks and time to first attack); these analyses were prospectively defined and are summarized below. What is also clear is that the therapeutic effect is to increase the interval between attacks; it is not realistic to expect to make the patient attack-free for life.

This aim of therapy (essentially, decreasing the frequency of attacks) should not be presumed trivial. If nothing more, PSVT is a major nuisance, causing the patient to interrupt whatever he or she is doing at the moment. It can last for days. Often it results in a trip to the emergency room or the doctor's office, and not infrequently it leads to brief hospitalization. Patients who were

entered into the above trials were required to have had two attacks within a four-week period (off all medication). When treated with flecainide, 79% of the PAT patients had no episodes of their arrhythmia over an eight-week period (having had at least two per month as a requirement for entry). This can, in my judgment, be considered a major benefit to patients afflicted by this relentless, recurring rhythm disorder.

The real treatment effect is most reasonably described and analyzed by the following life-table graphs. Figures 1, 2, and 3 show pertinent data obtained from patients with PAT, and Figures 7, 8, and 9 show similar displays of data obtained from patients with PAF.

As can be seen, the median time-before-recurrence of PAT in patients receiving placebo was about 11 to 12 days. In contrast, patients receiving flecainide enjoyed more than 30 days between episodes of PAT.

Similar comparisons in patients with PAF show about a four-fold increase in interval between attacks, with an increased time to first attack from about 2.5 days to 15 days. These are still impressive results, although less impressive than those obtained in the PAT population.

As can be seen from Figures 3 and 9, irrespective of the arrhythmia studied, doses below 50 mg b.i.d. appear useless, cardiac adverse events appear to bear no relationship to dose, and both efficacy and non-cardiac adverse events increase with dose over the range of doses studied. Total numbers are too small to ascribe quantitative meaning to the relationship between any two pairs of points, but the trends are clear enough.

The dose-response results (Figures 3 and 9) are derived from one trial (R-818-074), a placebo-controlled trial involving five, one-month treatment periods using doses of 25, 50, 100, or 150 mg of flecainide or placebo, twice a day, dose, drug and/or placebo being randomly assigned. The study involved only a total of 73 patients and was complicated. Nonetheless, it clearly excluded 25 mg flecainide b.i.d. as a useful dose. The remainder of doses can all be considered usable.

Figure 1

Time to First Attack For PAT Patients Who Received Both Flecainide and Placebo in Crossover Fashion R-818-065/068 Trial

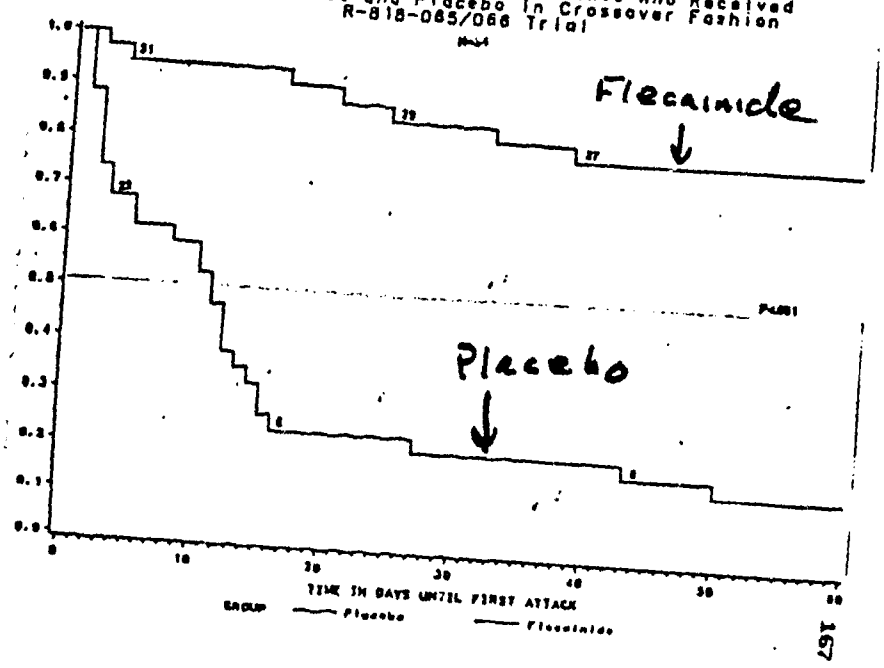

Figure 2

Interval Between Attacks For PAT Patients Who Received Both Flecainide and Placebo in Crossover Fashion R-818-065/068 Trial

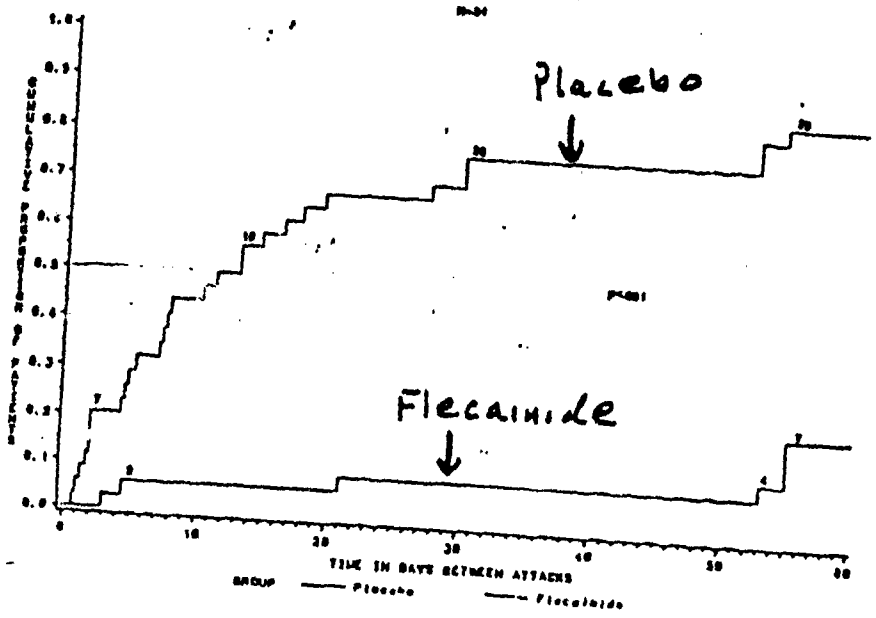

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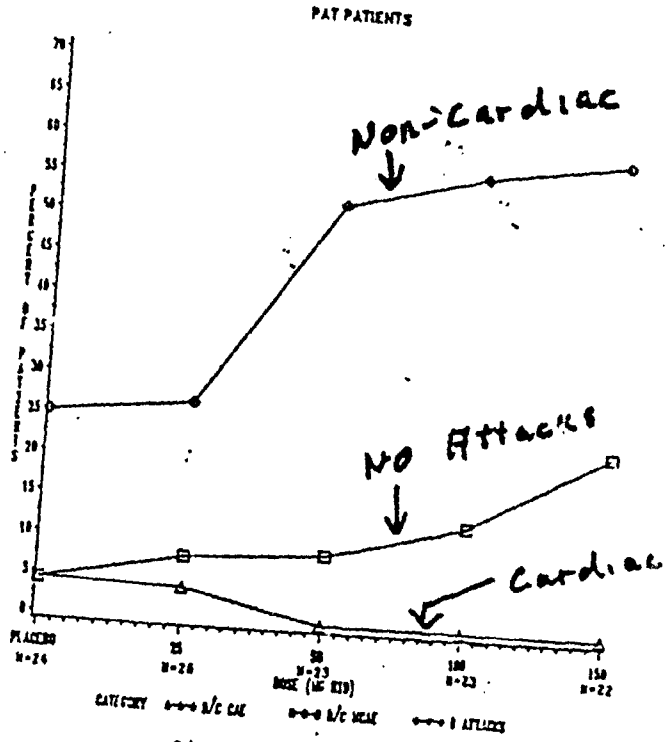
FIGURE 3

DOSAGE RECOMMENDATION ANALYSIS

PAT PATIENTS



D/C CAE = DISCONTINUED DUE TO CARDIAC ADVERSE EXPERIENCE
D/C NCAE = DISCONTINUED DUE TO NONCARDIAC ADVERSE EXPERIENCE
0 ATTACKS = NO PSVT ATTACKS REPORTED

FIGURE 7

Time to First Attack For PAF Patients Who Received Both Flecainide and Placebo In Crossover Fashion N=48

R-818-065/066 Trials

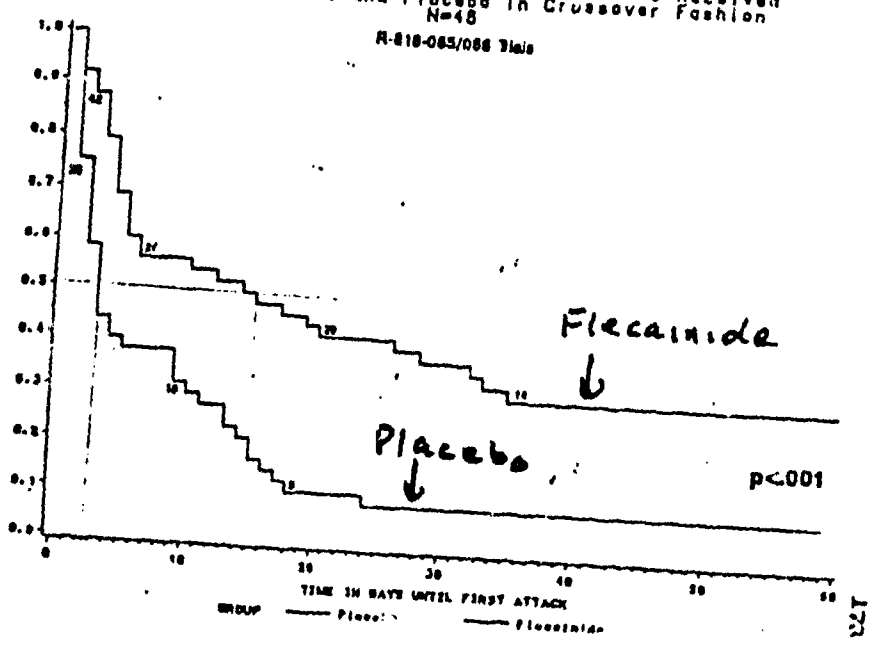


FIGURE 8

Interval Between Attacks For PAF Patients Who Received Both Flecainide and Placebo In Crossover Fashion N=48

R-818-065/066 Trials

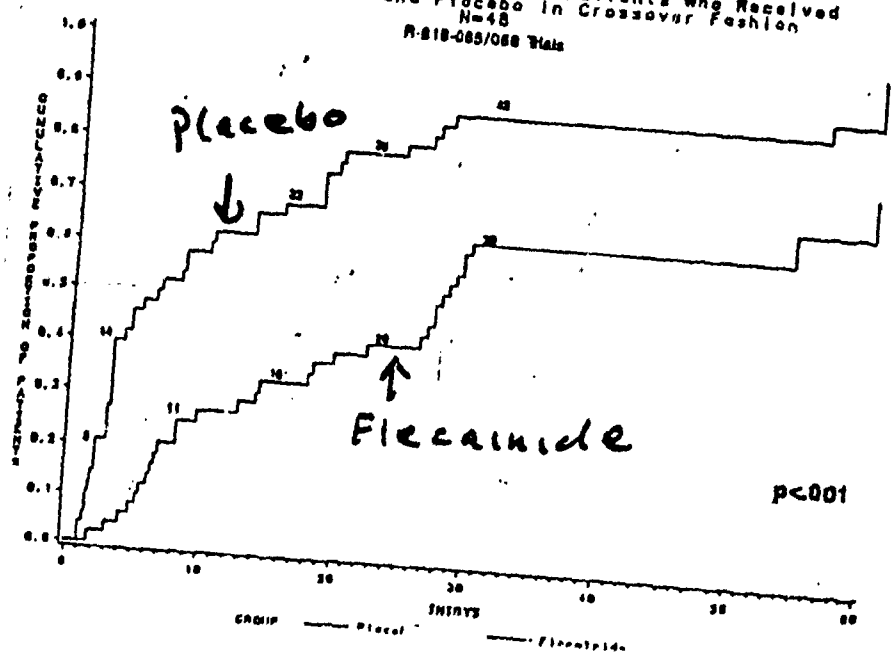


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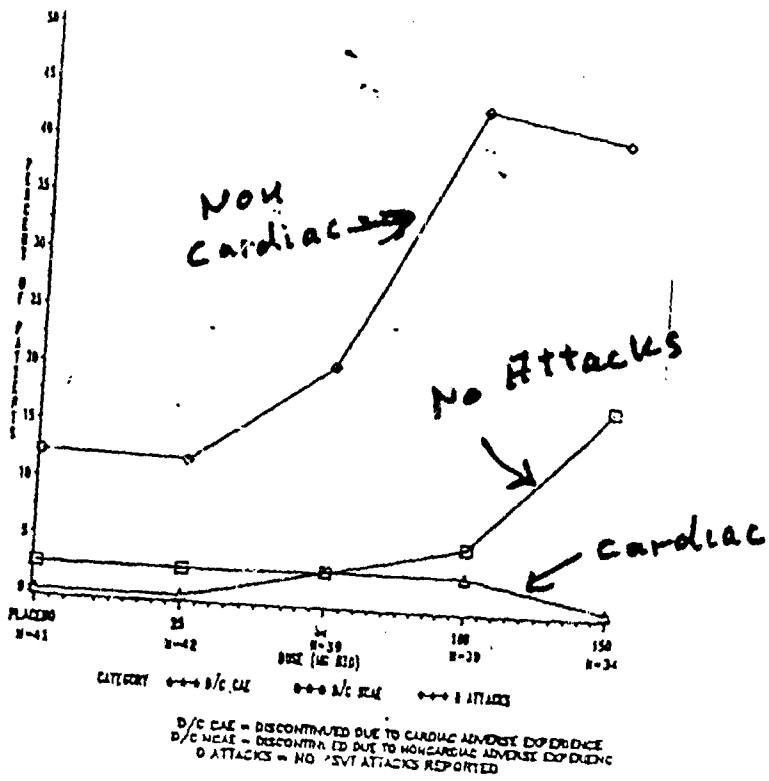
FIGURE 9

DOSAGE RECOMMENDATION ANALYSIS

PAF PATIENTS



D/C CAE = DISCONTINUED DUE TO CARDIAC ADVERSE EXPERIENCE
D/C NCAE = DISCONTINUED DUE TO NONCARDIAC ADVERSE EXPERIENCE
0 ATTACKS = NO PSVT ATTACKS REPORTED

Moreover, this trial can be viewed as a third trial showing efficacy of flecainide (a non-zero dose response was affirmed, p = 0.001).

There is no doubt about the efficacy of flecainide in supraventricular tachycardia. Although not compared head-to-head to verapamil in the same randomized population, in the trials that showed verapamil to be effective, verapamil increased the time to recurrence of PAT by only about two-fold (as opposed to four-fold for flecainide). No comparable data for quinidine are available.

SAFETY

Until recently, the issue of safety would not have needed a carefully considered section in this memorandum and, for sure, mortality would not have been addressed. One, at least I, would have been thankful for the introduction of a remarkably effective agent for the first time in the history of medicine and would have graciously accepted it. The results of CAST brought adverse mortality effects of antiarrhythmic agents to the forefront of everyone's thinking. Although not an easy task, because there exist a variety of disparate databases to consider, the risk/benefit assessment of flecainide in the treatment of patients with supraventricular arrhythmias needs to be addressed.

There are no mortality data for verapamil in patients who have survived a myocardial infarction but have asymptomatic ventricular premature contractions; such a trial has not been conducted. Mortality trials do exist for calcium channel blockers in patients post-myocardial infarction. The best way, short of reviewing each trial in detail, is to summarize these trials as neutral, except in patients with congestive heart failure where there appears to be an overall adverse mortality effect.

In a recent abstract (ACC meeting abstract, March 1991), Morganroth has reported a meta-analysis that shows quinidine to have an overall adverse effect on mortality in patients with P-V-Cs. A similar meta-analysis (Coplen, et al., Circulation 82:1106-1116, 1990) showed a similar adverse effect on mortality when quinidine was used in the treatment of patients with atrial fibrillation.

Of course, flecainide was one of the drugs used in CAST, the clearest demonstration of adverse effect on mortality in patients who survived a myocardial infarction and have asymptomatic ventricular premature contractions that has ever been seen.

We have struggled (and still are struggling) with how to apply the results of CAST to other antiarrhythmics and/or other patient populations, but all within the context of ventricular arrhythmias. We have concluded that it is prudent (not known, not demonstrated, not data driven) to assume all antiarrhythmics share similar risk (after all, all antiarrhythmics share proarrhythmic properties and negative inotropic properties) and to restrict the use of all antiarrhythmic agents (used in the treatment of ventricular arrhythmias) to only those ventricular arrhythmias that are life-threatening. This decision is based

as much on lack of known benefit when treating lesser (lesser being used in a life-threatening sense) arrhythmias as on the adverse mortality effect known from CAST.

Mortality data would be highly desirable if one wished to make a data-driven judgment, but supraventricular arrhythmias are not common. In protocol R-818-065 it took 30 months for 12 tertiary care centers to recruit 73 patients (39 PAF and 34 PSVT), about two patients/month, or one patient/five months/center. It is not surprising that lots of mortality data are not available on supraventricular arrhythmias. Based on the numbers that follow, in order to rule out a 50% increased mortality (compared to placebo) in flecainide treated patients with supraventricular arrhythmia, one would need to mount a placebo-controlled trial involving 2000 to 3000 patients for 3 years (a 5-year trial if one gave 2 years for recruitment). To expect to see the results of a trial of 2000 to 3000 patients is obviously not realistic. Furthermore, to evaluate the effects on mortality, one would require symptomatic patients to remain on placebo for three years. Aside from moral and ethical considerations, it is unlikely that patients or doctors would allow three years of two attacks/month; the trial could never be completed even if one were foolish enough to begin.

Nonetheless, there is a sufficient database that allows rational decision making. Dr. Pritchett, a member of our Cardiovascular and Renal Drugs Advisory Committee (chosen to sit on the Committee because of his obvious competence as an innovative clinical investigator when verapamil was being studied) and his staff are responsible for pulling the data together and performing analyses. Dr. Pritchett presented this information at the October 5, 1989 Advisory Committee meeting. The following summarizes the major aspects of Dr. Pritchett's work.

Dr. Pritchett used four sources of data for his analyses.

1) The mortality data from 158 patients that were not receiving encainide or flecainide, but were being followed in his supraventricular arrhythmia clinic between the years 1980 and 1989 (up to July 1989). These 158 patients were those who could be accounted for out of a total of 165 patients who had been seen in his clinic over the nine-year period.

2) All of the data collected by Bristol-Myers for encainide, and all of the data collected by 3M-Riker for flecainide; for prophylaxis of supraventricular arrhythmias; Bristol and 3M-Riker made all of their data available to Dr. Pritchett.

3) The U.S. Census Tables.

4) The results of CAST.

Of the 158 patients followed in Dr. Pritchett's clinic between 1980 and 1989 (average follow up of 270 days, longest 9.6 years) there were 10 deaths. None of the 10 patients who died was receiving either encainide or flecainide. The

average age of patients was 45 years, most were white, and 34% had some form of organic heart disease. The one-year mortality rate was 1.7%. Compared to an age and sex-matched general population from U.S. Census tables, patients with supraventricular arrhythmias (all being treated with something) had a higher death rate than did the general population. This was not a prospective randomized trial result. It is descriptive and doesn't deserve a p value. Nonetheless, it is useful as a beginning point for discussion.

The point estimate for a one-year death rate for patients being treated with encainide (eight deaths) was 1.4%, and for those treated with flecainide (one death) was 0.5%. The comparable point estimate for the CAST trial was 9.1%.

A series of assumptions needed to be made regarding the distribution of deaths as function of time in order to calculate a confidence interval. A worst case, exponential function was assumed. This gave the following comparisons.

	Flecainide	Encainide	Clinic Patients
Point estimate	0.5	1.4	1.7
95% Confidence	0.0-2.7	0.6-2.7	0.8-3.2

Clearly, none of these numbers approach the 9.1 point estimate obtained by CAST.

The one death that occurred during the 3M-Riker development program was a patient who had paroxysmal atrial fibrillation. He was a 59-year-old male who in addition to having had a carotid endarterectomy had angina and premature ventricular contractions; he was concomitantly receiving meclizine, metoclopramide, desipramine, diazepam, ranitidine, aspirin, and digoxin. He clearly, in addition to structural heart disease, had multiple pathologies in multiple organs. He died a sudden death and was not resuscitable.

Although there were a number of proarrhythmic events, only one was a ventricular proarrhythmia. The remainder were more frequent or different (i.e., conduction disturbances) atrial arrhythmias that could easily be viewed as simple non-efficacy, as opposed to proarrhythmia.

The sustained ventricular tachycardia occurred in a 68-year-old man who had had a coronary bypass and had angina, rheumatic heart disease, congestive heart failure, and a history of non-sustained ventricular tachycardia. Baseline ejection fractions were between 37% and 47%. His sustained ventricular tachycardia was able to be terminated and it was subsequently documented to be inducible by EPS after flecainide washout. Although one cannot rule out flecainide as a cause of this patient's sustained ventricular tachycardia, it does not seem likely.

The labeling reflects the judicious use of flecainide and the uncertainties of the risk. It is clear that patients with debilitating symptoms and an absence of structural heart disease can expect a reasonable benefit and a negligible risk. As one departs from this scenario, unknowns become more important.

Given debilitating symptoms and known structural heart disease (with or without functional impairment) a rather difficult decision needs to be made (if I were responsible for patient care, I would probably recommend using flecainide even in such a circumstance). The labeling reflects such ambiguity by silence, which I think is appropriate here.

Ray Lipicky

Raymond J. Lipicky, M.D.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA #18-830

Name of Drug: Tambocor (flecainide acetate) tablets

Sponsor: 3M Riker

Type of Submission: Safety Update Report

Date of Submission: 1/15/90

Date of Review: 1/18/90

Reviewer: Sughok K. Chun, M.D. HFD-110

This is a four month safety udate report for the Supplemental Application of Supraventricular Claims submitted to the Tambocor NDA on July 26, 1989. At the time of the submission, three clinical trials sponsored by 3M Pharmaceuticals were considered ongoing. Either part or all of the data from these trials were unavailable for analysis and were not included in the comprehensive safety and efficacy summaries.

Study R-818-074, Elective Open-Label Chronic Use Phase: Patients who were effectively treated with flec in the dose response study were allowed to continue on open-label, oral flec therapy for a maximum of 12 mos in the Chronic Use Phase of the study. A total of 46 pts, were treated with dosages ranging from 100 to 400 mg/day.

Open-label, Long-term, Chronic Efficacy Evaluation After Six or More Months of Flecainide Therapy in Patients With PSVT From Studies R-818-065, R-818-066, and R-818-074: The purpose of this evaluation was to objectively evaluate the long-term safety and efficacy of flec in the treatment of PSVT and PAF in pts who had previously completed the double-blind efficacy studies (-065 & -066) and double-blind dose response study (-074).

A total of 48 pts participated. An interim analysis and Sponsor's Clinical Report were completed on data from 32/48 pts who entered the study during June 1988 through September 1988. The report was submitted with the supplemental application. Data for the remaining 16/48 pts are currently being collected, reviewed, and entered in the data base. None of the 16 pts discontinued from the chronic efficacy evaluation.

Data of these studies (-065, -066, & -074) do not appear to affect the contraindications, warnings, precautions, and adverse reactions currently included in the draft labeling.

Study R-818-077: This study was a phase III, open-label multicenter trial designed to broaden the safety and efficacy profile of oral flec in pts with all types of supraventricular arrhythmias. Investigators at 21 centers reported enrollment of 142 consenting pts. One pt died as a result of respiratory failure due to metastatic adenocarcinoma to the lung while receiving flec in the trial. The event was included in the PSVT Pt Deaths section of the integrated safety summary. Data reviewed to date from this

study do not appear to affect the contraindications, warnings, precautions, and adverse reactions currently included in the draft labeling.

A possible seizure was reported as an interval medical event for a patient in this study. This case (pt no. 002 from study R-818-077-15) was a 35 y/m and the seizure like episodes did not appear to be related to flec. The pt was continuing to experience episodes of "fluttering" (not heart fluttering but a fluttering sensation) followed by a possible loss of consciousness or amnestic period of 10 minutes on and off even after d/c of flec for 6 mos follow-up period.

S K Chun 2/12/90

Sughok K. Chun, M.D. HFD-110

cc: Orig. NDA
HFD-110
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HFD-110/SChun
ml:1/18/90:#1178a

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

JAN 1 1990

NDA #18-830/SNC-012

Name of Drug: Tambocor (flecainide acetate) Tablets

Sponsor: 3M Riker

Type of Submission: Draft of Package Insert and Summary Basis of Approval

Date of Submission: 12/22/89

Date of Review: 1/16/90

Reviewer: Sughok K. Chun, M.D. HFD-110

The following items are discussed with Gene Harris, Sr. Regulatory Coordinator on 1/03/90 and Florence Wong, Manager, Dept of Regulatory Affairs on 1/17/90.

(1) Revised draft of package insert is generally satisfactory. However, proarrhythmia effects (page 7), line 9 "In patients treated with flecainide for sustained ventricular tachycardia, 91% (58/64) of proarrhythmic events occurred within 30 days of the onser of therapy." In original NDA evaluation, the sponsor defined proarrhythmia within 14 days of initial treatment or a change in dose as quoted several times in this SBA. If the proarrhythmia was counted within 30 days of treatment the sentence "In applying the sponsor's criteria, this patient's event, which occurred more than 14 days after the initiation of therapy, was not considered a proarrhythmic event." in pages 101, 125 & 148 should be deleted.

(2) SBA

1) The sponsor stated "no changes in atrial rate, ventricular rate in pts with atrial fibrillation."
There is no atrial rate in atrial fibrillation by definition that atrial rate should be deleted. There are statement of "change in ventricular rate" but it is not clear whether it is referred to during PSVT attacks or sinus rhythm (eg. page 20 2nd paragraph, page 26 2nd paragraph, page 33 2nd paragraph etc).

2)Page 19 end of first paragraph
"However, the total number of patients reporting NCAEs during Crossover as compared with Dose Ranging was lower which suggests flecainide dosing becomes more tolerable at lower doses and possibly more tolerable over time." is not correct statement. This difference was due to the forced titration during dose ranging period and many pts received reduced doses during crossover phase due to ADRs. The incidence of ADRs with Flecainide 300-400 mg/day was similar in both phases that it is unlikely due to tolerance. See page 97 2nd paragraph.

3) Page 20, 1st paragraph
Reference to concomitant treatment with verapamil, it should specify what treatment period (placebo or flec) verapamil was given and efficacy of verapamil.

4) Page 20, 3rd paragraph
"...within the established range of 0.2 to 1.0..." to be changed to "within therapeutic range of ..."

5) Page 25, Table 14
The maximal flec dose in protocol was 400 mg. In Table 14 PAF group 1 pt received 500 mg, 1 pt received 600 mg.
Explanation of these higher doses should be described as a footnote of table.

6) Page 31 Table 16
No. of pts d/ced. PAF group flec was 3, but the text described only 2 pts.

7) Page 41 Table 19 Footnote
"[c]Number of times this symptom was recorded and the ECG diagnosis was consistent with no arrhythmia, an attack of SVA, or possible other symptomatic arrhythmias."
Please describe possible other symptomatic arrhythmias.
"[d]Combined arrhythmia included symptoms reported as one or more of the following: paroxysmal atrial tachycardia, supraventricular arrhythmia, supraventricular tachycardia, atrial arrhythmia, arrhythmia, or atrial flutter."
combined arrhythmia does not belong to the symptom column. These arrhythmias belong to the footnote c above.

8) Page 64, 1st paragraph
"**Trough Plasma Flecainide Levels:** Trough plasma flecainide levels were required at the end of each treatment period. For both groups of patients, the plasma flecainide levels increased proportionately with increases in flecainide dosages." I think in this study only few plasma flec levels were measured and no data to support this statement. If the sponsor has the data to support this statement, it should be tabulated.

9) Page 66 1st paragraph ref to concomitant antiarrhythmic medication.
The results of these concomitant medication be described.

10) Page 66, Conclusion, last sentence.
"A substantial increase in efficacy, without a substantial increase in discontinuations for adverse experiences, was observed when PAF patients received 100 mg bid flecainide therefore, if PAF patients continue to experience arrhythmias on 50 mg bid flecainide, increased efficacy may be achieved on 100 mg bid flecainide."
How about PSVT pts?

11) Page 75 2nd paragraph
Reference to leukopenia patient. What was baseline or previous WBC count, differential count? Was there any report of significant leukopenia in original NDA database pts with VAs?

[illegible] 2nd paragraph
[illegible]stically significant change in vital signs noted in all [illegible] at month 1 where a statistically significant but [illegible]ficant increase in diastolic blood pressure was [illegible] actual data.

13) Page 83 last sentence
Two of 13 WPW patients were discontinued from the study due to suspected noncompliance based on plasma flecainide levels of ng/mL when the drug was supposedly being taken. ng/mL be changed to 0 ng/mL.

14) Page 87
"Blood samples for plasma flecainide levels were obtained at peak drug level times (2 to 3 hours postdose); none of the mean values were exceedingly high during the study."
Page 92 3rd paragraph stated that "dose information is not available. Which statement is true? If the sponsor has a data, make a table or figure to describe dose/plasma level vs efficacy and adverse effects.

15) Page 90 2nd paragraph last sentence
Typo error "statified" change to "stratified".

16)Page 96 Table 45 and last paragraph
"Hypothesis testing was done using the data for the 19 PSVT patients who received study drug in all five periods. A significant dose response was observed for autonomic nervous system disorders (flushing, sweating, or miosis)".
Is "miosis" same as "visual disturbance" described all other ADRs? Since visual disturbance is one of the common ADRs list it in Table 45.

17) Page 100 Figure 8 and page 114 Figure 9.
Footnote for each line.

18) Page 105 3rd paragraph
"There were no statistically significant differences in the number of patients discontinuing due to adverse experiences between flecainide and placebo in any of the double-blind studies." Describe actual number of pts discontinued due to ADRs out of total number of pts in each group.

19) Page 116 2nd paragraph and page 117 paragraph 2 reference to atrial flutter. What was ventricular rate?
"She experienced a sustained episode of atrial flutter with an atrial rate of 272 beats per minute (bpm) which did not break after the administration of 400 mg quinidine and 160 mg verapamil." "In exercise, the rate went to 1:1 conduction. In the investigator's opinion flecainide worsened the arrhythmia by making it long-lasting and transforming his atrial fibrillation into atrial flutter."

20) Page 143 4th paragraph
"Cardiac Adverse Experiences: None of the 13/14 patients who received [illegible] therapy experienced a significant conduction disturbance, new [illegible] CHF, or died while taking flecainide."
[illegible] 4th paragraph below, contradicts the above statement.
[illegible] Reported Conduction Disturbances and Arrhythmias During [illegible] patients tested by ETT while receiving flecainide alone, [illegible] reported to have SVT with aberrant conduction and 1/12 [illegible] urteen patients completed ETT while receiving digoxin [illegible] with aberrant conduction and nonsustained VT, and 1/14 [illegible] ed VT. Eleven patients underwent ETT while [illegible] mg bid with digoxin; 3/11 had SVT with aberrant [illegible] completed ETT while receiving flecainide 150 mg [illegible] rienced [illegible] vide-complex tachycardia compatible [illegible] nt co[illegible] tion or VT."

21) Page 150 2nd paragraph, last sentence
"No incidents of proarrhythmia occurred in the 25 patients with chronic atrial fibrillation who received oral flecainide. The overall incidence of proarrhythmia in patients receiving oral flecainide was 3.7% [see Table 65]."
Why the proarrhythmic events in study R-818-075 (Falk) page 143-144 are not included in this statement and Table 65?

S C. Chun 1/17/90
Sughok K. Chun, M.D. HFD-110

cc: Orig. NDA
HFD-110
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ml:1/17/90:#1173a

INDEX

NDA 18-830/SE-012: Tambocor for Supraventricular Claims

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICERS REVIEW

SEP 15 1989

NDA #18-830/S-012

Name of Drug: Tambocor (flecainide acetate, R-818)

Sponsor: Riker Laboratories, Inc.

Type of Submission: Supplemental Application for Supraventricular Claims

Date of Submission: 7/26/89, 8/7/89, 8/11/89, 8/17/89, 8/30/89

Date of Review: 7/28/89 - 9/15/89

Reviewer: Sughok K. Chun, M.D. HFD-110

This supplement contains information on the use of flecainide in the treatment of supraventricular arrhythmias (SVAs).

Orally administered flecainide (flec) was approved by the US Food and Drug Administration (FDA) in October of 1985 for the treatment (Rx) of ventricular arrhythmias (VAs) and has been used extensively in the US since that time. Flec has also been approved for marketing in approximately 50 foreign countries and has been specifically approved for Rx of certain SVAs in the following major countries: Australia, Belgium, Denmark, France, Finland, Germany, Holland, New Zealand, Norway, Sweden, Switzerland and the UK. In the US, Riker Laboratories, Inc (3M Riker) therefore decided to evaluate oral flecainide for the Rx of paraxysmal supraventricular arrhythmias (PSVAs); this supplemental New Drug Application (sNDA) reports the results of that program.

This program was essentially completed by April 1989, when the National Institutes of Health (NIH) discontinued flec from their Cardiac Arrhythmia Suppresion Trial (CAST) in post-myocardial infarction pts with asymptomatic VAs. The reason for discontinuing flec in CAST was the unexpected observation of a 2.2 fold higher risk of mortality and non fatal cardiac arrest in flec pts (16/315 or 5.1%) as compared to matching placebo pts (7/309 or 2.3%).

Paroxysmal supraventricular tachycardias (PSVT), ie, paroxysmal atrial tachycardia (PAT), and paroxysmal atrial fibrillation/paroxysmal atrial flutter (PAF) are intermittent arrhythmias of supraventricular origin during which the cardiac rate increases, usually accelerating to 100 to 200 beats/min and occasionally even higher.

Although most of SVAs may not be noticed by the pt, PSVT are frequently symptomatic. The resulting hemodynamic derangements may have consequences such as syncope, shock, congestive heart failure, angina pectoris, pulmonary edema or sudden death. Pts with paroxysmal atrial fibrillation are specifically at risk for emboli and stroke, which can also be fatal.

Because of the importance of symptoms both to the pt and the physician making therapeutice decisions, the relationship between episodes of PSVT, reported

symptoms and the effect of flec upon both has been a major focus of this clinical trial program and NDA.

The pivotal dose-response study and the two pivotal safety and efficacy studies were conducted using randomized, double-blind, placebo-controlled, crossover designs and utilized transtelephonic monitoring (TTM) to document the arrhythmias. PSVT pts were excluded form these pivotal trials if their PSVT episodes were associated with severe hemodynamic consequences (ie: fainting) which precluded their participation in placebo-controlled studies. Long-term safety and evidence of sustained efficacy were documented in pts form the pivotal trials who remained on oral flec for a minimum of 6 mos, although the mean duration of therapy (Rx) was approx 1.5 yrs at the time of this submission.

The objectives of this clinical trials program were as follows: to assess whether or not flec was effective in preventing the recurrence of and/or reducing the frequency of attacks of symptomatic PAT or PAF; to define the appropriate dosing regimen; and to profile the adverse experiences (AEs) encountered with flec in treating such patients (pts).

Efficacy and Safety: Two Pivotal Safety and Efficacy Trials

Two seperate but identical randomized, double-blind, placebo-controlled, multicenter, corssover trials (R-818-065 and R-818-066) involving 70 and 42 pts, respectively, were conducted to evaluate the efficacy and safety of oral flec in pts with PSVT. Each trial enrolled PAT and PAF pts. Pts in both of these pivotal studies documented their arrhythmias via TTM and, at the same time reported their symptoms to Survival Technology, Inc. In order to participate, pts had to exhibit and document frequent PSVT episodes during a 4 weeks screening period. With the exception of digoxin for PAF pts, no antiarrhythmic Rx was given during this time. Each pt then entered an open-label, dose ranging period to determine the highest tolerated dose of oral flec (200 mg, 300 mg, or 400 mg/day). Following the selection of the highest tolerated dose, each pt entered the randomized, crossover portion of the study, during which time the dose of flec selected during the dose-ranging period was compared in a double-blind fashion with matching placebo during two consecutive 8-wk periods. , in the screening period, TTM and simultaneous direct symptom reporting were mployed throughout the crossover periods. AE data were collected during the trial and were used to profile the incidence of cardiac and noncardiac AEs.

Dose-Response Considerations: A Pivotal Dose-Response Trial

Flec has been used extensively for the Rx of VAs, usually at total daily dosages of 200 to 400 mg divided into bid doses. In addition, these dosages have been commonly used outside the US to treat both SVA and VAs. Following initiation of the two studies (R-818-065 and R-818-066) described above, the FDA's Cardio-Renal Division requested that a dose-response study be done. Therefore, in consultation with FDA, a randomized, double-blind, placebo-controlled, multicenter, crossover trial (R-818-074) was designed to evaluate total daily doses of 50 mg, 100 mg, 200 mg and 300 mg (divided to

bid), as well as placebo, all given orally. Using TTM, pts underwent a qualifying period to document that their paroxysmal episodes were of sufficient frequency to detect changes which might occur. The pts then received all four dosing regimens of flec and matching placebo for 4 wks each and evaluated with TTM during the multiple crossover periods.

Relationships Between PSVT Reduction, Symptom Reduction and Flecainide Rx

This clinical trials program focused in an innovative way on the relationships between documented PSVT episodes, simultaneously reported symptoms and flec's effects on these parameters under randomized, double-blind, placebo-controlled conditions.

In seperate report (R-818-065/066 - Survival Technology Results), data from a total of 112 pts with either PAT or PAF from the two pivotal efficacy studies (R-818-065 and R-818-066) were evaluated to determine the degree of correlation between TTM-documented arrhythmias and reported symptoms and the effectiveness of flec in eliminating or reducing these symptoms.

Documentation of Effectiveness of Long-Term Flecainide Rx

In order to document the long-term effectiveness of oral flec in the Rx of PSVT, pts who successfully completed the pivotal safety and efficacy studies were entered into an open-label, chronic efficacy trial. The PSVT pts described above who had been in the open-label portion of the study for at least 6 months entered chronic efficacy amendments for protocols R-818-065, R-818-066 and R-818-074, during which they were reinstructed in the use of TTM in order to transmit any suspected PSVT episodes, along with direct reporting of associated symptoms, to determine if any changes in flec's efficacy or safety had occurred.

Additional Trials and Analyses of Wolff-Parkinson-White Patients

Data on flec's efficacy in pts with WPW syndrome were available form three trials and independent studies of Dr. Rodolphe Ruffy, St. Louis, MO (IND) and Dr. Helmut Neuss, West Germany with WPW syndrome and AV nodal reentrant tachycardia (AVNRT) are submitted.

Studies of Special Interest

Although oral flec was not systematically evaluated for ventricular rate (VR) control in the treatment of chronic atrial fibrillation (AFib) and this indication was not the subject of this clinical program and submission, potential benefits in treating these pts had been reported in a published abstract in 1983. Subsequently, 3M Riker was approached by an investigator, Rodney Falk, MD, Boston, Mass., who wished to do a pilot study of the effects of flec alone and in combination with digoxin for control of VR at rest and during maximal exercise. The results of this pilot study (R-818-075) are included in this submission.

A. CONTROLLED CLINICAL STUDIES

The list of controlled clinical trials are shown Table 1 and list of principal investigators and number of pts enrolled by study number are in Table 2.

1. Study R-818-065 Volumes 1 and 2
"Double-blind, Placebo Controlled Crossover Study of Flecainide in the Prophylaxis of Paroxysmal Supraventricular Tachycardia (PSVT)."
The objective of the study is to assess the safety and efficay of flec, at doses up to 400 mg/day, in preventing recurring attacks of PSVT.

Investigators at 12 sites enrolled 34 PAT pts with and 39 PAF pts.

STUDY DESIGN:

This was a 16-wk, double-blind, placebo-controlled, randomized crossover study which had three phases: a 4 wk screeening phase; a 3 wk Dose Ranging Phase; and a Crossover Phase with two 8 wk periods.

During the screening phase, pts documented two attacks of PSVT within 4 wks; (PAT with VR $\geq$ 120 beats per minute (bpm) or PAF with VR $\geq$ 80 bpm) at least 1/2 attacks was documented by TTM, the second attack could be by TTM of ECG rhythm strip.

The Dose Ranging Phase was an open-label, upward dose-titration phase to determine the maximum-tolerated dose for each pt. Pts received 200mg total daily dose (TDD) for wk 1, 300 mg for wk 2, and 400 mg for wk 3; pts who were intolerant to 200 mg received 100 mg for wk 2 therapy. Pts entered the Crossover Phase at the most tolerable dose level as determined during the Dose Ranging Phase. Efficacy was not evaluated during this phase.

The pts dose of flec was lowered or discontinued if a rhythm strip showed a PR > 0.30 sec, QRS > 0.18 sec, or second or third degree AV block. In addition, Survival Technology, Inc, was instructed to immediately call the investigator should any of the following be observed on a rhythm strip:

1. a ventricular rate greater than 160 bpm,
2. a ventricular rate less than 30 bpm,.
3. pause greater than 3.5 sec,
4. PR greater than 0.26 sec, or second or third degree AV block,
5. QRS of 0.18 sec or more,
6. pacemaker (if present) rate drops below the rate of implant,
7. pacemaker sensing or capture fails, or
8. salvos of three or more PVCs in a row.

The Crossover Phase was a double-blind, two-period crossover comparing placebo and flec for a maximum of 8 wks or four attacks in each period, whichever occurred first.

The effects of flecainide and placebo on the frequency and

severity of PSVT attacks were ccmpared using the following parameters: number of pts having no attacks, time to first attack, interval between attack, and VR during attacks. Data from all centers were combined in the analysis. All analysed were performed separately for pts with PAT and PAF arrhythmias.

In determining the time to first attack and the interval between attacks, the first 3 days of each treatment period were excluded. Day 4 of each period was defined as the first treatment day. Time to first attack was defined as the number of treatment days until the first attack. If a pt did not have any attacks during the Rx,, the time to the first attack was defined as the number of days plus one and was considered a censored observation. To determine the mean interval between attacks, the number of days on treatment was divided by the number of attacks. If a pt had no attacks, the mean interval between attacks was defined as the number of treatment days plus one and was treated as a censored observation in the data analysis.

According to the protocol, a treatment period was to end after 4 attacks or 8 wks, whichever came first. However, some pts had more than 4 attacks or went longer than 8 wks before crossing over to the next Rx. For those pts who went beyond 60 days during a treatment period, the length of the treatment period was truncated to 60 days and the determination of time to first attack and interval between attacks was determine as previously stated. If a pt had more than 4 attacks, the interval between attacks was defined as the number of treatment days up to the fifth attack or 60 days whichever came first divided by four.

Investigators obtained medical, cardiovascular, and drug therapy histories for each pt prior to enrollment. Baseline last day of the dose ranging phase and poststudy evaluations for monitoring safety included a PE, a 12-lead ECG, and clinical lab tests.

There were four amendments to this study. Amendment A allowed investigators to further characterize the underlying arrhythmia by eictrophysiologic (EP) testing and to test the effect of intravenous (IV) flec during EP testing on the prevention or alteration of induction of arrhythmia. IV flec was administered fast infusion of 2 mg/kg over 15 min followed by a slow infusion of 1 mg/kg over 3 hrs (total of 3 mg/kg over 3 hrs). Pts were required to continue into oral dosing phases of the study. Amendment B allowed for the double-blind treatment code to be broken following completion of the study provided the pt was judged effectively treated during one treatment period. Amendment C provided long-term, open-label Rx for pts effectively treated. Amendment D evaluated the effectiveness of flec by use of TTMs after 6 mos of long-term Rx.

This report summarizes data through the Crossover Phase of this study.

RESULTS:

Study population:

After 30 mos of pt enrollment, a total of 73 pts (34 PAT, 39 PAF) qualified and entered the study. The data for all pts from all participating centers were combined in the data analysis. Table 3 shows pt accountability throughout the study by PAT and PAF. Prior to entering the Dose Ranging Phase, 21 pts (16 PAT, 5 PAF) underwent EP testing with 3 PAT pts discontinuing from the study. Of the remaining 70 pts (31 PAT, 39 PAF) 15 pts d/ced during the Dose Ranging Phase. Fifty-five pts (22 PAT, 33 PAF) entered the Crossover Phase. Of these 55 pts, 2 d/ced during period A: 1 PAT pt on placebo for personal reasons and 1 PAF pt on flec for inadequate response. Of the 53 pts (21 PAT, 32 PAF) who entered period B, 4 pts d/ced: 2 PAT pts d/ced; 1 lost to follow-up and 1 for inadequate response. Only the pt who d/ced for inadequate response but had sufficient data to be included in the efficacy analysis. Two PAF pts d/ced period B, 1 for cardiac AE and 1 for a nonocardiac AE. Both pts had sufficient data to be included in the efficacy analysis. For pt discontinuation are discussed in the Safety Results section.

Reasons for Excluding Patients at the Time of Data Analysis: Of the 53 pts who entered period B and had data available for anlyses, 4 pts (1 PAT, 3 PAF) were not included in the efficacy analyses due to noncompliance to the protocol. Pt # 004/10, after receiving period B therapy, never returned to or called the study site again (lost to follow-up). Two pts, #103 and 104/02 had violations including starting and/or stopping digoxin Rx throughout the study. Pt # 101/10, received procainimide for 6 days during period A (placebo).

The sex and age and pts characteristics of the 20 PAT and 29 PAF pts included in the analysis are displayed below.

	PAT N (%)	PAF N (%)
Sex		
Male	6 (30.0%)	19 (65.5%)
Age (years)		
Mean ± SD	51.4 ± 14.6	54.4 ± 13.1
Range	18 - 78	23 - 73
[illegible] Previous Therapies	70	104
[illegible]	52 (74%)	80 (77%)
	3.5 ± 1.9	3.6 ± 1.5

8 (27.6)
2 (6.9)

Rheumatic Heart Disease	2 (10.0)	1 (3.5)
Hypertension	2 (10.0)	10 (34.5)
Conduction Disturbance	2 (10.0)	1 (3.5)
Cariomegaly	1 (5.0)	1 (3.5)
Atherosclerosis	0 (0.0)	7 (24.1)
Cardiomyopathy	0 (0.0)	1 (3.5)
Congestive Heart Failure	0 (0.0)	1 (3.5)
Sinus Node Disease	0 (0.0)	1 (3.5)

Table 4 list symptoms which pts felt were attributed to past or historical attacks of PSVT. Historical symptoms experienced most frequently by PAT pts were palpitation (90%), asthenia (62%), fatigue (48%), dizziness (35%) and dyspnea (24%). Historical symptoms reported by pts excluded from analysis were not significantly different.

Screening Results: Pts were required to have two documented attacks of PSVT in a 4 wk qualifying phase. Table 5 present the actual number of days in which pts documented two PSVT attacks.

For all PAT pts who entered the study, 76% (26/34) qualifjed within the first 28 days of screening; 32% (11/34) had two attacks of PSVT within the first 7 days of screening. Two pts entered the study even though their second attack occurred after 28 days, 4 pts entered even though they only had one documented attack, and 1 pt entered who had two attacks on the same day. One pt d/ced following EP testing never received a TTM. Of the 20 PAT pts included in the analysis, 25% (5/20) within the first 7 days of screenin; 75% (15/20) within the first 21 days. The average number of days until the second attack for PAT pts included in the analysis was 13.9 days and 11.4 days for pts excluded from the analysis. There was no statistical difference between pts included or excluded from the analyses.

For all PAF pts who entered the study, 97% (38/39) qualified within the first 28 days of screening; 67% (26/39) had two attacks of PSVT wihtin the first 7 days of screening. Of the 29 PAF pts included in the analysis, 18 (62%) within the first 21 days of screening. The average numbe of days until the second attack occurred was 9.2 days for PAF pts included in the analysis and 6.3 days for pts excluded from the analysis. There was no statistical difference pts included or excluded from the anlyses.

Symptoms reported during documented attacks of PSVT in the screening phase of the study are listed in Table 6. The most commo. PSVT symptoms experienced during screening period were palpitation, tachycardia, dyspnea, dizziness, asthenia and fatigue. Only 1 pt in PAT pts (excluded) and in PAF (included) group had syncope. Symptoms reported by pts excluded from the analyses were not clinically different.

Dose Ranging Phase

Of the 31 PAT pts who entered Dose Ranging all began receiving 200 mg/day flec. One pt had the dose lowered to 100 mg/day but subsequently entered the

Crossover Phase at 200 mg/day. One pt, after 2 days of 150 mg bid, experienced dizziness; she decreased her dose to 100 mg AM/150 mg PM for 2 days and the dizziness resolved. She then resumed dosing and completed 1 week of flec at 300 mg/day. Twenty-nine pts received 300 mg/day and 21 pts received 400 mg/day. Of the 22 pt who entered the Crossover Phase, 10 (45%) pts began at the maximum dose received during Dose Ranging, but 12 began at a lower dose due to AEs.

Of 39 PAF pts who entered Dose Ranging, all began receiving 200 mg/day flec. One pts dose was lowered to 100 mg/day; this pt entered the Crossover Phase at this dose. Thirty-seven pts received 300 mg/day, and 33 received 400 mg/day flec. Of the 33 pts who entered the Crossover Phase, 20 (61%) began at a lower dose than the maximum dose received during Dose Ranging due to AEs. Table 7 shows pt exposure to various dosage levels of flec during the dose ranging and initial dose for crossover phase.

EFFICACY RESULTS

Crossover Phase:

Although the protocol did not allow dosage adjustments during the Crossover Phase, 8 pts (5 PAT, 3 PAF) had dosage reductions; 6 dose changes were for noncardiac AEs: visual blurring, headache, tinnitus, hot-flushed face, dizziness, nausea and numbness around the mouth.

Table 8A number of attacks during crossover phase and Table 8B presents the efficacy results for PAT and PAF pts. For the PAT pts, the number who had no PSVT attacks while on flec (16) compared with placebo (4) was statistically significant ($p < 0.001$). Four PAF pts had no PSVT attacks during placebo vs 9 during flec Rx ($p = 0.228$).

Data for the time to first attack, for each pts are shown in Figure 1. Three out of four pts who did not have a PAF attack during placebo period had 1st attack at days 3,5,15 respectively while on flec Rx and 5/25 pts who had PAF attack during placebo Rx had no attack during 8 wks flec Rx. 4/4 pts who did not have PAT attack during placebo did not have attack while on flec, and 4/17 PAT pts who had attacks while on placebo did not have PSVT during 8 wks flec Rx.

Time to First Attack (Days) Figure 2

	PAT (N = 20)		PAF (N = 29)	
	Placebo	Flecainide	Placebo	Flecainide
Mean ± SE	>12.7 ± 2.2	>35.0 ± 2.2	>7.4 ± 1.2	>16.6 ± 2.4
Median	11.5	55[a]	3.0	15.0
P-value	< 0.001		0.021	

[a]Estimate based on median treatment duration. Only 20% of PAT pts had an attack while receiving flec.

Interval Between Attacks (Days) Figure 3

	PAT (N = 20)		PAF (N = 29)	
	Placebo	Flecainide	Placebo	Flecainide
Mean ± SE	>21.2 ± 4.6	>50.9 ± 3.3	>17.3 ± 3.7	30.6 ± 4.3
Median	12.8	> 55[a]	6.3	27
P-value	< 0.001		0.003	

[a]Estimate based on median treatment duration. Only 20% of PAT pts had an attack while receiving flec.

Only 4/20 PAT pts had PSVT attacks during both treatment periods and a decrease in their VR occurred while on flec (140 ± 22 bpm) as compared with placebo (178 ± 22 bpm); this was not statistically tested due to the small number of pts. Seventeen PAF pts (59%) had PSVT attacks in both treatment periods. A significant (p = 0.015) decrease in the mean VR occurred while on flec Rx (116 ± 4 bpm) as compared with placebo (124 ± 5 bpm).

Mean Duration of Therapy (Days)

	PAT (N = 20)		PAF (N = 29)	
	Placebo	Flecainide	Placebo	Flecainide
Mean ± SD	41.1 ± 24.6	55.1 ± 12.8	33.7 ± 21.0	48.3 ± 15.2
Range	6 - 89	15 - 69	10 - 63	10 - 69
P-value	< 0.05		< 0.01	

Symptoms Reported During PSVT Attacks are listed in Table 9. For the 4/20 pts who reported attacks while on flec Rx, reported symptoms: tachycardia, dyspnea, palpitation, chest pain, fatigue and increased sweating. Of the 16 PAT pts who reported attacks while receiving placebo, the most frequently reported symptoms incuded tachycardia, dyspnea, palpitation and chest pain.

For the 20/29 PAF pts who reported attacks while receiving flec Rx, the most frequently reported symptoms were palpitation, dyspnea, tachycardia, chest pain and dizziness. Of the 25/29 PAF pts reported attacks while receiving placebo with the most frequent symptoms were similar.

Intent to Treat Analysis: Of 11/31 PAT pts and 10/39 PAF pts who received oral flec were excluded from the primary efficacy analysis; 9/11 PAT pts and 6/10 PAF pts excluded because they d/c the study during the Dose Ranging Phase. To assess the effect of these pts on the overall success of flec for the treatment of PSVT an intention to treat analysis was performed. In general, results of the intention to treat analysis showed 74% (14/19) of PAT pts were effectively treated with flec. In PAF pts, 23% (8/35) were effective and in 43% (15/35) flec was judged partially effective.

Trough Plasma Flecainide Levels (Table 10): Trough plasma flec levels were required at the end of Dose Ranging, at crossover (end of treatment A and B). Due to the long elimination half-life of flec, 3M Riker defined a trough level as 8 to 16 hrs after the last dose of a bid dosing schedule, but only 40 % of the samples met this criteria. Table 10 present, by dose level, the mean trough plasma flec level at the end of Dose Ranging and during Crossover for all pts. Because of some irregularity of blood sampling time and appropriate therapeutic range in this pt population; however, mean trough levels did fall within the established range of 0.2 to 1.0 mcg/mL for VA pts.

Correlation of Results from IV EP to Results from the Oral Crossover Phase: Twenty-one pts (16 PAT, 5 PAF) received IV flec effectively prevented the induction of PSVT in 8/16 (50%) PAT and 3/5 (60%) PAF pts (Table 11).

Sixteen PAT pts received IV flec and 3/16 d/ced the study after EP testing: 2 for worsened arrhythmia and 1 for personal reasons. Of the remaining 13 pts, 6 were considered to be noneffectively treated, 6 were effectively treated, and 1 could not be evaluated; all 13 entered the Dose Ranging phase. Three of six noneffectively treated pts and 1/6 effectively treated pts d/ced Dose Ranging. Of the 9 PAT pts who entered the Crossover Phase, 7 completed the study; 2 "noneffective," 4 "effective," and 1 pt who could not be evaluated during EP testing. This pt. No. 005/08, was inducible on IV flec, however he was noninducible at baseline prior to receiving drug. During the Crossover Phase of the study this pt had 0 attacks on flec and 4 attacks on placebo that no efficacy correlation of IV dosing to oral dosing is possible for this pt.

Of the 2 pts noneffective on IV flec EP study 1 had zero attacks on oral flec Rx and 5 attacks on placebo; the other 1 pt had 1 attack during each Rx.
Of the 4 IV effectively treated pts, 3 had zero attacks during flec Rx and 1 had one attack; attacks during placebo for these pts ranged from 1 to 5.

Five PAF pts received IV flec, 3 pts were considered to be effectively treated and 1 noneffectively treated; 1 pt (#102/08) could not be induced prior to receiving flec, so effectiveness of IV flec on suppressing induction of arrhythmia could not be evaluated. Of the 4 pts who could be evaluated, 2/3 effectively treated pts had no attacks on oral flec and 1 to 3 attacks on placebo. The only 1/1 pt noneffectively IV treated pt had 2 attacks on oral flec and 5 attacks on placebo.

SAFETY RESULTS

IV Flecainide

Twenty-one pts (16 PAT, 5 PAF) received IV flec. Of 3/21 d/ced and 18 continued into Dose Ranging Phase of the study.
Reasons for Discontinuing After IV flecainide: Three pts d/ced the study after EP testing; all were PAT pts. Two d/ced for worsened arrhythmia (proarrhythmia) and 1 for personal reasons.

Brief medical Hx of these 2 proarrhythmia:

Pt #001/01 was a 38 y/m with a Hx of WPW associated with palpitations, weakness, and sweating. The pt underwent EP testing. After receiving IV flec, the pt was not inducible for PSVT; but a single PVC induced VF. The pt had no previous Hx of VF. The pt was resuscitated and the study was terminated.

Pt # 003/08 was a 40 y/f with a Hx of mitral valve prolapse, and WPW associated with palpitations, near syncope, weakness, and shortness of breath. The pt underwent EP testing. According to the investigator, IV flec blocked antegrade conduction over the AV bypass pathway but caused incessant reentrant AV reciprocating tachycardia. Verapamil (5 mg, IV) terminated the event. At the end of EP testing, antegrade conduction over the AV bypass pathway resumed. The pt was placed on oral verapamil and removed from the study.

Noncardiac AEs were noted in 2 PAT pts: dizziness, dizziness and headache.

Oral flecainide.

Seventy pts received oral flec and 21 pt d/ced the study. Reasons causing d/c of flec Rx 12/31 PAT pts were: personal (3 pts), noncardiac AEs (2), lost to follow-up (2), protocol compliance (2) and cardiac AE (1). Reasons causing d/c from placebo Rx: personal reasons (1) and inadequate response (1).

Nine of thirty-nine PAF pts d/ced: 2 for cardiac AE, 2 for personal reasons and inadequate response, and 1 for intercurrent disease, death and noncardiac AE. All events occured while the pts were taking flec.

Cardiac AEs: A total of 5 pts (7%) had cardiac AEs (Table 12): proarrhythmic events 2 (all PAF, 1 of them died), conduction disturbance 2 (PAF), MI 1 (PAT), CHF (0). Table 12 displays the incidence of reported cardiac AEs (5/70, 7%) by event.

Investigators reported a worsening of arrhythmia in 2 pts who were on oral therapy. Both were PAF pts. One pt had an increase in duration of attack and a transformation from atrial fibrillation to atrial flutter. The second pt died. The following case histories describe those events.

Proarrhythmias:

Pt # 102/12 was a 58 y/m with a Hx of PAF associated with weakness, fatigue, skipped beats, diaphoresis, and indigestion. The pt's arrhythmia had a history of lasting for "multiple-days-duration." Concomitant therapy included digoxin (0.375 mg, daily). The pt entered a treatment A, placebo, and had 2 attacks after 28 days of study drug. Per the pts request, he was crossed-over early into treatment B (flec). The pt recorded 2 attacks of SVT, the second of which began after 40 days of Rx and lasted over 1 week. The pt had never experienced such a long duration of arrhythmia and felt the event intolerable.

Pt # 101/09 was a 59 y/m with a Hx of ASHD, angina, PVCs, PACs, bradycardia, and PAF associated with palpitations and weakness. Concomitant therapy included meclizine, metoclopramine HCl, desipramine HCl, diazepam, ranitidine, aspirin, and digoxin. After 7 days of 200 mg/day flec and 2 days of 300 mg/day in the Dose Ranging Phase, he was brought to the ER in VF. He was electrically defibrillated and converted to NSR after receiving bretylium, lidocaine, epinephrine, and bicarbonate. However, his pupils remained dilated and fixed and he required ventilatory support. The next day he aspirated some bloody vomitus and was started on IV Keflin and Zantac, an hydrocortisone. He then developed PVCs, became hypotensive and went into a grand mal seizure follwed by asystole. Attempts to reverse his deterioration were unsuccessful. No autopsy was performed but other relevant data included a plasma flec level of 0.55 mcg/mL, a digoxin level of 0.62 ng/mL, and an ECG revealed a nonspecific ST depression which the investigator felt was suspicious of a subendocardial injury. The investigator felt his death was possibly related to flec Rx.

Conduction Disturbances -- Two out of 70 pts who received oral flec Rx experienced a conduction disturbance. Both events occurred in PAT pts during Dose Ranging; neither pt d/ced the study for this reason.

Pt # 103/14 had flec (150 mg bid) temporarily stopped to evaluate a questionable sinus pause and bradycardia. On restart of therapy (150 mg bid) the symptoms did not recur.

Pt # 103/01 experienced a presyncopal episode during wk 3 of dose ranging; the pt d/ced the study 9 days later for presyncope, nausea, and nervousness. An ECG recorded on the day of the presyncopal event showed first degress AV block and intraventricular conduction delay.

Myocardial Infarction -- One PAT pt # 001/08 d/ced the study during wk 2 Dose Ranging for a possible MI. The pt was a 61 y/f with a Hx of mitral valve prolapse, PVCs and PSVT associated with weakness and chest pressure. During wk 2 of Dose Ranging she developed ECG changes suggestive of a possibel MI. Subsequent angiography showed normal coronary arteries, this possible MI event was thought to be related to flec Rx.

Noncardiac AEs: The most frequent noncardiac AEs reported during the Dose Ranging Phase were similar for both PAT and PAF pts. Because pts were dosed to tolerance during this phase, the higher frequencies were not unexpected.

Noncardiac Adverse Experiences Dose Ranging Phase

	PAT (N=31)		PAF (N=39)	
Dizziness	11	35.5%	17	43.6%
Vision Abnormal	8	25.8%	17	43.6%
Headache	8	25.8%	5	12.8%
Nausea	5	16.1%	5	12.8%
Fatigue	3	9.7%	4	10.3%

No. pts reporting NCAEs	25	80.6%	29	74.3%

The most frequently reported NCAEs during the Crossover Phase are presented in Tables below. The most frequent complaints with flec Rx continued to be dizziness, headache, and vision abnormalities.

Crossover Phase

	PAT			PAF		
	Placebo N = 22		Flecainide N = 20	Placebo N = 32		Flecainide N = 33
Dizziness	2	9.1%	5 25.0%	3	9.4%	8 24.2%
Headache	4	18.2%	5 25.0%	1	3.1%	2 6.1%
Vision Abnormal	1	4.5%	4 20.0%	1	3.1%	5 15.2%
No. pts reporting NCAEs	9	40.9%	12 60.0%	10	31.2%	17 51.5%

Concomitant Medications:

Twenty-five PAF pts received digoxin Rx concurrently with flec. PAF pts who were on digoxin during screen period were required to remain on the same dose of digoxin throughout the study. One pt # 103/08 received concomitant digoxin therapy throughout Dose Ranging and period A (flec) but after approx. 1 mo. of period B (placebo) the pt d/ced digoxin. This pt is included in the efficacy analysis up to the date digoxin was d/ced. One PAT pt who received digoxin d/ced during the Dose Ranging Phase.

The administration of oral or IV verapamil was allowed in order to terminate attacks or PSVT. No pt received verapamil as continued, maintenance therapy; administration was on an "as needed" basis to terminate attacks. Seven PAT (2 pts flec dose range period, 4 on placebo, 1 IV flec PES test) and 1 PAF pt (flec crossover phase) received verapamil at some point in the study.

Two pts received another antiarrhythmic agent during the study. Pt # 004/04, began period A (placebo) on 12/8/86. On 12/27/86, the pt presented to the ER in AFib. The pt reported she had stopped taking period A drug. AFib was converted to normal sinus rhythm and began propafenone therapy. She continued propafenone Rx until 1/4/87. On 1/6/87, on study drug, period B (flec) was restarted. The pt completed the study with no attacks during period B (flec).

Pt # 101/10, received procainamide for 6 days during period A (placebo) for PSVT attacks in 13 days. He was then crossed over to period B (flec). He had PSVT attacks but they were short and tolerable that he completed the study on flec Rx alone. This pt was not included in the efficacy analysis.

Clinical Laboratory Abnormalities: A review of clinical lab data showed no clinically significant trends over time.

Blood Pressure: No clinically significant differences during flec Rx.

ECG changes: The effects of flec on the prolongation of intervals was consistent with known, previously reported results. PAT pts on flec experienced significantly ($p \leq 0.05$) increased HR as compared with baseline values, however, this increase was not clinically significant. Placebo values showed no difference from baseline. PAF pts on flec experienced statistically significant ($p \leq 0.05$) reductions in HR compared with placebo Rx.

COMMENTS

Attacks of PSVT are unpredictable; to quantify the occurrence of attacks is difficult given the spontaneous variability of the disease. This study quantified attacks of PSVT using TTMs which were pt activated when symptoms of an attack occurred. During the double-blind crossover 8 wks period 80% of PAT pts and 31% of PAF pts had no PSVT attacks while on flec Rx; this was statistically improved as compared with placebo Rx for PAT pts, but not for PAF pts. For those pts who did experience a PSVT attack on flec, PAT and PAF pts had a significantly longer interval of time until the first documented attack, and a longer interval of time between attacks. This significant decrease in the number of documented attacks also decreased associated symptoms.

Evaluation of data from EP testing showed IV flec effectively prevented the induction of PSVT in 8/16 (50.0%) of PAT pts. Three of five (60%) PAF pts were considered effectively treated with IV flec. Due to the small number of pts who received both IV and oral flec, it is not possible to correlate successful results from IV flec with successful oral flec results.

The study design was forced titration up to 400 mg/day unless pt has intolerable AEs that incidence and severity of AEs were higher than previous studies of pts with VAs. Almost 50% of pts were unable to take 400 mg/day due to AEs.

In all pts, reported noncardiac AEs were not different from those previously reported; dizziness, headache, and visual disturbances were the most frequently reported noncardiac AEs.

For cardiac AEs, PAT pts reported no clinically significant cardiac AEs while receiving oral flec. However, 2 PAF pts had proarrhythmic events and 1 of them died as a result of proarrhythmia.

Regarding dosage guidelines for this pt population, the effective dose range in this study was consistent with that established for ventricular indications ie. 100 mg or 150 mg bid; trough plasma flec levels were also maintained within the established range of 0.2 to 1.0 mcg/mL.

CONCLUSION

Oral dosing of flec effectively and safely prevents or significantly reduces the recurrence of PSVT attacks. Proarrhythmia was seen 2/21 pts (both had Hx of MPN) after IV dosing, 2/33 PAF pts during oral crossover phase. Two out of

31 PAT pts had conduction abnormality (1 presyncope, & 1 sinus pause) during dose titration period. No pt had new or worsening of CHF.

No definite conclusion can be made regarding the predictability of IV flec on the sucess of oral Rx.

2. Study R-818-066 Volume 3

"Double-Blind, Placebo Controlled Crossover Study of Flecainide in the Prophylaxix of PSVT." This study objectives and design are same as study R-818-605.

RESULTS

Study Population: Eight multicenters enrolled 42 pts (PAT 17, PAF 25) and all entered the Dose Ranging Phase; 5 pts (2 PAT, 3 PAF) d/ced during the Dose Ranging Phase. Thirty-seven pts (15 PAT, 22 PAF) entered the Crossover Phase. Of these 37 pts, 2 pts d/ced during period A; 1 PAT pt on flec for noncardiac AE and 1 PAF pt on flec for a noncardiac AE. Of the 35 pts (14 PAT, 21 PAF) who entered period B, all completed the study. Days to 2nd attack in screening to be qualified to the study is shown in Table 13. Number of pts enrolled and pt accountability throughout the study shown in Table 14. All 14 PAT pts who completed the study were included in the analyses. Of the 21 PAF pts who completed the study and had data available for analyses, 2 were not included in the efficacy analyses (1 due to digoxin dose adjustment, 1 comcomitantly received propranolol.) Two PAF pts were excluded for noncompliance to the prolocol.

	PAT (N=14)	PAF (N=19)
Sex		
Male	5 (35.7%)	11 (57.9%)
Age (years)		
Mean ± SD	48.4 ± 16.0	59.4 ± 13.6
Range	(22 - 74)	(33 - 83)
No. of Previous Therapies	59	80
No. of Therapy Failures (%)	21 (36%)	44 (55%)
Mean No. of Therapies per Patient ± SD	4.1 ± 3.1	4.2 ± 1.6
Range	0 -10	2 - 8

Associated Cardiac Disorder

None	4 (28.6%)	4 (21.1%)
Mitral Valve Prolapse	5 (35.7%)	2 (10.5%)
Hypertension	5 (35.7%)	8 (42.1%)
Cardiomegaly	3 (21.4%)	4 (21 1%)
Atherosclerotic Heart Disease	1 (7.1%)	7 (36.8%)
Rheumatic Heart Disease	1 (7.1%)	0 (0.0%)
Conduction Disturbance	1 (7.1%)	1 (5.3%)
Congestive Heart Failure	0 (0.0%)	3 (15.8%)

There were no statistically significant differences in cardiac disorders between pts included or excluded from the analysis in either PAT or PAF pt groups.

Table 15 list symptoms which pts felt were attributed to past or historical attacks of PSVT. The most frequent symptoms by pts included in the analysis were palpitation (>90%), dizziness (PAT 71.4%, PAF 21.1%), asthenia, fatigue and dyspnea. Syncope was noted PAT 5 pts (35.7%), PAF 2 (10.5%). Symptoms reported by pts excluded from the analyses were not clinically different.

Screening Results: Pts were required to have two documented attacks of PSVT in a 4-week qualifying phase. PSVT attack quality summary is shown in Table 13. The average number of days until the second attack of PAT was 6.4 $\pm$ 4.4 days, PAF 8.3 $\pm$ 5.8 days and there was no statistical difference between pts included or excluded.

Dose Ranging Phase.

All pts who entered Dose Ranging all began receiving 200 mg/day flec. Two pts had the dose lowered to 100 mg/day and entered the Crossover Phase at 100 mg/day (PAF 1, PAT 1). Fifteen PAT, 23 PAF pts received 300 mg/day and 11 PAT, 18 PAF pts receive 400 mg/day , 1 PAF pt received both 500 and 600 mg/day. Of the 37 pts who entered the Crossover Phase, 19 pts began at the maximum dose received during Dose Ranging, and 18 began at a lower dose due to AEs. Pt exposure to various flec dosage levels during the dose ranging and initial dose for crossover phase is shown Table 16.

EFFICACY RESULTS.

Crossover Phase: Although the protocol did not allow dosage adjustments during the Crossover Phase, 4 pts (1 PAT, 3 PAF) had dosage reductions; all were for noncardiac AEs while receiving flec Rx. These experiences included vision disturbances, dizziness, fatigue, syncope, difficulty in walking, and feeling "drugged out". Table 17A shows number of attacks during crossover phase and 17B presents the efficacy results. Figur 4 shows each pts response placebo vs flec Rx. Eight PAT, 6 PAF pts who had 1st attack within 4 wks while on placebo had no attack while on flec for 8 wks. Only 1 pt each had lesser days to first attack while on flec compared to placebo Rx.

Number of pts with no attacks

	PAT (N=14)		PAF (N=19)	
	Placebo	Flecainide	Placebo	Flecainide
Patients with No Attacks	1	11	0	6
P-value	0.002		0.031	

Data for the time to first attack, which is graphically displayed in Figure 5, measures the interval of time (in days) from day 4 of therapy until the next documented PSVT attack.

Time to First Attack (Days) Figure 5

	PAT (N=14)		PAF (N=19)	
	Placebo	Flecainide	Placebo	Flecainide
Mean ± SE	>15.2 ± 4.9	>22.0 ± 1.8	6.3 ± 1.6	>18.3 ± 3.6
Median	9.5	>61[a]	3.0	10.0
P-value	0.001		0.008	

[a]Estimate based on median treatment duration. Only 21% (3/14) of PAT patients had an attack while receiving flec.

Interval Between Attacks (Days) Figure 6

	PAT (N=14)		PAF (N=19)	
	Placebo	Flecainide	Placebo	Flecainide
Mean ± SE	18.5 ± 5.4	51.3 ± 4.2	10.2 ± 3.1	31.7 ± 4.9
Median	7.3	61[a]	6.0	29
P - value	0.001		0.001	

[a]Estimate based on median treatment duration. Only 21% (3/14) of PAT patients had an attack while receiving flec.

Rate of Attacks (Attack/Day)

	PAT (N=14)		PAF (N=19)	
	Placebo	Flecainide	Placebo	Flecainide
Mean ± SE	0.23 ± 0.07	0.03 ± 0.01	0.30 ± 0.06	0.07 ± 0.02
Range	0.02 - 0.75	0.02 - 0.22	0.02 - 1.00	0.02 - 0.33
P-value	0.013		0.003	

Ventricular Rates During Attacks

Only 3/4 (21%) PAT pts had PSVT attacks during both treatment periods and a decrease in their VR occurred while on flec (150 ± 23 bpm) as compared with placebo (177 ± 17 bpm) (NS). Thirteen PAF pts (68%) had PSVT attacks in both treatment periods. The decrease in the mean VR which occured while on flec Rx (121 ± 6 bpm) as compared with placebo (125 ± 7 bpm) (NS).

Symptoms reported during PSVT attacks while on flec or placebo were similar: tachycardia, palpitation, dyspnea, dizziness, headache, and asthenia and there was no case of syncope during the study period (Table 18).

Mean Duration of Therapy (Days)

	PAT		PAF	
	Placebo N = 13	Flecainide N = 14	Placebo N = 18	Flecainide N = 19
Mean ± SD	36.0 ± 21.1	61.4 ± 10.9	29.7 ± 21.0	49.9.±.14.4
Median	7- 62	31 - 76	7 - 63	18 - 63
P - value	< 0.001		< 0.01	

One PAT pt d/ced the Crossover Phase on flec for 14 days. One PAF pt d/ced the Crossover Phase on flec for 9 days. Neither of these pts received placebo during the Crossover Phase.

Intent to Treat Analysis: Of the 17 pts who received oral flec, 1 pt d/ced the study before efficacy could be measured and was, therefore, not included in the intent to treat analysis. The intention to treat analysis showed 75% (12/16) of PAT pts were effectively treated with flec. In 25 PAF pts 32% (8) were effectively treated with flec, 36% (9) were judged partially effective, and 32% (8) were drug failures.

Trough Plasma Flecainide Levels: Trough plasma flec levels were required at the end of Dose Ranging, at crossover (end of period A & B). Only 65% (44/68) of samples drawn 11 to 13 hrs after the last flec dose. For this reason no determination was made as to an appropriate thereapeutic range in this pt population; however, mean trough levels did fall within the established range of 0.2 to 1.0 mcg/mL for successfully treated VA pts (Table 19).

SAFETY RESULTS

Of the 42 pts who recieved therapy, 7 (17%) (3 PAT, 4 PAF) d/ced. All d/c occurred during flec Rx.

Three of the 17 PAT pts dc/ed: 1 each for inadequate response, noncardiac AEs, and personal reasons. Three of the 25 PAF pts enrolled, 3 d/ced for cardiac AEs, and 1 for a noncardiac AE.

Cardiac AEs is shown Table 20: proarrhythmic events 2 pts (4.8%), conduction disturbance 2 (4.8%) and there was no MI, CHF or death.

Pt listing reported cardiac AEs is shown Table 21.

Proarrhythmic events were both PAF pts during dose ranging period:

Pt #102/07, was a 60 y/m with PAF associated with weakness. Concomitant therapy included digoxin, 0.25 mg daily. During initial screening the pt transmitted attacks of PAF with VR not exceeding 90 bpm. During wk 2 of Dose Ranging and after three doses (150 mg bid) of flec the pt complained of an irregular heart beat which was "jumping out harder than ever." The investigator found a VR of 145 bpm. The pt was d/ced for either an inadequate response or a proarrhythmic event.

Pt #102/08, was a 24 y/f with a Hx of first degree AV block, incomplete LBBB, Epstein's anamoly and PAF associated with palpitations, lightheadedness, and weakness. The pt also had left axis deviation and PVCs. To qualify for study entrance, she had 3 seperate PAF attacks during a 4-day period. The pt began Dose Ranging receiving flec 100 mg bid. After 3 doses the pt transmitted an attack with usual symptoms but the rhythm strip revealed a prolonged PR interval (from a baseline of 0.24 to 0.32 sec) and QRS interval (from a baseline of 0.09 to 0.16 sec). The investigator withheld flec Rx to further evaluate. The pt had 6 more attacks over a 6 day period; flec (100 mg bid) was restarted. Afte 2 doses the pt again had an episode of PAF which spontaneously broke after 20 hrs. Due to the duration prolongation of the episode the pt was removed from the study.

Conduction disturbances were seen 1 PAT, 1 PAF pt.

Pt #002/01 was a 55 y/f with WPW associated with lightheadedness, chest pain, headache, and shortness of breath. The pt began Dose Ranging receiving 100 mg bid flec. On that same day the pt transmitted a strip to Survival Technology, Inc, that showed sinus rhythm with pauses followed by a junctional escape beat. The investigator chose to closely monitor the pt while continuing her in the study. Throughout the study the pt experienced sinus pause: at one point while on placebo she experienced sinus arrest after receiving 10 mg verapamil intravenously (IV) to convert an attack. The pt completed the study with flec, 100 mg bid.

Pt #108/01 was a 75 y/f with a Hx of PAF associated with palpitations, throat tightness, and headache. Other associated cardiac disorders included HTN, first degree AV block (baseline PR=0.22), and cardiomegaly. Concomitant therapies included furosemide and HCTZ for HTN, and Darvocetand Tylenol for arthritis. During wk 2 of Dose Ranging the pts family found her in a lethargic state and called the paramedics. She was found to have a heart rate "in the 30's" for which she received IV atropine, then epinephrine. Following administration of these agents the pt developed sustained VT which converted with IV lidocaine. A temporary

ventricular pacemaker was placed followed by a permanent pacer for "intrinsic disease." On review of the case, the investigator felt it to represent latent sick sinus syndrome; the pt was d/ced from the study. The development of sustained VT was due to administration of atropine and epinephrine and the relationship of flec Rx could only be most clearly associated with the initial bradycardia.

Noncardiac AEs during the dose ranging period is shown in Table 22. The most frequent complaints with flec Rx were vision abnormal (PAT 47%, PAF 52%), dizziness (PAT 29%, PAF 40%), and fatigue (12%). Two pts d/ced during period A (flec) for noncardiac AEs. Pt # 003/04 d/ced after 13 days of flec for fatigue and headache. Pt # 101/06 d/ced after 1 mo of flec Rx for an increased tremor and a "drugged out" feeling.

Concomitant medications:

Eleven PAF pts received digoxin Rx concurrently with flec. Pts who were screened while on digoxin were required to remain on the same dose of digoxin throughout the study. One PAF pt received digoxin twice in one day to help terminate an attack of PAT.

The administration of oral or IV verapamil was allowed in order to terminate attacks of PSVT. Six PAT (2 during dose ranging period, 5 pts crossover placebo Rx) and 3 PAF pts (3 crossover flec and 2 of them received during placebo Rx period, 1 pt #002/05 received verapamil 4 doses 3rd wk of dose ranging period and d/ced the study. Four out of 6 PAT pts and 2/3 PAF pts were receiving placebo at the time of verapamil administration.

Twelve pts (4 PAT, 8 PAF) received other antiarrhythmic agents during the course of the study for PSVT attacks:

PAT pts

001/03	propranolol, placebo Rx period.
002/03	propranolol, 9 doses early dose ranging, 5 doses crossover placebo and 2 doses flec Rxs.
001/04	procainamide, crossover placebo Rx.
005/05	propranolol temporarily stopped for surgery and on propranolol flec crossover period.

PAF pts

102/01	procainamide and PO Verapamil, dose ranging, 5 doses PO Verapamil placebo period.
107/01	quinidine, 3 doses crossover placebo (A) & 1 dose flec Rxs (B).
108/01	atropine, epinephrine, lidocaine dose ranging; see above conduction disturbances.
101/03	procainamide, crossover placebo Rx.
102/03	propranolol, crossover flec period.
101/05	disopyramide, 1 dose 1 wk dose ranging period.
103/05	quinidine, crossover placebo & flec Rx.
104/07	propranolol for HTN, dose ranging & crossover flec Rx (excluded for analysis).

Clinical Laboratory Abnormalities: A review of clinical lab data showed no clinically significant trends over time.

Blood Pressure: No clinically significant changes.

ECG: There were known prolongation of the intervals while on flec. PAT pts on flec showed a statistically, but not clinically, significant ($p \leq 0.05$) increase HR as compared with baseline values during both Dose Ranging and Crossover Phases. PAF pts on flec experienced no difference in HR compared with baseline or placebo values.

COMMENTS AND CONCLUSIONS

Forty-two pts (17 PAT, 25 PAF) with frequent episodes of PSVT were enrolled this dose ranging and crossover studies (14 PAT, 21 PAF) using TTMs which were pt activated when symptoms of an attack occurred. Seventy-nine percent of PAT pts and 32% of PAF pts had no PSVT attacks while on flec Rx; this improvement was statistically significant as compared with placebo for both diagnoses. For those pts who did experience a PSVT attack on flec Rx, PAT and PAF pts had a significantly longer interval of time until the first documented attack, and time between attacks.

In all pts, reported noncardiac AEs were not different from Study-065; dizziness, headache, and visual disturbances were the most frequently reported noncardiac adverse effects.

For cardiac AEs, no pt experienced new or worsened CHF and no pt died during the course of this study. PAT pts had only one clinically significant cardiac AE during Rx; sinus pause conduction disturbance but completed the study. One PAF pt experienced a severe bradycardia (30 bpm) and d/ced flec Rx for that reason. However, on review of this case the investigator felt the event was due to latent sick sinus syndrome; should this have been diagnosed at prestudy, the pt would have been disqualified from study participation. Two PAF pts experienced proarrhythmic event occurring within 3 days of the start or a change in dose; increase in severity or duration of attack and both stopped taking flec.

Therefore, flec effectively decreased the number of recurrent attacks of PAT and PAF and decreased the number of reported, associated symptoms. Efficacy and safety were achieved within previously established dosing guidelines and therapeutic range.

3. **R-818-065/066 - Survival Technology Results** Volume 4

"Transtelephonic Monitoring and Assessment of Flecainide Effects of PSVT Symptoms in R-818-065/066" by Transtelephonic monitoring performed by Survival Technology, One Penn Plaza, New York, NY 10119.

The unpredictability of the occurence of attacks of PSVT makes it difficult to assess the effectiveness of therapy in diminishing the number of attacks. Transtelephonic monitoring (TTM) has been used in clinical trials as an objective means to document attacks of PSVT. Patient-activated telephone transmission of live or pre-recorded ECGs makes it possible to correlate symptoms with the presence or absence of an underlying attack.

The objectives of this analysis are 1) to determine the degree to which symptoms, documented at the time of the TTM transmission, are predictive of attacks of PSVT; and 2) to evaluate the effect of flec Rx in reducing the symptoms frequently associated with PSVT attacks.

STUDY DESIGN:

R-818-065 and R-818-066 were randomized, double-blind, placebo controlled, crossover studies of safety and efficacy of flec in Rx of symptomatic PAT and PAF. Following a 3 wk dose titration period, pts took either placebo or flec (for a mximum of 8 wks), then crossed over to the alternate treatment (for a max of 8 wks).

During the study pts were asked to make TTM transmissions for various reasons, including 1) to enroll in the study; 2) to train in the use of TTM; 3) to report symptoms of attacks when evident; 4) to followup, once symptoms resolved; and 5) to ensure proper function of equipment. As each of these transmissions were received, Survival Technology recorded the cardiac rhythm on ECG paper; date and time of the call; symptoms reported by the pt; and the reason for the call. Interpretation or diagnosis of the rhythm was made at Survival Technology. Information for all TTM transmissions were subsequently entered into a computer database maintained by Survival Technology.

In addition, a copy of the recorded ECG along with the other information was sent to the study investigator for review. At the study site, the investigator reviewed the ECG recording and determined if an attack of PSVT had occured.

Because the 3M Riker database is limited to only those symptoms reported during documented attacks of PSVT, the database alone is not appropriate for evaluating the effect of flec on reducing the frequency of symptoms. The database maintained by Survival Technology, which includes information of symptoms irrespective of the presence or absence of a PSVT event, was sent to 3M Riker for use in this analysis.

The TTM transmissions included in this analysis were for all pts who qualified and subsequently entered the R-818-065 and R-818-066 trials.

Correlation of Symptoms and PSVT attacks: All calls (TTM transmissions) in the database were used in this analysis to determine the association of symptoms and the presence or absence of a PSVT attack. Calls in which the pt reported "no symptoms" or "no symptoms, called as per MD" were considered asymptomatic calls for purposes of this analysis. Calls where any symptom was recorded symptomatic calls. The dictionary of ECG interpretations, as

establised by Survival Technology personnel, was reviewed by the 3M Riker medical monitor to classify the diagnoses as normal, indicative of PSVT, or possibly other symptomatic arrhythmias. To further evaluate the association of specific symptoms with the presence or absence of PSVT attacks, those calls where the pt reported a specific symptoms were examined to determine if that symptoms was predictive of a PSVT attack. Symptoms considered most common to pts experiencing attacks of PSVT were examine individually. Specific symptoms included palpitations, asthenia, tachycardia, dizziness, fatigue, dyspnea, chest pain, nausea, nervousness, increased sweating and syncope.

Efficacy of Flecainide: To determine the effect of flec in reducing the frequency of symptoms associated with PSVT attacks as compared to placebo Rx, the database was limited to those TTM calls made by pts who completed the double-blind Crossover Phase and were acceptable for inclusion in the efficacy analyses.

To assess the frequency rate of symptoms, the interval in days between reports of each symptom was estimated for each pt and each treatment during the Crossover Phase. All calls where the symptom was reported were used in this analysis whether or not an attack of PSVT was noted. The interval between occurences of a symptom was estimated as the number of days on therapy divided by the number of occurences of the symptom. The first three days of each treatment period in the Crossover Phase were not included in this analysis to allow for washout. For those pts who had no occurences of a particular symptom the interval between occurences was estimated as the number of days on therapy plus one and the observation was considered censored in the data analysis. Patients who did not report a specific symptom during both treatment periods were considered censored observations at the minimum time on either Rx.

RESULTS

The database used in this analysis consisted of all TTM transmissions during the Screening, Dose-Ranging phase, and Crossover Phase for those pts who recieved and transmitted rhythm strips with TTMs and qualified for entry into the trials. Of the 115 pts who qualified for the R-818-065 and R-818-066 trials, TTMs for 113 pts (49 PAT, 64 PAF) were included. One PAT pt, #006/65-04 never received a TTM and subsequently d/ced from the study following EPS testing. Another PAT pt, #003/65-08 documented attacks during the screening phase by ECG and later d/ced during Dose-Ranging without any TTM transmissions being recorded. There were a total of 3,319 records of transtelephonic transmissions included in this analysis.

Demographics

The demographic characteristics and associated cardiac disorders reported by PAT/PAF pts are summarized in Table 23.

Correlation of Symptoms with Attacks of PSVT

The ECG diagnoses (DX), considered indicative of a PSVT attack are presented in Table 24. Table 25 lists all other ECG Dx which could be associated with symptoms but without a PSVT Dx, the call was classified as being an "other symptomatic rhythm disorder." Most frequently reported Dx considered possibly symptomatice included APCs (349), VPCs (356), sinus tachycardia, (181), and sinus bradycardia (76). If a PSVT Dx and "other symptomatic arrhythmia" Dx were both present in the ECG interpretation of a call, the call was classified as a PSVT attack.

A summary of the Dx associated with all symptomatic and asymptomatic TTM calls is presented in Table 26. For PAT pts, 46.9% (443/944) of the calls were asymptomatic and 53.1% (501/944) of the calls occurred with symptoms. Of the 443 asymptomatic calls, 30 (6.8% - false negative rate) were associated with an ECG Dx of PSVT. Of the 501 symptomatic calls, 314 (62.7%) were associated with a PSVT event. An additional 115 (22.9%) of the symptomatic TTM transmissions were made when only other rhythm disorders were diagnosed. The remaining 72 (14.4% - false positive rate) of the symptomatic calls were associated with NSR or other ECG Dx considered unlikely to be symptomatic by the Riker medical monitor.

For PAF pts, 1314 (55.3%) of the 2375 calls were associated with symptoms. The remaining 44.7% of the calls were asymptomatic. Of the 1061 asymptomatic calls, 112 (10.6% - false negative rate) were associated with a PSVT attack. Of the 1314 symptomatic calls, 909 (69.2%) documented attacks of PSVT. Another 240 (18.3%) were associated with only other possibly symptomatic rhythm disorders. Finally, 12.6% (false positive rate) of the symptomatic calls were actually diagnosed as NSR other likely asymptomatic ECG Dx.

In both PAT and PAF pt groups, there was a statistically significant association between the presence of symptoms and attacks of PSVT.

Table 27 lists the frequency that each of the preferred terms were reported on TTM calls for PAT pts along with the percent of the calls when that symptom was reported with asymptomatic arrhythmias during whole study period. In over 70% of the calls in which pts complained of dyspnea (75.6%), tachycardia (73.3%), nausea (76.9%), and/or increased sweating (72.2%) an attack of PSVT was documented. Other symptoms which tended to be associated with attacks of PSVT included dizziness (69.2%), palpitations (62.9%), and fatigue (66.7%).

For PAF pts, the predictability of attacks of PSVT based on these symptoms was also excellent. Of the symptoms examined, palpitations (78.4%), dizziness (76.8%), dyspnea (76.4%), tachycardia (73.3%), and increased sweating (79.2%) were associated with attacks of PSVT in over 70% of the calls when they were reported alone or in combination with other symptoms. Symptoms with a lower degree of association with PSVT attacks included asthenia (69.7%) and chest pain (65.6%). Figure 7 displays the most frequently reported symptoms and their association with attacks of PSVT for these pts.

Results of these analyses indicate that pts are able to determine when and if they are having an attack of PSVT by their symptoms. In general, the symptoms

most frequently reported by these pts were also most likely to be associated with PSVT attacks. If a symptom was reported without an attack of PSVT, it was most frequently associated with another potentially symptomatic rhythm disorder.

f Flecainide

ffect of flec in diminishing the recurrence of documented attacks of PSVT estab hed in the ndividual Sponsor's Clinical Reports. Because the p ence of symptom as been shown to be associated with occurence of PSVT a acks flec's effect was evaluated on reducing the frequency of symptoms associated with these attacks. The symptoms discussed previously were analyzed to compare the frequency of each on flec or placebo Rx during the double-blind Crossover Phase of 34 PAT pts and 48 PAF pts in the combined database for the R-818-065/066 trials who were included in the efficacy analyses. The summary data for each pt lists the number of TTM calls, the number of calls with an ECG Dx of PSVT, number of asymptomatic and symptomatic calls, number of days on each treatment, and the number of calls where each of the symptoms of interest were reported either alone or in combination with others is shown Table 28.

These results indicate fewer pts reporting each symptom while on flec as compared with placebo during the Crossover Phase of the studies. The differences in the number of pts reporting at least one occurrence of tachycardia, palpitations, or dyspnea reached statistical significance ($p < 0.05$). For the most frequently reported symptoms, the percent of patients reporting at least one occurrence is shown in Figure 8. The analysis comparing the interval between occurrences of each of these symptoms indicate a statistically significant ($p \leq 0.05$) increase in the days between occurrences of tachycardias, palpitations, dyspnea, dizziness, and chest pain while patients were on flec Rx. There were too few reports of asthenia, fatigue, syncope, nausea, nervousness, or increased sweating to perform the statistical analysis.

COMMENTS

The pts who participated in these two identical protocols (R-818-065 and R-818-066) had either documented PAT of PAF. Pts who experienced significant cerebral ischemia such as syncope or serious exacerbations of angina pectoris during arrhythmia episodes were excluded. Therefore, the main efficacy endpoints were reduction in arrhythmia events as documented by TTM and reduction in symptoms associated with these same arrhythmias.

In this detailed analysis, symptoms have been shown to be related temporally to documented paroxysmal episodes of PAT and PAF. Specifically, PAT pts who thought they were having an arrhythmia were correct 86% of the time (PAT 63%; other symptomatic arrhythmias 23%), while PAF pts correctly identified arrhythmia episodes during 87% of their TTM calls associated with symptoms (PAF 69%; other arrhythmias 18%).

There was false negative (calls without symptoms but ECG tracing showed PSVT) 30/443 (68%) calls with PAT and 112/1061 (iv 6%) with PAF. This false negative could be due to lower HR (100-130 bpm) than true positive (calls with symptoms & ECG Dx of PSVT) probably HR ≥ 130 bpm. I called the sponsor Mr. Gene Harris, Sr Regulatory Affair Coordinator on 8/17/89 to give me the information of mean HR of each of these subgroups. It is the first prospective well designed clincal study to evaluate clincal symptoms vs pt triggered TTM. Pts appeared to be very well motivated and aware of their cardiac dysrhythm that most calls were due to PSVT or APCs, VPCs or sinus tachycardia. It is of interest to find out the HR and ectopic beats rate of other symptomatic rhythm disorders listed on Table 25 but it is beyond the sponsor's responsibility.

The relationship between flec Rx and a reduction in these same symptoms has been established. More PAT and PAF pts were free of symptoms while on flec as compared with placebo and, in instances where PSVT-associated symptoms did occur, they did so less frequently while pts were on flec.

The sponsor submitted the following HR data (mean bpm) on 8/30/89.

Mean Heart Rate (± SD) During Transtelephonic Monitor
Transmissions with or Without Symptoms

PAT Patients

Diagnosis	Calls With Symptoms	Calls Without Symptoms
Normal Rhythm	81.0 ± 10.9 N = 71	79.6 ± 9.6 N = 296
PSVT Attack[a]	157.6 ± 33.8 N = 314	108.5 ± 38.7 N = 30
Other Symptomatic[b] Rhythm Disorders	109.4 ± 30.2 N = 114	90.6 ± 23.3 N = 116

PAF Patients

Diagnosis	Calls With Symptoms	Calls Without Symptoms
Normal Rhythm	77.4 ± 13.5 N = 165	74.7 ± 9.2 N = 746
PSVT Attack[a]	118.2 ± 27.5 N = 907	105.4 ± 25.9 N = 109

Other Symptomatic[b] Rhythm Disorders	81.3 ± 21.1 N = 238	72.7 ± 16.1 N = 199

[a]Diagnosis of PSVT
[b]Diagnosis of "other symptomatic rhythm disorder" without presence of PSVT.

It is conceivable that pt with PSVT felt attack but at the time TTM transmission may missed PSVT. As expected pts with PSVT attack transmission pts with/without symptom(s) were related Hr and calls with symptom.

CONCLUSION

This analysis of TTM indicates pts symptoms are associated with rapid HR of PSVT and documents the effectivenss of transtelephonic monitors as a means to confirm attacks of PSVT. These results also show the high degree of predictability that reported symptoms have with the occurrence of ECG documented attacks of PSVT and/or other symptomatic rhythm disorders.

With the use of transtelephonic monitoring in these double-blind randomized placebo controlled trials, the efficacy of flec in reducing the frequency of symptoms associated with attacks of PSVT has been demonstrated for both PAT and PAF.

4. "Open-label, Long-term Flecainide Therapy in Patients with Tachycardias Who Completed Studies R-818-065 and R-818-066." Volume 7

This was 15 mulitcenter sites long-term follow up studies of 66 pts (25 PAT, 41 PAF) who had successfully completed either study R-818-065 or 066 and were judged to be effectively treated with flec for PSVT to continue to receive long-term oral therapy and follow-up.

STUDY DESIGN:

These amendments were open-label, long-term therapy extensions to two identically designed phase III, double-blind, placebo controlled, randomized, two 8 wk period crossover studies in pts who documented frequent attacks of PAT or PAF. After completing both periods and undergoing end of study procedures, the investigator and the pt reviewed the responses to both Rxs. The investigator initiated long-term Rx if both agreed the response to flec Rx was more favorable than and continued Rx was warranted. Pts continued to receive flec as long as it was safe and effective or until 3M Riker and the investigators mutually agreed to terminate the follow-up period.

The investigator monitored each pt at monthly intervals by either telephone calls of clinic visits. Suppression of arrhythmias was based on questioning the pt on the number of PSVT attacks and associated symptoms experienced since the last visit/call. Flec dosages were adjusted as needed to maintain efficacy and tolerance.

At the time of the final study visit, the monthly evaluations, clincal lab tests, and pt status were completed. Final visits were required when a pt discontinued flec Rx for any reason or at the end of study participation.

RESULTS

Total daily oral dosages used were from 50 to 400 mg for PAT pts and 100 to 600 mg for PAF pts. Flec > 400 mg/day was taken by 0/25 PAT, 4/41 PAF pts. The most commonly used daily dosages were 200 and 400 mg/day.

Long-term therapy with mean duration of on drug PAT 15 mos, PAF 14 mos; median number of mos was 13 for both groups. Table 29 shows number of pt months and number of pts on each total daily dose of flec.

Test Drug Dosage Changes: Dosage changes were allowed during the study to accomodate efficacy and tolerance. Flec dose was changed in 16 occasions within the 25 PAT pts, 64 occasions with 41 PAT pts. Reasons for dosage changes is shown in Table 30.

Final Patient Status

Final Patient Status	PAT (N = 25)		PAF (N = 41)	
End of Study	18	72%	25	61%
Discontinued From Study Due to				
Inadequate Response	0	0%	4	10%
Arrhythmia Worsed and Inadequate Response	0	0%	1	2%
Adverse Experience	1	4%	2	5%
Therapy No Longer Needed	2	8%	0	0%
Lost to Followup	2	8%	2	5%
Personal	2	8%	4	10%
Noncompliance	0	0%	2	5%
Other (concomitant use of beta blocker)	0	0%	1	2%

Seventy-two percent (18/25) of the PAT and 61% (25/41) of the PAF pts continued to be effectively treated with flec when their study participation ended (End of Study). Only 1 (4%) PAT pts d/ced for AE and none (0%) for lack of efficacy. In the PAF group, 5 (12%) d/ced for inadequate responses and 2 (5%) for AEs. Events associated with individual patient discontinuations are shown in Table 31.

Efficacy Results

At each clinic visit or phone contact with the pt, the investigator solicited arrhythmia data by questioning the pt about the number of PSVT attacks and associated symptoms he/she had experienced since the last visit/call.

The efficacy results that follow are based on the number of PSVT attacks occurring per month for each pt during his/her time on long-term flec Rx.

Frequency of PSVT Attacks: A linear regression was performed separately for each pt who reported arrhythmia data at two or more visits to determine the change over time in the number of PSVT attacks reported at monthly intervals. Twenty-two of 25 PAT pts and 39/41 PAF pts had arrhythmia data at two or more visits and were included in the linear regression analysis. The 3 PAT and 2 PAF pts excluded had only one visit before discontinuing from the study from the analysis.

Linear regression analysis showed all but three time points, the median number of attacks/mo was zero. The exceptions were months 17 and 19 for PAT pts and month 14 for PAF pts; in each case, the median was one attack/mo. The median estimated slopes were 0.0 for both pt groups, indicating no changes in the number of reported attacks/mo over time.

The mean estimated slopes were 0.02 ± 0.11 for PAT and -1.3 ± 6.3 for PAF pts; neither slope was significantly different from zero. The negative mean slope (indicating a tendency towards fewer attacks with time) in the PAF group was influenced by the responses for 2 pts. Pt # 105/065-10 had an estimated slope of -11.0. The pt was first seen for follow-up at month 3 when she reported 36 attacks of PSVT (12 attacks/mo) while taking flec 100 mg bid. When seen at month 4, the patient reported one attack during the previous month; however, it lasted 3 to 4 days and caused her to increase dose to 150 mg bid. The investigator decided at that point (month 4 visit) to d/c pt from the study due to an inadequate response. The 2nd pt # 109/066-01 had an estimated slope of -38.0. This pt experienced partial control of VR during PAF while receiving flec in the double-blind study. The investigator prescribed a beta blocker as concomitant medication when the pt started long-term Rx. The pt reported 41 PAF attacks at the month 1 visit. At month 2, he had only 3 attacks. Because the concomitant use of flec and a beta blocker for arrhythmia control the pt was d/ced from the study after 4 mos.

Number of PSVT Attacks by Month: The numbers of PSVT attacks reported by month over 1 yr of long-term flec Rx are presented in Table 32. All pt visits with reported arrhythmia data for 25/25 PAT pts and 41/41 PAF pts are included in this analysis. Table 33 shows the percentage of PAT pts with no (0) attacks by month ranged from 54% to 88% over 1 year of long-term flec Rx and the PAF from 62% to 74% by month. The distribution of patients with 1, 2, 3, or ≥ 4 PSVT attacks by month was similar from month to month with no noticeable trends between number-of-attack categories or over time for both the PAT and PAF pts.

Number of Patient Months Without PSVT Attacks: In this analysis, all pt visits with arrhythmia frequency reported were examined for all pts (25 PAT and 41 PAF) who received long-term flec Rx. Table 33 shows PAT pts reported efficacy data for a total of 367 and PAF of 506 pt months of long-term flec Rx. The number of PSVT attacks reported for each of those months was calculated. Seventy-five percent (276/367) and 64% (322/506) PAF pt months with efficacy data had no reported attacks.

Symptoms Associated With PSVT Attacks: The symptoms pts associated with attacks of PSVT are presented in Table 34. The symptoms most frequently reported and the percent of pts reporting at least one symptom during long-term therapy are summarized below.

Incidences (%) of Reported PSVT Symptoms

Symptom	Percent of Patients Reporting Symptom PAT (N = 25)	PAF (N = 41)
Palpitation	52%	80%
Tachycardia	36%	17%
Chest Pain	20%	15%
Dizziness	20%	15%
Arrhythmia	12%	15%
Asthenia	12%	15%
Dyspnea	12%	22%
Fatigue	12%	10%
Patients reporting at least one symptom	76%	85%

Discontinuations Related to Therapeutic Response: As previously noted in Table 31, none of the 25 PAT pts d/ced from the study due to an inadequate response to flec. However, investigators determined 2/25 (8%) pts no longer needed Rx. Pt # 001/061 d/ced flec prior to elective surgery to excise the bypass tract. Following the procedure, the arrhythmia was longer present. Pt # 005/066 stopped taking flec on her own accord on a daily basis (50 mg every 12 hours) after 3 mos to "see how she would do" without Rx. PSVT events did not recur during the next 2 mos: therefore, the investigator d/ced her from the study as treatment was no longer required.

Five of 41 (12%) PAF pts d/ced long-term flec Rx due to inadequate therapeutic responses (Table 31). For 4 pts, flec no longer controlled the frequency and/or duration of attacks. Pt # 102/065-01 d/ced flec after 672 days due to short bursts of AFib and frequent PACs occurring at a rate of 7 to 8/minute during the 2 mos prior to d/c. Pt # 105/065-10 reported 36 PSVT attacks (4 - 5/wk) during the first 3 mos of Rx. When seen at month 4, the pt reported one attack that lasted 3 to 4 days, causing her to increase her dose of flec. The investigator discontinued the pt from the study due to an increase in the duration of attacks. Pt # 104/066-01 experienced approx 35 attacks (1-2/day) during the first 3 wks of long-term Rx. Norpace was added and dosages of both drugs adjusted to achieve efficacy. The combination therapy suppressed arrhythmia for several mos before the frequency and duration of attacks increased (4 - 5/mo) during the last few mos of Rx resulting in d/c of both drugs due to inadequate effect. Pt # 104/066-07 was d/ced from the study after approx 7 mos of Rx when the pt was in incessant AFib for an unknown length of time. The pt was unable to detect the arrhythmia. Pt # 103/066-01 was d/ced due to lack of efficacy and new or worsened arrhythmia compared to baseline. See Cardiac AEs below.

Safety Results

Discontinuations Due to Adverse Experiences: One of the 25 (4%) PAT pts and 2/41 (5%) PAF pts d/ced long-term flec due to AEs (Table 31). Pt # 006/065-08 d/ced from the study after 12 mos of Rx due to the onset of forgetfulness and questionable memory loss which the investigator felt was possibly related to flec. The drug was restarted outside the protocol 1 wk later; no additional follow-up was provided. Pt # 104/065-01 (PAF) had no side effects during 19 mos of long-term Rx. At the month 20 visit, he complained of constipation which the investigator felt was possibly related to flec. The drug was d/ced and the pt withdrawn from the study. At the month 1 visit, pt # 104/066-08 (PAF) complained of impotence. Flec was d/ced on a trial basis. Upon reevaluation 1 month later, the pt still complained of impotence although with some improvement. Flec was not restarted. The pt had not complained of impotence while taking either flec or placebo in the double-blind, parent study.

Adverse Experiences: AEs reported 76% of the pts in each group (19/25 PAT and 31/41 PAF) reported at least one AE while receiving long-term Rx. Within the PAT pt group, the most commonly reported complaints (≥ 10%) were vision abnormal in 28% (7), and asthenia and headache each reported by 12% (3): PAF pts visoin abnormal 41% (17); dizziness, 34% (14); and constipation, impotence, and palpitation, 10% each (4).

Cardiac Adverse Experiences: One investigator categorized a worsened arrhythmia leading to d/c of Rx as a proarrhythmic effect probably related to flec. Pt # 103/066-01 was a 55 y/m with a Hx of PAF associated with palpitations, chest discomfort, and headache. The pt completed the double-blind, crossover study without event and continued of flec 100 mg bid. He was also taking digoxin 0.375 mg per day. After approx 2 mos of long-term follow-up, the pt experienced a lengthy episode of AFib which was resistant to conversion with IV verapamil and oral quinidine. Two wks later, the investigator d/ced the pt from the study due to an inadequate response and worsened arrhythmia (more sustained, but slower AFib).

There were no other cardiac AEs reported in this study. No pt died during long-term follow-up.

Concomitant Medications: Four of 25 PAT pts received concomitant medications for arrhythmia control: 2 with single doses of verapamil, one time each, to terminate PSVT attacks. The other 2 took either atenolol for tachycardia or digoxin for cardiac dysrhythmia as routine daily Rx in conjunction with flec.

Concomitant use of digoxin and flec was allowed in pts with PAF throughout the study and 19/41 PAF pts continued digoxin as concomitant medication during the long-term therapy period. Eleven PAF pts received concomitant therapies for arrhythmia control: 5 were treated prn to terminate attacks of PSVT; 3 received

prn medication during the early months in the long-term follow-up but were subsequently treated with concomitant daily therapy. The remaining 3 PAF pts took continuous concomitant therapy for cardiac dysrhythmias or tachycardia beginning either at the start of long-term flec Rx (2) or after 3 mos of flec (1). Medications used as prn therapy were disopyramide, verapamil, quinidine, pronestyl, diltiazem, and propranolol. Those prescribed as daily concomitant antiarrhythmic therapy were quinidine, diltiazem, propranolol, disopyramide, and atenolol. There were no apparent AEs related to flec Rx and other medications given in combination for arrhythmia control.

A possible synergistic effect of flec and verapamil on PR intervals was noted for pt # 006/066-01. PR intervals of 0.22 sec were recorded on ECGs performed at baseline and twice in the double-blind study while the pt was taking flec 200 mg bid. After 6 mos of long-term therapy (200 mg bid), verapamil 80 mg bid was prescribed for HTN. The pt took both medications, plus coumadin through the remaining 6 months of study participation. At the final visit, the PR interval was 0.435 sec. Flec was continued and verapamil was d/ced. At 3 and 9 mos after follow up ECG showed PR intervals of 0.30 and 0.25 sec respectively.

Other Clinically Significant Events: Three PAF pts required electrical intervention to terminate attacks of AFib: 2 pts on one occasion each, and 1 pt on two occasions. All 3 of them were effectively treated and continuing on flec when their study participation ended.

There were no clinical lab abnormalities or abnormal physical findings related to flec Rx and no pt d/ced Rx as a result of ECG changes associated with the drug.

CONCLUSION

Pt who had PSVT due to PAT (25) and PAF (41) pts who had responded favorably to oral flec Rx during a placebo controlled clinical trial continued to effectively treated during long-term follow-up for periods averaging more than 1 yr, 61% of the PAT pts and 72% of the PAF pts continued to tolerate and respond to flec. Suppression of arrhythmias was based on questioning the pt on the number of PSVT attacks and associated symptoms experienced per month during long-term therapy. In the two pt populations treated, none (0%) of the PAT pts and only 12% of the PAF pts d/ced Rx for lack of therapeutic effect. One of the nonresponding PAF pts was noted to have a worsening of his arrhythmia as more sustained, but slower AFib episodes that decreased in frequency but possibly increased in duration.

Eight percent of the PAT and 15% of the PAF pts received concomitant medications as combination daily Rx. Other pts (8% PAT, 12% PAF) took additional medication as needed to break individual attacks of PSVT. There were no adverse events related to interactions between flec and these medications.

5. Study R-818-074 Phase II study Volume 5 & 6.

"Dose-response Study of Flecainide in Pts with PSVT"

STUDY DESIGN:

This was a 20-wk, phase II, double blind, placebo-controlled, multicenter, dose-response study in pts with frequent attacks of either PAT or PAF. During the screening phase, pts documented 2 attacks of PSVT within 4 weeks; at least 1/2 attacks was documented by TTM, the second attack could be by TTM or ECG rhythm strip. Pts inclusion and exclusion criteria are same as studies -065 & -066. Investigators were instructed to exclude pts if they had symptoms, ie, syncope, angina or transient ischemic attacks associated with their PSVT attacks. Pts were allowed to crossover early to the next treatment if they had 4 PSVT events in less then 28 days and to have medical intervention for termination of persistent attacks of PSVT.

After qualifying for the study, pts were randomly assigned to one of four different ascending dose treatment sequencess, each of which consists of five consecutive 4 wk treatment periods.

Dosage Sequences

A.	P---	F_{50}---	F_{100}---	F_{200}---	F_{300}
B.	F_{50}---	P---	F_{100}---	F_{200}---	F_{300}
C.	F_{50}---	F_{100}---	P---	F_{200}---	F_{300}
D.	F_{50}---	F_{100}---	F_{200}---	P---	F_{300}

Key: F_{50} = Flecainide 25 mg po bid
F_{100}= Flecainide 50 mg po bid
F_{200}= Flecainide 100 mg po bid
F_{300}= Flecainide 150 mg po bid
P = Placebo

At the conclusion of the dose-response phase if the pt and the investigator agreed the pt could benefit from flec Rx, the pt was allowed to remain on open label flec under the investigators supervision for 1 yr.

For PAF pts receiving digitalis preparations or beta blocker therapy for indications other than dysrhythmia were allowed to remain on previously stabilized dosage regimens.

RESULTS

Study Population:

Seventy-three (28 PAT and 45 PAF) pts with PSVT were enrolled across 17 study centers. Efficacy results are based on 14 PAT and 28 PAF pts who completed

the study or had sufficient data for analysis from all five treatment periods. Pt accountability is shown on Table 35. The primary efficacy analyses included all pts who had analyzable efficacy data from all five periods. Table 36 lists pts, by PAT and PAF, who entered period 5 but were excluded from the primary efficacy analyses. Pts characterization who are included in the primary analyses:

	PAT (N = 14)	PAF (N = 28)
Sex male	9 (64.3%)	16 (57.1%)
Age (yrs) mean ± SD	47.9 ± 14.7	60.3 ± 12.4
No. of Previous Therapies	31	94
No of Therapy Failures(%)	21 (68%)	62 (66%)
Mean No. of Rxs/pt ± SD	2.2 ± 1.2	3.4 ± 1.9

The baseline Dx of 14 PAT pts were 6 with AVNR, 2 with WPW syndrome only, 3 with PSVT only, 1 with atrial reentry tachycardia and WPW, 1 with AVR and WPW, and 1 with concealed bypass tract and AVNR. Of the 28 PAF pts arrhythmia Dx was 18 AFib, 8 AFib/AFlu and 1 AFlu.

Associated Cardiac Disorder[a]	PAT (N = 14) N (%)	PAF (N = 28) N (%)
Hypertension	5 (35.7%)	8 (28.6%)
Mitral Valve Prolapse	2 (14.3%)	6 (21.4%)
Cardiomegaly	2 (14.3%)	8 (21.4%)
Atherosclerosis	1 (7.1%)	4 (14.3%)
Rheumatic Heart Disease	1 (7.1%)	1 (3.6%)
Conduction Disturbance	1 (7.1%)	1 (3.6%)
CHF (Class I or II)	1 (7.1%)	0 (0.0%)
Cardiomyopathy	0 (0.0%)	1 (3.6%)
Sinus Node Disease	0 (0.0%)	4 (14.3%)
Other Disorders	5 (35.7%)	12 (42.9%)
None	4 (28 6%)	8 (28.5%)

[a]Patients may have more than one cardiac disorder.

The most frequently reported symptoms associated with PSVT were same as studies -065 and -066. PSVT attacks in a 4 wk qualified period is shown in Table 37. Thirteen of 14 PAT pts included in the primary analyses qualified within the first 21 days of the screening period; the 1 remaining pt recorded 2 attacks on the same day. Of the 28 PAF pts included in the primary analyses, all but 4 pts qualified for the study in the first 28 days of the screening period.

Efficacy Results

The followin PSVT attacks were excluded from the analysis: (Table 38)

1. Attack Occurred During First Three Days on Study Drug
   The first 3 days of each period were considered time to reach steady state plasma flec levels during a flec period, or a washout phase during a placebo period. There were 17 attacks reported during the first 3 days.

2. Before Adjusted Start Date and Period Deleted
   Nine PAF pts experienced a PSVT attack before starting a period or within the first 3 days where the attack continued for several days or wks. It was decided that these attacks would not be counted, and the start of the treatment period for these pts would be adjusted to the first date that normal sinus rhythm was documented following the attack. For 4/19 PAF pts, the attack lasted throughout an entire treatment period, and therefore, efficacy was not analyzable during that period. A total of 10 reported attacks were excluded in these categories.

3. Patient Already Reported Four Attacks During the Period or Attack Occurred After Day 31 of the Study Period.

   In each period of the study, pts were to continue treatment until experiencing 4 attacks or 4 wks, whichever occurred first. However, some pts had more than 4 attacks before crossing over, and some remained on treatment for more than 4 weeks. The analyses that are effected by excluding attacks after these cutoffs are those which use frequency of attacks or interval between attacks as the measure of efficacy.

   To avoid bias introduced by allowing pts responding well to the study drug to continue longer than 4 weeks, all data were truncated at day 31 to allow 28 days on study drug (Day 4 through Day 31).

   In addition, bias may be introduced by allowing some, but not all pts to continue on study drug after 4 attacks. To avoid this source of bias, the data were truncated on the date of the 5th attack, and pts were said to have experienced 4 attacks up to that date. There were 14 attacks reported after Day 31 and [illegible] reported after the 4th attack was recorded. These attacks are included in Tables 39, 40 & 41 primary efficacy analyses.

4. Attack Occurred After Study Stopped
   One pt # 301/02, had the final visit on 2/13/88, but made one more call on 2/18/88.

Number of attacks for each period included and excluded in the primary efficacy analysis is shown Table 39 for PAT and Table 40 for PAF pts and Table 41 for all pts. This data shows a trend of increased efficacy with increase of dosage and the most efficacious dosage was 200 mg/day.

Dose Response Results: Patients were allowed to crossover early to the next treatment period if their PSVT events were intolerable. Table 42 presents by PAT and PAF the pts who crossed over in any treatment period along with the reasons for early crossover. Early crossover due to severity or inadequate control of attacks was seen in 1 PAT pt with flec 300 mg, 6 PAF pts among the included, and 2 PAT & 3 PAF pts excluded.

Primary Efficacy Analyses: The efficacy results of pts who completed with evaluable data of entire 5 treatment period is shown in Table 43. For the PAT pts, 4/14 (29%) and PAF (2/28 7%) had no attacks while on placebo and the number of pts remaining attack-free increased with successive increases in flec doses.

No. (Percentage) of Patients with No Attacks by Treatment

	Placebo	Flecainide mg bid			
		25	50	100	150
PAT (N=14)	4 (29%)	5 (36%)	8 (57%)	9 (64%)	12 (86%)
PAF (N=28)	2 (7%)	5 (18%)	6 (21%)	15 (54%)	17 (61%)

The analysis of variance showed a significant ($p < .001$) linear dose-response in the percentage of PAT and PAF pts remaining attack free. This clearly indicates that successive increases in efficacy are achieved in PAT and PAF pts as flec dosages are increased from 25 to 150 mg bid. None of the pairwise comparisons (McNemars test) with placebo for the PAT group showed statistical significance at this level and only for the PAF group were significant between placebo vs 100 mg and 150 mg bid flec.

For time to first attack, over half of the observations for PAT pts and 30% of the observations for PAF pts were censored, i.e., pts did not have any attacks during the 28-day treatment period: therefore, product limit estimates were used. The results are summarized below.

Median Time to First Attack (days)

	Placebo	Flecainide mg bid			
		25	50	100	150
PAT (N=14)	11.0	7.0	>24.0[a]	>26.0[a]	>23.0[a]
PAF (N=28)	3.0	4.0	5.0	>25.5[a]	>14.5[a]

[a] A > symbol indicates product limit median was undefined and sample median was reported.

For PAT pts, the time to first attack more than doubled for the three highest flec dosage levels (50, 100, and 150 mg bid) when compared with placebo; however, none of the PPW comparisons were statistically significant. For PAF pts, the time to the first attack was significantly ($p < 0.125$) increased for the 100 and 150 mg bid flec dosages when compared with placebo.

Median Interval Between Attacks (days), Median Rate of Attacks

For PAT pts, the increase in median interval between attacks were not significantly different between any of the flec dosages and placebo. For PAF

pts, the PPW tests showed a significant ($p < .0125$) increase in the interval between attacks for the 100 and 150 mg bid flec dosages when compared with placebo.

There were no significant differences of VR during PSVT events between placebo and any of the 4 flec dosages. This was principally due to the fact that only a few pts were having attacks at the higher flec dosages; therefore, there was little power for comparison against placebo. The mean number of days counted for each treatment period for PAT and PAF pts showed no differences except 200 mg/day flec period for PAF pts was the only significantly ($p < .01$) different from placebo.

Symptoms reported during documented attacks of PSVT in the dose response phase of the study for pts included in the primary efficacy analyses are presented by treatment in Table 44. For PAT pts the most frequently reported symptom across all treatment periods was tachycardia. Other symptoms frequently reported during one or more treatment periods included palpitations, chest pain, dizziness, and dyspnea. For PAF pts the most frequently reported symptoms across all treatment periods included palpitations, tachycardia, dyspnea, fibrillation, asthenia, chest pain, and arrhythmia.

Dosage Recommendation Analysis (based on an Intention to Treat Analysis): The dosage recommendation analysis relates drug tolerance and efficacy for all pts enrolled in the study. In this analysis, each dosage level is treated as if all pts enrolled in the study had started at that particular dosage level; therefore, some assumptions are made on pt outcomes. This analysis provides estimates of the percentage of pts who may have complete PSVT suppression and the percentage of pts who may develop AEs requiring d/c at each dosage level. The safety and efficacy results for each pt were reviewed and pts were placed into one of the following categories for each dosage level: D/C due to cardiac AE; D/C due to noncardiac AE; inadequate response; successfully treated; or not evaluated. Table 45 present the result of the dosage recommendation analysis.

The safety results of the dosage recommendation analysis for each treatment period are summarized below:

Dosage Recommendation Analysis
Number (Percentage) of Patients Discontinuing for
Cardiac (CAE) and Noncardiac Adverse Experiences (NCAE)

Treatment (mg bid flec or placebo)	PAT Patients			PAF Patients		
	N	CAE	NCAE[a]	N	CAE	NCAE[a]
Placebo	24	1 (4.2%)	1 (4.2%)	41	0 (0.0%)	1 (2.4%)
25	26	1 (3.8%)	2 (7.7%)	42	0 (0.0%)	1 (2.4%)
50	23	0 (0.0%)	2 (8.7%)	39	1 (2.6%)	1 (2.6%)
100	23	0 (0.0%)	3 (13.0%)	39	1 (2.6%)	3 (7.7%)
150	22	2 (0.0%)	5 (22.7%)	34	0 (0.0%)	6 (17.6%)

a Cumulative

In the above table, 6 PAT pts d/ced for noncardiac AEs: 1 while on placebo, 2 while on 25 mg bid flec, 1 while on 100 mg bid flec, and 2 while on 150 mg bid flec. Based on the study results, if all PAT pts were started on 150 mg bid flec, 22.7% of the pts would be expected to develop noncardiac AEs significant enough to cause D/C. Similarly, if all PAF pts were started on 150 mg bid flec, 17.6% of the pts would be expected to develop noncardiac AEs significant enought to cause D/C. No pt developed cardiac AEs with 150 mg bid but with lower dosages in both groups.

The following table summarizes the effi y results of the dosage recomm ndation analysis.

Dosage Recommendation Analysis
Number (Percentage) of Patients Who
Tolerated the Drug and Had No Attacks

Treatment (mg bid flec or placebo)	PAT Patients		PAF Patients	
	N	No. (%)	N	No (%)
Placebo	24	6 (25.0%)	41	5 (12.2%)
25	26	7 (26.9%)	42	5 (11.9%)
50	23	12 (52.2%)	39	8 (20.5%)
100	23	13 (56.5%)	39	17 (43.6%)
150	22	13 (59.1%)	34	14 (41.2%)

Based on the study results, if pts started flec at 150 mg bid, 59.1% of the PAT and 41.2% of the PAF pts would be expected to tolerate the drug and have no attacks. Although none of the pairwise comparisons were statistically significant for both PAT and PAF pts, the 50 mg bid flec dosage showed the greatest clinical improvement over placebo with a complete PSVT suppression rate of 52.2% and an AE d/c rate of 8.7%. The PSVT suppression rate on 50 mg bid and 100 mg bid was aproximately double compared to that on placebo.

Comment: I called the sponsor on 7/25/88 and asked to evaluate the dose response relationships of efficacy measures in PAT and PAF pts if the completion of at least four treatment periods rather than all five was used as the criteria for inclusion in the data analyses.

In the R-818-074 study report of the submission, pts were excluded from the primary efficacy analyses for several reasons including: study-drug noncompliance, changes in concomitant medications, unanalyzable data and discontinuing the study before efficacy could be evaluated in Period 5 at 150 mg bid flec. Four PAT pts and 6 PAF pts who were excluded from the primary efficacy analyses were compliant and had analyzable data through period 4 at doses of 0, 25, 50, and 100 mg bid. In order to determine the effect of these pts' results on the overal. efficacy, the data for "Number of Patients with No Attacks" and "Interval Between Attacks" were re-analyzed with these pts included.

Table 45A show the results for doses of 0, 25, 50, and 100 mg bid. In the PAT group, the interval between attacks was significantly longer for pts on 100 mg bid flec than on placebo. For PAF pts, the 100 mg bid treatment showed a statistically significant improvement over placebo for the number of pts with no attacks, and the interval between attacks. These results are similar to the R-818-074 report except the interval between attacks was not significant for the PAT pts in the original report.

Trough Plasma Flecainide Levels: Trough plasma flec levels were required at the end of each treatment period. Blood samples were taken only 1/3 of PAT pts and 2/3 of PAF pts around the trough level (8-16 hrs post last dose). Table 46 presents the mean trough plasma flec levels only by flec dosage level for all pts included in the primary efficacy analyses. The data for all pts are presented graphically in Figure 9. The plasma flec levels increased proportionately with increases in flec dosages.

Safety

Seventy-three pts were enrolled in the study and 69 (26 PAT, 43 PAF) received oral flec Rx. The remaining 4 pts d/ced during period 1 while receiving placebo. The following table presents the number of pts who received each treatment during the study.

Number of Patients Receiving Each Treatment

	Placebo	Flecainide mg bid			
		25	50	100	150
	N	N	N	N	N
PAT	25	26	21	21	19
PAF	43	43	40	38	33

Reasons for Discontinuation (Table 47): Of the 73 pts who participated in the dose-response phase, 28 (38%) d/ced. Of the 28 PAT pts enrolled in the dose-response phase, 11 (39%) d/ced: 6 while receiving flec and 5 while receiving placebo. Reasons causing d/c of flec included noncardiac AEs (5) and cardaic AE (1). Reasons causing d/c from placebo included personal (1), noncardiac AE (1), cardiac AE (1) and other (2).

Of the 45 PAF pts enrolled, 17 (38%) d/ced: 13 while receiving flec and 4 while receiving placebo. Reasons causing D/C of flec included personal (3), inadequate response (1), noncardiac AE (6), cardiac AE (2) and other (1). Reasons causing d/c from placebo included personal, lost to follow-up, noncardiac 1 each.

Cardiac Adverse Experiences (CAEs): Table 48 displays the overall incidence of reported CAEs on flec by event, number of pts. Table 49 is a list of the pts reporting CAEs on flec, the treatment period in which the CAE was reported and a brief description on each event. A total of four (4/73, 5.5%) pts had CAEs while receiving flec.

Proarrhythmic Events - - Investigators reported worsening of arrhythmia in 3 pts (1 PAT, and 2 PAF pts). The PAT pt developed sustained, intractable PAT. One PAF pt developed sustained AFlu with an increased vent response rate, and 1 PAF pt developed susVT. The followin case histories describe these events:

Pt # 003/06, was a 23 y/m, with a Hx of PAT associated with AV nodal re-entry and symptoms of palpitations, lightheadedness, and near syncope. Concomitant Rx digoxin 0.125 mg qd. This pt d/ced from the study after 25 days in period 1 (flec 25 mg bid) when he experienced prolonged and intractable PAT with a VR of 220 bpm. The PAT could not be broken by Valsalva maneuvers or IV verapamil. The addition of verapamil resulted in some hypotension. The pt was cardioverted in a few beats of sinus rhthym with reversion immediately back to PAT. After the administration of digitalis and quinidine, the pt reverted to sinus rhythm. Due to the incessant nature of patient's PAT which was "clearly different" from his previous "multiple episodes of PAT," the investigator chose to withdraw the pt from the study.

Pt # 101/05, a 49 y/f with a Hx of PAF associated with a vague sense of fluttering. No concomitant medications. The pt d/ced from the study after 7 days in period 3 while receiving 50 mg bid flec. She experienced a sustained episode of AFlu at a rate of 136 bpm which did not break after the administration of oral dose 400 mg quinidine and 160 mg verapamil. On exercise, the rate went to 1:1 conduction. Later the same day, the pt spontaneously returned to NSR. This pt's Hx of PSVT prior to study entry included palpitations occuring once per day with episodes usually lasting from a few min to an hour.

Pt # 101/11, was a 68 y/m with a Hx of CAD with MI, rheumatic heart disease, class II CHF non-susVT, PAF associated with palpitations, weakness, shortness of breath, a racing heart, skipped beats, and pounding. A baseline Holter showed 114 couplets, 12 triplets, and 2,733 PVCs/24-hr. Baseline EF by MUGA was between 37% and 47%. Concomitant Rx aspirin, furosemide, digoxin, potassium, verapamil (PRN to terminate persistent attacks of PSVT), flurazepam, meclizine, psyllium, Parepectolin, and tetracycline. After 21 days in period 1, while receiving 100 mg bid flec, the pt developed a wide complex tachycardia and presyncope. The pt was brought to an ER where he received 50 mg of lidocaine followed by two direct current cardioversions resulting in a return to NSR. No evidence of MI. His flec level was between 0.62 and 0.71 mcg/mL (therapeutic range, 0.2 to 1.0 mcg/mL). An EP study performed after flec washout showed inducible susVT. It is "difficult, if not impossible" to decide if the susVT truly represented a proarrhythmic event.

Congestive Heart Failure -- One pt # 001/11, after was considered to have developed new CHF while participating in the study.

This 61 y/m had a Hx of CAD with angina, HTN, COPD, and PAT associated with AV nodal re-entry, palpitations, lightheadedness, near syncope,

weakness, fatigue, rapid heart beat, dizziness, and dyspnea. Concomitant Rx: acetaminophen, Fiorinal, Maalox, cimetidine, theophylline, albuterol, verapamil (PRN), clonidine, and metoclopramide. Thirteen days after start period 3, 50 mg bid flec, the pt developed symptoms of CHF which included pedal edema, SOB, and abdominal distention. The pt received placebo during period 2. The pt was started on furosemide 40 mg bid and KCL and the symptoms of CHF resolved 5 days later. A chest X-ray performed the same day as the onset of CHF symptoms showed no evidence of CHF and LVEF determined by MUGA, 4 days after the onset of symptoms, was 42%. The pt was without symptoms of CHF during period 4 (100 mg bid flec), but he developed an increase in SOB, a ventricular gallop, jugular vein distention, and pedal edema during period 5 (150 mg bid). After completing period 5, the pt continued in the elective open-label chronic use phase of the study on flec 50 mg bid. At the end of 1 month of open-label Rx, the pts flec dosages was increased to 100 mg bid. Furosemide dose was reduced from 40 mg bid to 40 mg qd. The pts CHF symptoms resolved during month 2 of open-label Rx. At the end of 15 mos of open-label Rx, the pts flec dosage was increased to 150 mg bid without return of CHF symptoms.

One PAT and 2 PAF pts had Hx of CHF at baseline; these pts had no worsening of their CHF while participating in the study. With new CHF reported in only 1 pt, the incidence of new CHF in the study population was 1.4% (1/70).

Conduction Disturbances -- None of the pts reported to have conduction disturbances while taking flec during the study. One pt d/ced from the study after sinus bradycardia (HR = 44 bm) and 1 degree AV block (PR=0.30 sec) were noted at the end of period 4 while he had received placebo for 28 days. The flec plasma level drawn at the end of this period was 0.0 mcg/mL. The PR interval on a repeat ECG performed 1 day after the study medication was d/ced was 0.18 sec.

No pt experienced an MI or death while participating in this study.

Noncardiac Adverse Experiences (NCAEs): Table 50 presents the most common AEs along with the percentage of pts experiencing at least one NCAE. A significant dose-response was observed for autonomic nervous system disorders (flushing, sweating or visual disturbance) and for the number of pts reporting at least one AE.

One pt # 102011 d/ced from the study after 14 days in period 1 while receiving 25 mg bid flec due to left sided CVA/TIA occuring 1 hr after an episode of PAF. The pt had similar event approx 6 mos earlier, and this TIA was not considered to be due to flec Rx.

Vital Signs: No clinically significant changes from baseline were found.

ECG Intervals: ECG interval dose-response results are presented in Table 51 with data at all five dose levels and with analyzable ECGs. The results showed increased interval prolongation with increased flec dose levels for both PAT and PAF pts.

One pt #0104/25 was noted to have QRS widening (0.16 sec) on a Survival Technology transmission during period 5 (150 mg bid flec). After reviewing the rhythm strip, the investigator cut the pts dose in half. When the pt was seen in the investigator's office 2 days later the patients's QRS interval was 0.12 sec. The QRS widening was noted as an AE, but is not considered a conduction disturbance.

Clincal Laboratory Abnormalities: A significant increase of BUN change from baseline median change 2.5, mean change 1.8 ± 3.6 was seen in PAT pts, although they were WNL. None of the pts had significant increase of BUN. In PAF pts BUN changes were median 2.0 mean 0.7 ± 3.9 (NS). No changes in creatinine was seen in both groups of pts.

Two pts experienced lab abnormalities which may be attributed to flec Rx. Pt # 101/11, had an elevated SGOT (61 IU/L) and SGPT (158 IU/L), at study D/C. At the time of D/C the elevated SGOT and SGPT were recorded as possible related to flec or to hypotensive VT. Follow-up lab data 7 days later, indicated the SGOT and SGPT levels had returned to normal. SGOT & SGPT were elevated again after 7 days procainamide Rx but returned later while on higher dose of procainamide. Liver and bone marrow biposies showed nonspecific hepatitis and ill-define noncaseating granuloma, respectively. HBc Ab was positive. Procainamide was then d/ced after 24 days of Rx and liver function test returned to normal 1 month later.

Pt # 104/25 completed all 5 periods of the study. This pt had a long standing Hx of anemia thought to be secondary to myelodysplastic syndrome; her Hct has range between 27% to 30%. Baseline Hgb and Hct were 9.5 g/dL and 27.4% respectively. At the time of poststudy procedures, she was noted to be very pale and tired. Her Hgb was 4.5 g/dL, Hct 12.4%, WBC 2,200/mm^3 with a normal platelet count. The pt was hospitalized and received a transfusion of 6 units packed red cells. A bone marrow aspirate/biopsy was performed 4 days postdrug and it showed marked decrease in the erythroid precursors, with infrequent' othochromic normoblasts. There was an Auer rod see in a granulocytic precursor; 3% blasts were also present. Upon discharge the Hct was 26% and maintained baseline range. The investigator's opinion, "flec was most likely the offending agent that caused a severe drop of Hct in this pt; although the possibility of spontaneous aggravation of her underlying myelodysplastic disease cannot be excluded." It was a reversible complication.

Concomitant Medications: Twenty-one (21/45) PAF pts and one (1/28) PAT pt received maintenance digoxin during the study. One PAT pt # 104/02 had changes made in her digoxin dose during periods 1 and 4; therefore, this pt was excluded from the primary efficacy analyses. The one PAT pt who received digoxin was also not included in any of the analyses. She d/ced from the study during period 1.

Pts were allowed to receive concomitant beta-blocker Rx during the study for indications other thatn dysrhythmia as long as they were maintained on previously stabilized dose regimens of these beta-blockers during the study.

Two pts (#0102/05, 001/02) changed the dosage of the beta-blockers that they were not included in the primary efficacy analyses. One pt (#102/11) was on diltiazem but was d/ced during period 1 for a noncardiac AE and was excluded in efficacy analyses.

During the study, persistent attacks of PSVT could be terminated using pharmacologic therapy under the direction of the investigator. Thirteen (8 PAT and 5 PAF) pts received verapamil, 4 (1 PAT and 3 PAF) pts received quinidine, 1 PAF pt received propranolol and diltiazem, 1 PAF pt received lidocaine, 1 PAF pt received procainamide, and 1 PAF received digoxin for persistent attacks of PSVT.

COMMENTS AND CONCLUSIONS

During this study, PAT/PAF pts recorded symptomatic attacks of PSVT by TTM while receiving placebo or ascending doses of flec to determine the dose-response profile of flec in the prophylactic treatment of PSVT. The percentage of PAT pts reporting no PSVT attacks while on placebo was 29%. This percentage increased with successive increase in flec dosages up to 86% for 150 mg bid flec. For PAF pts, the percentage of pts reporting no PSVT attacks increased from 7% while on placebo to 61% while on 150 mg bid flec.

For both PAT/PAF pts, there was also a clinically and statistically siginificant linear dose-response in the percentage of pts remaining attack free. This increase was statistically and clinically significant for the 100 and 150 mg bid flec dosages.

For both PAT & PAF pts who continued to experience PSVT attacks during the study, the time to first attack more than doubled for the three highest dosage levels of flec when compared to placebo and VR during attacks was statistically decreased for the 100 mg bid flec dosage.

The most frequently reported TCAEs for all pts were headache, dizziness, nausea, vision abnormal, and dyspnea and there was a statistically significant dose-response for autonomic nervous system disorders and for the number of pts reporting at least one AE.

Two PAT and two PAF pts reported cardiac AEs while receiving flec during the study. One PAT pt developed sustained, intractable PAT while receiving 25mg bid flec which was clearly different from his previous multiple episodes of PAT. The other PAT pt developed new CHF while receiving 50 mg bid which resolved after diuretics. Both PAF pts reporting cardiac AEs developed a worsening of their arrhythmias. One pt developed sustained AFlu with an increased ventricular response rate while receiving 50 mg bid flec, and the other developed VT while receiving 100 mg bid flec.

A significant increase from baseline occurred for BUN with no change in creatinine for PAT pts at the end of study lab analyses; however, none of the end of study BUN values were outside of the normal range. Two pts had some increase of SGOT and SGPT and 1 pt who had myelodysplastic anemia became severely anemic at the end of study and returned to baseline after D/C of flec.

The results of the dosage recommendation analysis indicated that both PAT and PAF pts, 50 and 100 mg bid flec showed a clinically significant improvement over placebo.

This dose-ranging study showed a clincally and statistically significant linear dose-response in efficacy for prevention of recurrence of PSVT attacks and drug side effects.

Based on the results of this dose-response trial, flec Rx should be initiated at 50 mg bid for PAT and PAF pts experiencing PSVT. A sustantial increase in efficacy, without a substantial increase in D/C for AEs, was observed when received 100 mg bid flec.

B CHRONIC, UNCONTROLLED STUDIES

1. Open-Label, Long-Term, Chronic Efficacy Evaluation After Six or More Months of Flecainide Therapy in Patients With PSVT From Studies R-818-065, -066, and -074. Volume 8.

This was multicenter study of pts who entered the Chronic Efficacy amendment period and finished their participation between June and October 1988. Other pts who complete this study after October 1988 are discussed in a separate report. Investigators at 14 sites enrolled 32 pts who had previously completed the double-blind efficacy studies (R-818-065 and -066) or the double-blind dose-response study (R-818-074) and had received a minimum of 6 mos of uninterrupted open-label flec Rx since completion of those studies.

STUDY DESIGN:

This was an open-label study lasting 8 wks for pts from studies -065/-066, and 4 wks for pts from -074. Pts continued, the same flec dosage they had been receiving during long-term Rx. Pts transmitted all symptomatic attacks of PSVT by TTM and reported their symptoms during the same telephone call. Flec's effect in preventing recurrent PSVT attacks during the Chronic Efficacy study was compared to both the flec period and the placebo period of the parent studies.

Investigators obtained drug therapy histories for each pt prior to enrollment and confirmed that pts continued to meet the identical inclusion/exclusion criteria as specified in the parent protocols. Prior to beginning the amendment period, any concomitant antiarrhythmic not used during the double-blind studies was d/ced for a period of at least 4 half-lives. Baseline and poststudy evaluations for monitoring safety included a 12-lead ECG, of vital signs, and a flec plasma level determination, and clinical lab tests at the beginning and final visit. Pts from studies 065/066 completed an intermin visit/telephone contact after 4 weeks of monitored therapy.

RESULTS

Study Population: Thirty-two pts, (14 PAT, 18 PAF) were enrolled (13 males; mean age: PAT 56 ± 12, PAF 61 ± 13 yrs). Seventy-nine percent (11/14) of PAT pts and 83% (15/18) of PAF pts received either 200 or 300 mg of flec per day.

Time on drug prior to this amendment period was PAT group median 19 (mean 17) mos, ranged from 6 to 35 mos; PAF group median 17.5 (mean 18) mos ranged from 6 to 36 mos. Baseline arrhythmia diagnosis is shown Table 52.

Of the 32 pts who entered the Chronic Efficacy amentments study, 6 (4/14 PAT, 2/18 PAF) were not included in any efficacy analyses. Reasons for exclusion are shown Table 53. Five of the 6 excluded pts received concomitant arrhythmic Rxs during the Chronic Efficacy study that were not used during the double-blind studies and 1 pt d/ced after 3 days of study due to a decreased WBC noted on baseline laboratory results. Thus, the usual number of pts included in the statistical analyses are 10 PAT and 16 PAF pts.

Efficacy Results

When compared to the placebo period of the parent studies, significantly more PAT and PAF pts in Chronic Efficacy were free of attacks, had longer intervals of time until the first attack, and had longer intervals of time between attacks. In addition, PAF pts had significantly fewer documented attacks per day. Table 54 presents the efficacy results.

Patients With No Attacks:

	PAT (N = 10)		PAF (N = 16)	
	Double-Blind Placebo	Chronic Efficacy Flecainide	Double-Blind Placebo	Chronic Efficacy Flecainide
Patients with No attacks	2	9	2	9
P-value	0.004		<0.001	
Time to First Attack (Days):				
Mean ± SE	19.1 ± 6.9	>29.0 [a]	>7.8 ± 2.2	>34.5 ± 5.0
Median	7.0	>29.0 [a]	3.0	48.0
P-value	0.016		0.002	
Interval Between Attacks (Days)				
Mean ± SE	21.6 ± 6.8	>29.0 [a]	>17.9 ± 5.6	>44.9 ± 5.2
Median	12.9	>29.0 [a]	6.9	58.0
P-value	0.026		0.002	

[a]Estimate based on median treatment duration.

The mean rate of attacks for PAF pts receiving flec in Chronic Efficacy significantly decreased (p = 0.010) compared with placebo. Statistical significance was not found for PAT pts (p = 0.147). There were no PAT pts who had PSVT attacks during both periods; thus, an analysis of VR during attacks could not be performed. For the 7 PAF pts who had attacks in both periods, no statistically significant difference was found.

When only those pts who were on the same dose level of flec during both the double-blind crossover study and the Chronic Efficacy study were compared the two flec treatment periods, no statistically significant differences were found for any parameter between flec Rx during the double-blind studies and the Chronic Efficacy study.

Plasma Flecainide Levels: Overall, trough plasma flec levels fell within the therapeutic range of 0.2 to 1.0 mcg/mL established for pts with VAs. Only 1 pt had higher plasma flec levels in the Chronic Efficacy study as compared to the parent studies, the increase for that pt averaged (0.18 mcg/mL after 37 mos of flec Rx).

Symptoms Reported During PSVT Attacks: Symptoms reported during documented attacks are listed in Table 55. Pts may have reported more than one symptom during an attack. Of all pts in the study, only 4/14 PAT and 7/18 PAF pts documented attacks by TTM and, therefore, reported symptoms.

Safety Results

Thirty-two pts (14 PAT, 18 PAF) received oral flec Rx in the Chronic Efficacy study.

Reasons for Discontinuation: Two of the 32 (6.3%) pts d/ced.
Pt # 103/R-818-074-02 experienced leukopenia (see below lab data).
Pt # 101/R-818-066-5 d/ced after 32 days in the Chronic Efficacy study. She misunderstood dosing instructions for concomitant medications and stopped flec in error. Data for this pt up until D/C was used in the efficacy comparison.

Cardiac Adverse Experiences: There were no pts who experienced conduction disturbance, new or worsened CHF, proarrhythmic event, MI, or died while participating in the Chronic Efficacy amendment period.

Noncardiac Adverse Experiences (NCAEs): Four of 14 (29%) PAT pts reported a total of 8 AEs. Table 56. The most frequently reported side effect for PAT pts was visual disturbances (14%). Nine of 18 (50%) PAF pts reported a total of 39 AEs. The most commonly reported AEs for PAF pts were vision abnormal (28%), fatigue (17%), and dyspnea (17%).

Vital Signs: No clinically significant changes in vital signs were found following a medical review.

ECG Results: Repeated 12-lead ECG showed known effects of flec on the prolongation of intervals and no clincally significant results were noted.

Clinical Laboratory Abnormalities: Overall, a review of clinical laboratory data showed no clinically significant trends. One pt, however, # 103/R-818-074-02, d/ced the study due to leukopenia, after 3 days in Chronic Efficacy. Clinical laboratory tests drawn at the initial visit of the amendment period, after 8 mos of long-term flec Rx, revealed a WBC of 2,700/mm^3. This result was not confirmed by repeat analysis. The investigator felt the leukopenia was due to flec administration. The patient's WBC, analyzed 13 days after discontinuation, was normal (8,300/mm^3). The pt was not rechallenged with flec.

Concomitant Medications Twenty-five of the 32 pts received at least 1 concomitant medication. Fifteen took concomitant antiarrhythmic drugs for PSVT either as continuous therapy (digoxin 9, verapamil 1, propranolol 1) or as needed (verapamil 4).

COMMENTS AND CONCLUSION

The Chronic Efficacy trial was conducted to objectively evaluate the long-term ($\geq$ 6 mos) safety and efficacy of flec in the treatment of PSVT in 32 pts who had previously completed the double-blind efficacy/dose ranging study.

When compared to the placebo period of the parent study, significantly more PAT and PAF pts in Chronic Efficacy were free of attacks, had longer intervals of time until the first attack, and had longer intervals of time between attacks. In addition, PAF pts had significantly fewer documented attacks per day. Since this was not a parallel placebo control study that the reduction of "no attacks", longer intervals between attacks etc should not be account only due to the drug effect.

In all pts, reported noncardiac AEs were not different from those previously reported: visual disturbances, fatigue and dyspnea were the most frequently reported noncardiac AEs effects. There were no pts who experienced a cardiac AE or died during the course of this study.

Seventy-nine percent of PAT pts and 83% of PAF pts received either 200 or 300 mg of flec/day. Overall, trough plasma flec levels were also maintained within the established therapeutic range of 0.2 to 1.0 mcg/mL. This chronic study indicated, though very small number and uncontrolled data, oral flec remained safe and effective in the long-term prophylaxis of PSVT attacks in pts for whom flec was well-tolerated for at least 6 mos and who demonstrated an efficacious response to therapy during short-term clinicai trials and subsequent long-term therapy.

2. STUDY R-818-074, ELECTIVE OPEN-LABEL CHRONIC USE PHASE
Volume 9 pages 0-48

When a pt finished the dose-response phase of the study (R-818-074), the double-blind dosing sequence code for that pt was broken, and the investigator and the pt reviewed the responses to all treatments. If both agreed the response to flecainide was favorable and continued flec Rx was warranted, the investigator continued the pt in the elective open-label chronic use phase of the study on the lowest effective dose. The pt was maintained on open-label flec under the supervision of the investigator for 1 yr or until the drug was no longer safe and/or effective, whichever occured first. Dosage adjustments were allowed as needed to maintain efficacy and tolerance, provided the dose did not exceed 600 mg per day.

During the long-term therapy period, the investigator monitored each pt at monthly intervals by either telephone calls or clinic visits and recorded his findings on a one-page case report form. In contrast to using TTM during the dose-response phase to objectively document PSVT attacks, suppression of arrhythmias was based on questioning the pt on the number of PSVT attacks and associated symptoms he/she had experienced since the last visit or call.

Investigators at 17 sites enrolled 73 consenting pts in the dose-response study (R-818-074). Forty-six pts (18 PAT, 28 PAF) at 15 sites were considered effectively treated with flec and continued into the chronic use phase beginning in March 1988. As of this submission, all 46 pts have finished their participation in the elective open-label chronic use phase of the study. Thirty-one of 64 completed the allowed 12 mos Rx and 8 d/ced before the end of 12 mos. The remaining 7 d/ced from the study at 3M Riker's request on 4/26/89, following the National Heart, Lung & Blood Institute's (NHLBI) announcement of results from an interim analysis: "an unexpected observation of 2.2-fold higher rate of mortality and nonfatal cardiac arrest in the pt group on flec as compared to the matching placebo group in a clinical trial designed to determine whether antiarrhythmic drugs reduce sudden cardiac death in post-myocardial infarction patients with asymptomatic VAs."

A summary of the final status for all pts in the study follows:

Final Patient Status

Final Patient Status	No. of Patients (N=46)	
End of Study	31	(64%)
Study Terminated by 3M Riker	7	(15%)
Discontinued from Study Due to		
Adverse Experience	4	(9%)
Inadequate Response and AE	1	(2%)
Inadequate Response	1	(2%)
Personal	1	(2%)
Other	1	(2%)

The AEs resulting in D/C of long-term flec Rx are identified below by study site and pt number.

Site-Pt No.	Adverse Experience	Comment
02-103	Decreased WBC count	Leukopenia
06-101	Myalgia	
06-103	Blurred vision	
07-102	Nausea	Inadequate response also
27-103	1:1 conduction and increased heart rate	

Due to the ongoing status of this study, the data for the 46 pts who received chronic therapy after completing the dose-response evaluation are not included in the data base reviewed and summarized in the integrated safety section of the submission.

3. STUDY R-818-077: OPEN-LABEL SAFETY AND EFFICACY STUDY OF FLECAINIDE ACETATE IN THE TREATMENT OF SUPRAVENTRICULAR ARRHYTHMIAS (SVAs)
Volume 9 pages 49-89

This was a phase III, open-label multicenter trial designed to broaden the safety and efficacy profile of oral flec in pts with all types of SVAs. The original intent was to involve investigators at 30 centers to enroll approx 10 pts per center Rx of their documented SVAs. The criteria for judging efficacy was left to the investigator. Once established on an effective therapy, the pt was seen and his/her progress evaluated at regular intervals. Pts remained in the study on open-label flec Rx as long as the investigator felt the drug was beneficial or for one year, whichever occurred first.

The recommended starting dose was 100 mg bid. Dosages increases in increments of 50 mg bid every 4 days to a maximum dose of 400 mg/day were allowed to achieve efficacy. Follow-up examinations performed 1 to 3 wks after initiation of Rx and at 3 mo intervals thereafter.

The study was initiated in March 1988. Investigators at 21 centers and enrolled 142 pts but studies were d/ced in response to the intermin report of CAST. Only a small portion of the data were co lected. One pt death was reported before the termination of the study. Pt # 003/R-818-077-08 was a 74 y/f who had a Hx of CHF, COPD and severe mitral stenosis. She died 8/24/88, of respiratory failure due to lung cancer. The lung cancer was probably a result of metastatic progression of ovarian adenocarcinoma. Prior to valvuloplasty, the pt experienced several episodes of SVT characterized as AVNR tachycardia. Following the surgery, the episodes of SVT became more frequent and were treated with procainamide which was subsequently d/ced due to a rash. Flec 50 mg bid was initiated 7/30/88 followed by a dose increase to 100 mg bid 8/7 after a recurrence of SVT. The dose was decreased 8/11 to 75 mg bid and then to 50 mg bid on 8/12 due to worsened CHF and increased PR and QRS intervals. The pt remained stable on flec 50 mg bid with an improvement in hemodynmic status and suppression of SVT until her death 8/24/88.

4. STUDY R-818-078: FOLLOW-UP STUDY OF CHRONIC FLECAINIDE THERAPY IN PTS WITH PSVT
Volume 9 pages 81-119

The objective of this single-blind, placebo-controlled, multicenter study was to evaluate the long-term effectiveness of flec in the Rx of PSVT who had successfully completed 3M Riker study R-818-065/066 or R-818-074 and been maintained on chronic for a minimum of 6 mos were enrolled.

After enrollment of 2 pts between Novemeber 1987 and February 1988 when 3M Riker cancelled the study because, after discussion with US FOOD and Drug Administration reviewers, the comparative design was not felt to be an appropriate method of evaluating chronic efficacy.

Of the 2 pts entered, 1 completed all three periods of the study without AEs. He had 1 attacks of PSVT during 4 wks of flec Rx and 4 attacks in 8 wks of placebo. The second pt d/ced due to study cancellation after 2 wks in period 1 (flecainide). He had no attacks during that time. He reported continuing decreased libido of mild severity which was an ongoing AE at the time of study enrollment.

C. IND /Oral EPS
Volume 8 pages 152-255
1. IV/Oral EPS study

"Measurement of the Effect of Flecainide Acetate During EP Testing in Patients With Bypass Mediated Reentrant Tachycardia, Preexcitation Syndrome, and AV Nodal Reentrant Tachycardias"

Investigator: Rodolphe Ruffy, MD
Jewish Hospital
Washington University Medical Center, St Louis, MO

This study was to safety & efficacy of flec in pts with by-pass mediated reentrant tachycardia, preexcitation syndrome, or AVNR tachycardia as measured during EPS prior to and after administration of flec to identify its effect on the mechanism of action for the arrhythmias.

STUDY DESIGN

This was an open-label controlled study to evaluate the effect of flec on the mechanism of the pts underlying arrhythmia based on a comparison of EP test results conducted prior to and after administration of flec. Prior to the baseline EP testing, a complete medical Hx including a cardiovascular Hx; an arrhythmia/conduction; antiarrhythmic therapy; and other drug therapy were collected. Chest x-ray, radionuclide LV ejection fraction measurement (RNEF) if there was a Hx of CHF; hematologic, blood chemistry and urinalysis tests were done.

Baseline determination were obtained after pts had d/ced previous antiarrhythmic Rx for a minimum of 4 drug half lives. The baseline evaluations included a Holter recording (if clinically indicated), a 12-lead ECG, and EP studies consisting of a control study followed by a second study performed after an IV dose of flec 2 mg/kg infused over 10 to 20 mins. Immediately after infusion, programmed stimulation and recordings were repeated and completed within 30 mins.

Following the first dose of oral flec pts were hospitalized for a minimum of 7 days. Pts were not discharged on flec unless an efficacious and tolerable dose, not greater than 400 mg/day, was achieved.

Oral flec was initially administered at a dose of 100 mg bid. This dose was increased by 100 mg/day at 4-day intervals to achieve efficacy or until AEs occurred or a maximal dose of 400 mg/day was achieved. Efficacy was determine by telemetry monitoring. A plasma sample was collected just prior to the morning dose on the 3rd day of each 4-day dosing interval. Efforts were made to maintain trough plasma flec levels between 400 and 1000 ng/ml. In selected pts a second EP study was done when steady-state plasma con of flec were reached.

During EP study anterograde and retrograde conduction properties were evaluated by incremental pacing. Block cycle length was defined as the cycle length at which there was failure of 1:1 conduction during incremental pacing. For comparison, identical basic atrial and ventricular cycle lengths were used before and after IV administration of flec.

RESULTS

Study Population (Table 57): Thirty pts enrolled and 29 received IV flec. One pt # 902, received only oral flec and had an EP study performed on oral flec. This pt is not included in the efficacy analyses. Twenty-four pts were diagnosed as having AV reentrant tachycardia (AVRT) and 6 were diagnosed with AV nodal reentrant tachycardia (AVNRT). Of the 24 pts included in AVRT group, 16 were diagnosed with WPW, 2 had atrial arrhythmias and preexcitation; 5 had concealed bypass tract, and 1 had a paroxysmal form of junctional reentrant tachycardia (JRT).

The mean age for pts with AVRT was 39.4 $\pm$ 16.1 yrs (range was 16 to 71 yrs); AVNRT was 42.3 $\pm$ 10.2 yrs (range was 25 to 54 yrs).

Although pts were to be refractory or intolerant to other antiarrhythmics, 3 pts, 2 with AVRT and 1 with AVNRT, had not received prior antiarrhythmic Rx. The mean number of previous antiarrhythmic Rxs for the AVRT was 2.8 (0-10) and AVNRT was 3.3 a (0 - 6). The previous antiarrhythmic therapies were propranolol, verapamil, digoxin, quinidine, procainamide, atenolol, disopyramide etc.

Effects of Intravenous Flecainide on Inducibility: Twenty-seven pts who were tested before and after IV flec had inducible sustained SVT prior to

flec. Of the 21 pts with inducible AVRT, 12 (57.1%) pts had no inducible tachycardia following the administration of flec. Of the 6 pts with AVNRT, 4 (66.7%) pts were noninducible after flec.

Electrophysiologic Observations in Patients With AV Reentrant Tachycardia (Tables 58 and 59): The cycle length, AH interval, HV interval, VA interval and AV interval were compared before and after flec in pts who tachycardia could be induced after IV flec. The cycle length of tachycardia could be increased from 313 ± 44 ms to 386 ± 58 ms after flec (p=.006). Lengthening in the cycle length of the tachycardia was mainly due to an increase in the VA interval from 105 ± 30 ms to 153 ± 69 ms (p=.019). Although not statistically significant (p=.071) the mean HV interval increased and changes in AH intervals were variable and showed a slight decrease.

The anterograde block cycle length of the AV node was compared in 11 pts. The cycle length significantly increased (p=0.046) from 288 ± 37 ms to 318 ± 53 ms. Exact comparison of the anterograde refractory period of the AV node before and after flec was impossible because of atrial refractoriness. Flec did not abolish anterograde conduction over the accessory pathway in 4 pts. Although not significant (p=.176) the mean anterograde block cycle length of the accessory pathway increased from 230 ± 12 ms to 285 ± 55 ms.

The retrograde block cycle length of the accessory pathway before and after IV flec could be compared in 19 pts. Of the 12 pts whose tachycardia was no longer inducible after IV flec administration, ventriculoatrial (VA) block was demonstrated at all paced cycle length in 8 pts while the VA block cycle length increased markedly in 3/4 remaining pts. In the 7 pts whose tachycardia was still inducible after flec, retrograde block cycle length increased significantly from 237 ± 32 ms to 324 ± 86 ms (p=.012). The mean VA block cycle of the accessory pathway during the control study was longer in pts who had complete retrograde block in the accessory pathway after flec administration (305 ± 63 ms) than in those who did not (237 ± 28 ms). In the 7 pts whose tachycardia remained inducible and in the 4 pts whose tachycardia was not inducible but did not have VA block, the mean retrograde block cycle length of the accessory pathway increased from 237 ± 28 ms to 356 ± 101 ms (p=.001). Thus, flec had a pronounced, selective depressant effect on the retrograde limb of the reentry circuit. There were no statistically significant changes in refractory periods following IV flec administration. These data, however are difficult to interpret because of the difficulties encountered in the systematic collection of paired data at similar paced cycle lengths.

Electrophysiologic Observations in Patients With Atrioventricular Nodal Reentrant Tachycardia (Table 60): AV nodal reentrant tachycardia was noninducible in 4 of 6 pts as a result of IV flec. Tachycardia cycle length, HA interval and AH interval before and after IV flec were no statistically significant differences. Retrograde block cycle length measurement showed VA conduction was abolished at all ventricular paced cycle lengths in 3 pts and 1 pt marked, 1 modest increase from the pre-flec retrograde block cycle length. Thus in 4/5 pts flec resulted in a depressant effect on retrograde conduction over the fast AV nodal pathway.

Anterograde block cycle length increased in 3 pts and overall, the mean anterograde blocked cycle length increased from 288 ± 26 ms to 314 ± 43 ms. Although the increase was not statistically significant, the data suggest flec may also have a depressant effect on anterograde slow pathway conduction. Anterograde and retrograde effective refractory periods did not changes significantly following flec.

Effects of Intravenous Versus Oral Flecainide: The EP effects of IV versus PO flec could be compared in 9 pts. Reentrant SVT remained noninducible in 7 pts and inducible and sustained in 2 pts (#s 901 and 921) following treatment with oral flec. Four of the 6 pts whose tachycardia was noninducible after IV flec because of complete VA block continued to have complete VA block during oral flec. The other 3 pts with AVRT regained VA conduction during oral flec but had longer retrograde block cycle lengths than during the control study. In these 7 pts, reentrant tachycardia remained noninducible during oral treatment as well as after IV flec because of depression of conduction in the retrograde limb of the reentry circuit.

Pt # 901, whose tachycardia remained inducible, had similar anterograde and retrograde block cycle lengths and characteristics of tachycardia after IV and oral Rx. Pt # 921, whose tachycardia also remained inducible, had longer anterograde and retrograde block cycle lengths and induction of a slower tachycardia during oral flec.

Safety of Intravenous Flecainide

Adverse experience data was not specially collected during EP testing. Pt # 927, however, became hypotensive with a wide QRS during IV infusion. The pt did not tolerate this and lost consciousness and required DC shock and dopamine infusion. There were no other reports of any problems occuring during or following the infusion of IV flec.

Long-term Follow-up

Twenty-five pts went onto oral Rx. Five pts did not continue on long-term flec Rx. Pt # 914,946 and 962 had an inadequate response during EP testing, # 927 preferred conventional drug therapy and # 937 experienced hypotension during EP testing and was not put on long-term oral Rx.

COMMENTS AND CONCLUSION

Twenty-seven pts who were tested prior to and after IV flec had inducible sustained SVT prior to flec. Twelve of 21 pts (57%) with AVRT and 4/6 pts (67%) with inducible AVNRT at baseline were no longer inducible following administration of at baseline and 1 pt did not have EP tests performed on IV flec.

For pts with AVRT who were still inducible following administration of IV flec, the cycle length of the tachycardia was significantly ($p=0.002$) increased, primarily due to the significant ($p=0.019$) increase in the VA

interval. There were no statistically significant differences in the tachycardia cycle lengths, HA interval, and AH interval for the 2 pts with AVNRT still inducible following IV flec.

The retrograde block cycle length of the accessory pathway was compared before and after IV in 19 pts with AVRT. VA block was demonstrated at all paced cycle lengths for 8 pts. In 7 pts whose tachycardia remained inducible and 4 pts whose tachycardia was not inducible but did not have VA block, the mean retrograde block cycle length was significantly increased (p=0.001).

The anterograde block cycle length of the AV node increased significantly (p=0.046) in 11 AVRT pts. An increase in the anterograde block cycle length of the accessory pathway was observed in 4 pts for whom flec did not abolish anterograde conduction over the accessory pathway (NS).

In 6 AVNRT pts retrograde block cycle lengths were measured in the 5 pts. VA conduction was abolished at all paced cycle lengths in 3 pts and was markedly increased over baseline in 1 pt. Anterograde block cycle lengths was measured in 5 pts and showed an increase in the cycle length was observed but the difference was not statistically significant. Anterograde and retrograde effective refractory periods did not change significantly for either pts with AVRT or AVNRT.

Comparison of EP results on oral and IV flec could be made in 9 pts, 6 with AVRT and 3 with AVNRT. Similar EP results were observed for these 9 pts following oral and IV flec. Of the 30 pts who participated in this study, 25 went onto long-term oral flec Rx.

Adverse experience data was not specifically collected during EP testing. One pts became hypotensive with a wide QRS during IV infusion, lost consciousness, and required DC shock and dopamine.

In conclusion, flec exhibited a dramatic depressant effect on retrograde accessory pathway conduction and to a lesser degree a depressant effect was also observed in anterograde conduction over the accessory pathway.

2. IND Oral, long-term study
Volume 8 pages 257-431

"Treatment of Bypass Mediated Reentrant Tachycardia, Preexcitation Syndrome, and AV Nodal Reentrant Tachycardia with Flec" by Rodolphe Ruffy, MD, Jewish Hospital, Washington University Medical Center St. Louis, Missouri.

This study was to determine the safety and efficacy of flec in pts with bypass mediated reentrant tachycardia, preexcitation syndrome, or AVNRT.

STUDY DESIGN

This was a phase III, open-label study design. Pts were allowed to continue in the study as long as, in the opinion of the investigator, flec remained

safe and effective within the range of prescribed dose levels. The study allowed alterations in dose levels and dosing schedules. Dosage was from 150 to 400 mg/day. Baseline and follow-up procedures varied for each pt depending on the pts cardiac disease. After the initial inpatient phase, pts returned at 1 mo and 3 mos after discharge and at quarterly intervals thereafter. At each interval visit a global evaluation of arrhythmias was recorded and the presence or absence of recurrent tachycardia was documented by 12-lead ECG or telemetry. Safety evaluations included interval medical history, clinical lab tests, CHF, AEs and concomitant medication.

RESULTS

Study Population: Thirty pts were included in the analyses. Twenty-four pts had overt or concealed AV accessory pathways. All had spontaneous or inducible paroxysmal tachycardia utilizing an anomalous AV connection. For purposes of analysis, these pts were grouped into AVRT. Six pts had AVNRT.

EFficacy Results Table 61

Based on the global impression of arrhythmias and the evaluation of SVT, in most instances, were well controlled. Once an efficacious dose was determined, most pts had no further episodes of SVT or had only transient recurrences of SVT which abated without medical intervention. There was no baseline data or control group to compare the efficacy.

Reasons for Discontinuation: Twelve of the 24 pts with AVRT d/ced the study: 5 for AEs, 3 for personal reasons, 2 for inadequate response, 1 for new or worsened arrhythmia, and 1 was lost to follow-up. Three of the 6 pts with AVNRT d/ced: 2 for AEs and 1 for inadequate response.

Safety Results

Abnormal vision (about 58%) and dizziness (46%) were the most frequently reported AEs. Most pt complaints were mild or moderate in severity and resolved without medical intervention. None of the pts had a history of CHF and no pt developed any signs or symptoms of CHF while taking flec. There were no unexpected or clinically significant changes in ECG intervals, vital signs, or clinically lab values noted during the study.

CONCLUSION

These uncontrolled open studies of 36 pts (24 AVRT, 12 AVNRT) with PSVT showed supportive evidence of effectiveness of flec in suppressing SVT in all but one pt who received long-term therapy.

D. Study R-818-065, Amendment A EP Study pre & post IV flec.

This was a multicenter (4 sites) study to determine the effects of IV flec on various EP measurements, including the ability to prevent or alter the induction of these tachycardias.

STUDY DESIGN:

Study R-818-065 was a 16 wk, double-blind, placebo-controlled, randomized, crossover study which had three phases: a 4-wk Screening phase; a 3-wk Dose Ranging phase; and a Crossover phase with two 8-wk periods.

Prior to beginning the oral-dosing portions of the study, investigators were allowed to further characterize the underlying arrhythmia by EP testing. Amendment A further allowed investigators to test the effect of IV flec during EP testing on the prevention or alteration of inducible arrhythmia. Pts were required to continue into the oral dosing phases of the study.

The sinus cycle length, P-A interval, AV intervals, and H-V interval were recorded during sinus rhythm. The corrected sinun nodal recovery time was measured at pacing cycle lengths 600, 500, and 400 msec. Using incremental atrial or ventricular pacing, the minimum cycle length which sustained 1:1 AV nodal conduction or VA conduction, respectively, were recorded.

After the control EP observations were made, IV flec was administered using a two-stage infusion: a fast infusion of 2 mg/kg over 15 mins followed by a slow infusion of 1 mg/kg/hr for up to 3 hrs. Beginning 30 min after the start of the flec infusion (15 mins into the slow infusion), EP measurments were repeated.
Blood samples were obtained for plasma flec level determinations at time zero, 30 mins after initiating the flec infusion, and then every 30 mins until completion of the study.
Pts began the oral Dose Ranging phase of the study between 3 to 10 days after completing the EP testing.

RESULTS

Study Population: A total of 21 pts (16 PAT, 5 PAF; male 6; mean age 52.4 ± 14.1; number of previous antiarrhythmics used 4.4 ± 1.6) were enrolled the study.
The baseline arrhythmia diagnoses for all 21 pts were determined through EP testing. Of the 16 PAT pts: 2 had ectopic atrial tachycardia, 4 WPW, 4 concealed bypass tract, and 6 AVNR. Of the 5 PAF pts, 4 had AFib and 1 AFib/AFlu (Table 62). In the PAT group, 8/16 had AV reentry (using an accessory pathway); 4/8 had WPW and 4/8 had concealed accessory pathways (that conducted only in the retrograde direction). Six of the 16 PAT pts had AVNRT, in which the reentry circuit was contained entirely within the node and 2/16 had ectopic atrial tachycardias. Table 63 lists all reported associated cardiac disorders.

Screening Results: For the 16 pts, 10 (63%) qualified within the first 28 days of screening; 4 had 1 documented attack in 28 days, 1 had 2 attacks on the same day; and 1 who d/ced following EP testing, never received a TTM.
For the 5 PAF pts, all qualified within the first 28 days of screening.

Basic Conduction Intervals: - Basic conduction intervals recorded before

and after flec administration were compared in 12 PAT pts who did not have WPW. (Table 64). Flec significantly ($p \leq 0.01$) shortened the sinus cycle length from 892.2 ± 87.6 msec to 748.3 ± 101.0 msec; significantly ($p \leq 0.01$) lengthened the H-V interval from 49.2 ± 6.3 msec to 59.2 ± 9.5 msec. In pts with WPW compared with PAT pts without WPW, no clinically significant difference in basic conduction intervals was measured. Of the 5 PAF pts, neither the sinus cycle length, P-A, A-H, nor H-V intervals recorded during sinus rhythm were significantly different after flec administration.

Efficacy Results Table 65

Of 15/16 PAT pts inducible at baseline, IV flec effectively prevented induction of PSVT in 7/15 PAT pts. Of 3/5 PAF pts inducible at baseline, 2/3 PAF pts were noninducible after IV flec and considered effectively treated. One of the two pts noninducible at baseline after receiving IV flec was also judged effectively treated.

The most consistent changes observed in cardiac conduction were an increase in the cycle length at which Wenkeback periodicity was observed during atrial pacing; complete VA conduction block during ventricular pacing; increased V-A intervals recorded during PAT; and suppression of inducible tachycardia.

Correlation of results from IV EP to results from oral crossover phase is shown Table 65. Due to the small number of pts who received both IV and oral flec, it was not possible to correlate results from IV flec with oral flec results.

Reasons for D/C: Of the 21 pts who received IV flec, 3 PAT pts d/ced following EP testing; 2 PAT pts for worsened arrhythmia and 1 PAT pt for personal reasons. The remaining 18/21 (13/16 PAT, 5/5 PAF) pts continued into the double-blind, placebo-controlled, oral therapy study.

Safety Results

Cardiac Adverse Experiences - No pt had a conduction disturbance, new or worsened CHF, or died while receivinf IV flec. Two PAT pts experienced proarrhythmic events. In both pts intervention was necessary to convert the arrhythmia; both pts recovered and were d/ced from the study.

Pt # 001/01, was a 38 y/m with a Hx of WPW associted with palpitations, weakness, and sweating. The pt underwent EP testing. After receiving IV flec, the pt was not inducible for PSVT; but a single PVC induced VF. The pt had not previous Hx of VF. The pt was resuscitatied by electrocardioversion, the EP study was terminated, and study participation d/ced. On review by electrophysiologic consultants, this arrhythmia was considered an electrically-induced laboratory phenomenon secondary to the stimulus delivered on the T-wave of the preceding beat (R on T phenomenon).

Pt # 003/08, was a 46 y/f with a Hx of mitral valve prolapse, and WPW associated with palpitations, near syncope, weakness, and dyspnea. The pt entered the study and underwent EP testing. According to the

investigator, IV flec blocked antegrade conduction over the AV bypass pathway but caused incessant reentrant AV reciprocating tachycardia. Verapamil (5 mg, IV) terminated the event. At the end of EP testing, antegrade conduction over the AV bypass pathways resumed. The pt was placed on oral verapamil, 360 mg daily, and removed from the study.

Noncardiac AEs - Two PAT pts had NCAEs on IV flec. One pt reported dizziness and the other reported dizziness and headache.

Concomitant Medications: All 5 PAF pts received digoxin concurrently with flec and no PAT pt received concomitant digoxin. One PAT and no PAF pts received IV verapamil during EP testing (see above).

The administration of atropin (0.04 mg/kg, IV bolus, to a maximum of 3.0 mg/kg) was allowed to facilitate induction of SVT during EP testing. If atropine was used to induced SVT during baseline measurements off flec, atroping was required (at the same dose) during induction procedures while administering flec. Atropine could not be used to induce SVT on flec if atropine was not used at baseline. One PAT pt and no PAF pts received atropine during EP testing to induce arrhythmia at baseline and post flec infusion. No pt received any other antiarrhythmic agent during EP testing.

CONCLUSION

Flec causes significant slowing in cardiac conduction in pts with PSVT. Evaluation of data from EP testing showed IV flec effectively prevented the induction of PSVT in 8/16 PAT pts; 3/5 PAF pts were considered effectively treated. Due to the small number of pts who received both IV and oral flec, it is not possible to correlate results from IV flec with oral results.

E. STUDY R-818-EG-11 LONG-TERM RX AND WITHDRAW TRIAL
by Helmut Neuss, MD at the Kerckhoff Clinic, Bad Nauheim, West Germany.
Vol. 9 pages 289-387
This study was to determine the long-term effects of flec with respect to arrhythmias and to other organ systems in pts with SVT.
The pts with Hx of PSVT and specific Dx was made with EP study and responde with IV flec, entered this open-label, long-term clinical trial. Oral flec was titrated to an effect dose and treated for a minimum of 1 yr with treatment pauses. Flec was withdrawn and the pretreatment arrhythmia allowed to return, after which Rx was reinstated. The reappearance and subsequent disappearance of arrhythmias were documented by pt diaries.
Interval visits were scheduled for 1, 3, 6, 9, and 12 mos after initiation of flec to evaluate efficacy and safety.

RESULTS

Study Population: Nineteen pts (9 males) with SVT received long-term flec therapy in this study. Thirteen had an arrhythmia diagnosis of WPW syndrome (mean age 45.3 ± 14.0), and 6 AVNRT (mean age 49.3 ± 9.2).

A mean duration of long term Rx was 59 wks (range 5 to 133 wks). Twelve of 19 pts took daily flec for at least 1 yr. Drug-free intervals for 14/19 pts were averaged 10 wks in length (range, 1 to 28 wks). Initial and final flec total daily doses, duration of flec Rx, and duration of drug-free interval by pt and Dx is shown Table 60.

Efficacy Results: Efficacy evaluations were based on predrug arrhythmia characteristics and on diary information recorded by pts on the frequency, duration and severity of SVT attacks occurring during flec Rx and drug-free interval. Eleven/13 pts with WPW and 6/6 with AVNRT were included in the analysis; 2/13 WPW pts were excluded due to suspected noncompliance with the daily dosage regimen based on plasma flec levels of zero or almost zero when the drug was supposedly being taken.

Pt status at the last visit is shown Table 67.

Summary of Patient Status at the Last Study Visit

	No. of Patients		
Patient Status	All (N=19)	WPW (N=13)	AVNRT (N=6)
Continuing Daily Flecainide Therapy	10 53%	6 46%	4 67%
Continuing Flecaninide PRN to Terminate SVT Attacks	3 16%	2 15%	1 17%
Discontinued From Study	6 32%	5 38%	1 17%
Due to Inadequate EFfect	1	1	0
Adverse Experiences	2	1	1
Suspected Noncompliance	2	2	0
Lost to Follow-up	1	1	0

Sixty-eight percent (13/19) of the pts were continuing oral flec at the time of the last CRF entry, either as daily dosing to prevent recurring attacks of SVT or as single doses on PRN basis to terminate individual attacks. The last-entry dates for all of these pts were during the months of March through October 1982. Kettelhack Riker Pharma introduced flec into the West German marketplace in September 1982 after the German Registration Authority granted approval for the drug that additional follow-up data is not recorded in the CRF.

Although the discontinuation rate (6/19, 32%) was high for this study, only 3/6 were related to pt responses to the drug: flec was judged ineffective in suppressing SVT attacks in 1/3 pts and intolerable AEs resulted in discontinuation for 2/3 pts. The remaining pt discontinuations were due to suspected noncompliance (2/6) with the prescribed flec daily dosage regimen and lost to follow-up (1/6) after the drug-free interval.

The efficacy evaluation were based on diary information and there was no objective verification. Table 68 summarized the individual pt arrhythmia data based on diary information. Except 1 pt (#034 WPW group) who had treatment failure the majority of the pts were selected for long-term oral therapy following a positive response to IV flec during EP testing. All other pts (16/17) included in the efficacy analysis showed an excellent response to long-term oral flec Rx.
Ninety-one percent (10/11) of the WPW pts and 100% (6/6) of the AVNRT pts experienced either complete or significant suppression of their arrhythmias when compared to predrug and/or drug-free interval arrhythmia frequencies.

Ten of 11 WPW and 4/6 AVNRT pts had daily flec Rx interrupted during the study to allow return of arrhythmias (Table 68). No arrhythmia data was reported for 1 pt (# 006, WPW) during a 1-wk drug-free interval. All other pts reported an increased number of SVT attacks during the drug-free interval compared to the flec Rx period. In addition, the severity of the attacks during the drug-free interval was greater. For the 7/11 WPW pts experiencing attacks during flec Rx, all attacks converted spontaneously or with application of the Valsalva maneuver. In contrast, 5/9 WPW pts participating in the drug-free interval required medical intervention on two or more occasions to control attacks: 2 were treated by family physicians (means of intervention not specified); 2 took individual doses of flec to terminate attacks; and 1 received IV verapamil on one occasion and single doses of flec on others. In the AVNRT group, 4/6 pts experienced attacks while taking flec which terminated spontaneously, with Valslava, or with IV verapamil (1 pt on 1 occasion). Of the 4/6 pts evaluated during a drug-free interval, IV verapamil was used in 2 and single-dose flec in 1 to terminate attacks; the remaining pt required no medical intervention.

Pt #033 was followed for a total of 71 wks in the flec Rx period. During the first 33 wks, he received flec as a single antiarrhythmic agent. Therapy was initiated at a dose of 300 mg/day, followed shortly by an increase to 400 mg/day which had little or no effect (74 attacks). A dose of 500 mg/day completely suppressed the arrhythmia but caused a significant widening of the QRS duration. Therefore, the dose was gradually decreased to 200 mg/day and amiodarone, 400 mg/day five or six/wk, was added. Before starting the concomitant therapy, the pt experienced ten more SVT attacks, resulting in a total of 84 attacks in 33 wks (2.54/wk) while receiving flec alone. Flec and amiodarone were continued for 38 additional wks with only two attacks reported. During a drug-free interval of 2 wks with amiodarone alone, the pt experienced 12 attacks. Attack rate 2.54/wk during flec Rx was considered a significant suppression when compared with predrug and flec-free-interval frequencies of 6.00/wk. In this pt, the combination of flec and amiodarone was effective when neither agent alone was.

Three WPW pts (#s 002, 024, and 030) and 1 AVNRT (# 020) took single doses of flec (200, 250, or 300 mg) during the drug-free interval to convert SVT attacks. All 4 pts reported resolution of SVT-associated symptoms within 1 to 2 hrs after a single oral dose of flec. Pt #s 002, 020, and 030 did not resume daily therapy after the drug-free interval but, instead, continued to

take single doses as needed. In contrast, pt # 024 returned to daily flec which provided complete suppression of SVT attacks.

Safety Results
Discontinuations Due to Adverse Experiences: Two of 19 (11%) pts d/ced from the study after 5 to 6 wks due to AEs. One pt complained of visual disturbances, excitabiltiy, nightmares, and unsteady gait; the other refused to continue due to annoying extrasystoles that were particularly noticeable at rest.

Seventy-nine percent (15/19) of pts reported at least one AE while receiving flec. The most common side effect was vision abnormal in 42% (8/19) of the pts. Headache, dizziness, dyspnea, and eye pain each had a 16% (3/19) incidence. Proarrhythmic events, CHF, conduction disturbances, and clinically significant lab changes did not occur in this pt population.

In one case (# 033) a single peak plasma level of 1675 ng/mL, drawn during 500 mg/day dosing may correlate with a significant widening of the QRS duration which prompted the investigator to decrease the dose (see above).

COMMENTS AND CONCLUSION

The long-term efficacy of flec in the treatment of SVT was evaluated in 17 pts who were preselected for oral therapy based on positive responses to IV flec. Complete or clinically significant arrhythmia suppression was observed in 16/17 (94%) pts. Supraventricular arrhythmias due to either WPW or AVNRT were successfully treated with oral flec dose ranging from 200 to 500 mg/day for up to 133 wks. When treatment and drug-freee intervals were compared, a marked increase (return of arrhythmia) in the number of attacks of SVT was noted during the drug-free interval which further documents the efficacy of flec in treating SVT. Although most pts were preselected based on a positive response to IV flec, the amount of long-term suppression remains clinically significant. The most common AE was abnormal vision.

PUBLICATIONS INCLUDING RESULTS FROM STUDY R-818-EG-11

Neuss H, et al: Effects of flecainide on electrophysiological properties of accessory pathways in the Wolff-Parkinsion-White syndrome. Eur Heart J 1983;4:347-353.
Neuss H: Long Term Use of Flecainide in Patients with Supraventricular Tachycardia. Drugs 1985;29(4):21-25.
Neuss H and Schlepper M: Long-Term Efficacy and Safety of Flecainide for Supraventricular Tachycardia. Am J Cardiol 1988;62:56D-61D.

F. CONTROLLED STUDIES OF USES OTHER THAN THOSE CLAIMED IN THE APPLICATION

R-818-075-01: Double-Blind, Three-Period Crossover, Efficacy and Safety Study of Flecainide Versus Digoxin for Ventricular Rate Control and Exercise Tolerance in Patients With Chronic Atrial Fibrillation (AFib)
by Rodney H. Falk, MD, Boston City Hospital, Boston, MA. Volume 10.

Study Objective: To determine whether flec, either alone or in combination with digoxin, could improve ventricular rate (VR) control and/or exercise tolerance in pts with chronic AFib. A secondary objective was to determine whether improved VR control during exercise might prevent chronic damage to the left ventricle (LV).

Study Design: This was a 6-wk double-blind, randomized three-period crossover trial in 12 pts. During the screening phase, while receiving their stabilized, prestudy digoxin therapy, pts documented 1) controlled, resting VR at two evaluations; 2) a therapeutic trough plasma digoxin level; and 3) abnormal increased in heart rate (HR) on two exercise tolerance tests (ETT) with the Modified Bruce protocol.

The crossover period consisted of three consecutive, 2-wk treatment periods. Each pt was to randomly receive all of the following treatments: 1) flec and digoxin; 2) flec and digoxin-placebo; and 3) flec-placebo and digoxin. Pts received digoxin in a dosage equivalent to their baseline dosage; the flec dosage was 100 mg bid.
The investigator obtained medical Hx, pre and post 24h Holter recording, 12-lead ECG, PE, echocardiogram and ETT and pt diary ratings at the end of each treatment period.
Pts who did not respond to any of the three treatments in the crossover study could enter a fourth, open-label, 2-wk treatment period. This period consisted of flec 150 mg bid and digoxin in a dosage equivalent to baseline to determine whether a higher dosage of flec was required for effective therapy. Safety and efficacy evaluations were repeated at the end of the treatment period. There would be 3 mos and 6 mos of chronic, follow-up therapy in pts whose exercise tolerance improved over baseline during one or more treatment periods.

RESULTS

Study Population: Fourteen pts (6 males, with a mean age of 53.9 years: range, 27 to 68) entered the study. In addition to their arrhythmia diagnosis of chronic AFib, 9 demonstrated PVCs, and 4 pts had nonsusVT at baseline. The most frequent cardiac diagnosis was "valvular disorders and cardiomegaly" (Table 69). Chronic AFib was defined as AFib with a duration of at least 6 mos which had been refractory to attempts at conversion to normal sinus rhythm (NSR), either by antiarrhythmic drug Rx or electrical cardioversion.

Early Termination of Study: The investigator terminated the study on Nov 24, 1987, after ventricular proarrhythmic events during exercise occurred in 3 pts. One of the 3 pts required DC-cardioversion and 1 had sudden death. See cardiac AEs..

Treatment Period Completion: At the time of study termination, 14 pts had entered the study. Ten of 12 pts completed the crossover study; 6/10 entered and completed the open-label, 4th treatment period. Eight of 10 pts continued on long-term Rx; 3/8 completed allowed 6 mos. The investigator did not discontinue the 5 remaining pts in long-term therapy when the study was terminated because he felt they were not at immediate risk for events similar to those above described. At the investigator's option, those 5 pts were later d/ced after either 2 or 3 mos of long-term therapy; discontinuations were not due to AEs.

Discontinuations: Of the 14 pts who entered the study, 4 d/ced before completing the crossover study: 3 due to AEs, 1 VF (Table 70). Of the 3 AEs experiences causing D/C, 1 occurred on digoxin alone and 2 occurred on flec alone. The 4th pt was d/ced because the investigator terminated the study.

Efficacy: Efficacy was objectively evaluated by ETT, 24-hr Holter monitoring and echocardiography during the three blinded treatment periods; subjective evaluation was by pt diary. Only those pts who had efficacy data from all 3 periods were included in the analyses. Ten pts completed the crossover study and had data available for all 3 treatment periods. Two of the 10 pts were excluded from the analyses, because of plasma level results contradictory to assigned drug treatments.

24-Hour Holter Results -- Minimum, mean and maximum HR over each 15-min interval were compared. Statistically and clinically significant differences were found for all 3 results. The flec-digoxin minimum, mean and maximum HR were significantly lower than the flec rates (Table 71).

Efficacy parameters --- Since there was no baseline without medication or placebo Rx that flec effect on HR cannot be determined. No statistically or clinically significant differences between treatments were found for duration of exercise, resting HR, max HR, diastolic BP at max exercise, or max pressure-rate product. Statistically significant differences between treatments were found for systolic BP at max exercise; the flec-digoxin result was significantly higher than both the flec result and the digoxin result (Tables 72 & 73).

Exercise HR Over Time -- Statistically significant differences were found between treatments at 9 and 11 min of exercise. At 9 mins, the flec-digoxin rate. At 11 min, the flec-digoxin HR was significantly lower than both the flec rate and the digoxin rate.

Recovery From Exercise -- A statistically and clinically significant difference between treatments at 0 min post-exercise was found. The flec-digoxin recovery HR was significantly lower than both the flec rate and the digoxin rate (Table 74).

M-Mode Echocardiographic Parameters -- No statistically significant differences between treatments were found for any parameter.

Patient Diary Ratings -- No statistically significant differences between treatments were found.

Anecdotal Data From Period 4 -- Data from this period were not incorporated into the statistical analyses of the three-period crossover study. Six of the 14 pts entered and completed period 4. The reduction in max HR was judged to be clinically significant for the flec 150 mg bid and digoxin combination in 4/6 pts. Changes in duration of exercise, resting HR, and exercise HR at 3, 6, and 9 mins were not clinically significant.

Safety:
Adverse Experiences: During the crossover study, 18% (2/11) of the pts reported at least one AE while taking digoxin alone compared to 33% (4/12) during the time they were receiving flec only and 9% (1/11) during the combination of flec and digoxin. In period 4, 33% (2/6) pts on the combination of flec 150 mg bid and digoxin reported at least one AE. The most commonly reported AEs were dizziness (2), and edema (reported by 1 pt in two different treatment periods). As previously discussed, three of the 14 pts d/ced the study due to AEs.
Investigator-Reported Conduction Disturbances and Arrhythmias During ETT: Of the 12 pts tested by ETT while receiving flec alone, 5 pts were reported to have SVT with aberrant conduction and 1 experienced VF (see cardiac AE below). Fourteen pts completed ETT while receiving digoxin alone; 1 pt was reported to have SVT with aberrant conduction and nonsusVT, and 1 pt experienced nonsusVT. Eleven pts underwent ETT while receiving flec 100 mg bid with digoxin; 3 pts experienced SVT with aberrant conduction. Six pts completed ETT while receiving flec 150 mg bid with digoxin; 1 experienced a wide-complex tachycardia compatible with either SVT with aberrant conduction or VT.

Plasma Flecainide and Digoxin Levels: Overall, the plasma flec levels ranged from 0.00 to 0.99 mcg/mL (mean, .052 mcg/mL) during the crossover study; plasma digoxin levels ranged from 0.5 to 2.5 ng/mL (mean 1.14 ng/mL). Three pts were reported with plasma drug level results contradictory to that treatment period's therapy; 2 pts were not included in the data analyses for this reason and 1 pt d/ced the study in period 1.

Concomitant Medications: All 14 pts received at least one concomitant medication. No clinically significant effects or patterns of interaction could be attributed to concurrent administration of flec and other medication.

Clinical Laboratory Tests: There were no clinically significant or flec-related lab abnormalities found.
Vital Signs: There were not statistically significant differences noted between study periods for vital signs. However, clinically significant increases in HR occurred in 3 pts when their usual digoxin therapy was withdrawn.
ECG Interval Changes: As expected, the QRS interval statistically significantly longer with flec than with digoxin. No statistically or clinically significant differences were found for the QT or JT intervals.

Cardiac AEs: There were 3 pts with proarrhythmia.*

Pt # 1: A 44 y/m developed asymptomatic AFib. He was physically fit and ran 80 miles per week. He had had chronic benign PVCs for several years. Echocardiography showed a mildly dilated left atrium with normal ventricular and valvular function. Holter monitoring during digoxin therapy, 0.5 mg daily (digoxin level, 1.4 nmol/L), showed AFib with a mean dialy HR of 80/min and peak HR of up to 190/min during activity. An asymptomatic 8-beat run of wide complex tachycardia was consistent with either aberant conduction or VT. Exercise testing during digoxin therapy, showed a resting HR of 80, with a rapid rise at a low level of exercise. The pt exercised for 18 to 19 min on three consecutive occasions with a normal BP response and a peak HR of 230 to 250/min with no PVC.
Digoxin was d/ced and flec 100 mg bid was begun. After 2 wks of flec Rx, he had another exercise test. Flec conc at the time of the test was therapeutic (0.4 ug/mL). His peak HR during exercise was 208/min; the exercise duration was similar to that at baselin. There was no PVC during exercise. When the pt stopped exercise because of fatigue, within 10 sec, while still upright, he developed ventricular flutter that evolved into rapid polymorphous VT. The QRS complex immediately preceding the arrhythmia was conducted with an R-R interval of 220 ms. Defibrillation was successful with reversion to AFib. Holter monitoring for 24 hrs after this event showed AFib with moderately frequent couplets and one 4-beat run of VT. A signal-averaged electrocardigram was normal. At discharge he was receiving digoxin an atenolol and another exercise test had shown no ectopy.

Pt # 2: A 35 y/m who had had a prosthetic mitral valve inserted because of mitral stenosis, had poorly controlled AFib despite high-dose digoxin, alone or in combination with beta-blockade and verapamil therapies. Electrical cardioversion had been successful in the past for restoring NSR and improving symptoms, but AFib had always recurred shortly afterward. At catheterization his ejection fraction was 60%, and Holter monitoring showed no evidence of PVC. He received flec, 150 mg bid for 4 wks before a cardioversion attempt, which again restored NSR. However, he reverted to chronic AFib after 2 wks. Because both his HR rate control and symptoms improved, flec 150 mg bid, was continued for 2 mos, and Holter monitoring during this period showed no PVC. Flec was d/ced to be enrolled in a study. In the study, exercise testing was done during digoxin 0.375 mg daily; during flec 100 mg bid; and during therapy with a

combination of the two drugs in the same dosages In all cases, there was no PVC and Holter monitoring during each therapy showed only AFib. After 2 wks of Rx with digoxin, 0.375 mg, and an increased dosage of flec, 150 mg bid, he had another exercise test. The flec conc was 0.58 ug/L and the digoxin conc was 1.5 nmol/L. He exercised for 17 min, 19 sec on a modified Bruce protocol, stopping because of fatigue. His peak HR was 178/min. Within 15 sec of ending exercise, while still standing, his HR regularized and increased to 210/min in a wide complex tachycardia consistent with VT. His BP did not fall significantly and he was aware only of palpitations. The arrhythmia ended abruptly after 2 min with reversion to AFib with narrow complexes and a VR of approximately 100/min. In view or the previously tolerated drug regimen, his flec was reduced to 100 mg bid and the digoxin dose remained at 0.375 mg twice daily. He had another exercise test 4 weeks later during therapy with this combination; ventricular arrhythmia did not occur.

Pt # 3: A 29 y/f had a 2-year Hx of symptomatic, paroxysmal AFib and hypertrophic cardimyopathy. PAFib were poorly controlled with verapamil and quinidine and were associate with dyspnea. She never had dizziness or syncope and when in NSR she was symptom-free. On four occsaions 24-hour Holter monitoring showed frequent atrial ectopic beats but no PVC. She was hospitalized because of recurrent AFib; quinidine and verapamil was d/ced, and she was started on flec, 100 mg bid. The drug was well tolerated, ECG showed no new abnormalities, and she was discharged after a 3-day observation period. One day after discharge she was advised to increase the dose 150 mg bid because of another episode of well-tolerated AFib. Three days later she had an episode of blurred vision lasting about 30 min an unassociated with palpitations or lightheadedness. The blurred vision occured several hours after taking a dose of flec and was not considered to coincide with peak drug level. She was advised to alter the dosage schedule to 100 mg tid and to immediately report any further symptoms. A week later she collapsed and died while waiting for a bus. The terminal rhythm documented by the paramedics was VF from which she could not be resuscitated. An autopsy confirmed the diagnosis of hypertrophic cardiomyopathy with normal coronary arteries.

*Data obtained from the publication Falk RH: "Flecainide-Induced Ventricular Tachycardia and Fibrillation in Patients Treated for Atrial Fibrillation." Annuals of Int Med 111:107-111, 1989.

There were 3 pts with CHF: one pt with a Hx of mild CHF, was reported with an increased HR, right heart failure, and rales when his usual digoxin therapy was withdrawn. He d/ced the study. A second pt experienced peripheal edema during all 3 Rx periods. Diuretic therapy was instituted and maintained for the duration of the study and the digoxin dosage was increased following completion of the crossover study. The edema did not resolve and was present in both period 4 and long-term therapy. A third pt, who had a Hx of mild CHF

and who was taking diuretic therapy, presented with an increased HR and hepatomegaly when digoxin was withdrawn. Digoxin was resumed, symptoms improved and the pt continued into chronic follow-up.

COMMENTS AND CONCLUSION

This study was designed to evaluate HR control of pts with chronic AFib at rest and during ETT. Clinically, oral flec 100 mg bid is effective as adjunctive therapy with digoxin for VR control in chronic AFib compared with flec or digoxin alone. In addition, a suggestion of better ventricular rate control was present at the higher flec dosage of 150 mg bid with digoxin. No definitive statistical conclusions can be made as to the safety and efficacy of oral flec in pts with chronic AFib due to the early termination of the study and the small number of pts in this study.

However, based on this trial, some pts with chronic AFib underlying structural heart disease, and PVC, may develop new ventricluar arrhythmias if exercised to exhaustion while receiving flec. VT/VF developed in 3 pts and 1 of them died. These incidences suggest that pts with chronic AFib may be more susceptible to flec-induced VT/VF. However, until these data are confirmed by further clinical experience with flec and other class IC antiarrhythmic agents, it is prudent to do exercise testing in any patient who is receiving flec for atrial or ventricular arrhythmias and to closely monitor pts at the initiation of antiarrhythmic therapy or when dosage is increased.

G. SUMMARY OF WORLDWIDE POSTMARKETING ADVERSE DRUG EXPERIENCE: 1986, 1987, 1988
Volume 11

The postmarketing adverse drug experience (ADE) reporting during the first 3 yrs (1986, 1987, 1988) of prescription use of flec in the United States have been submitted in the 12 Quarterly Periodic Reports submitted to FDA during those three yrs.

DISTRIBUTION OF FDA 1639s

	US SPONTANEOUS	CLINICAL TRIALS	FOREIGN SPONTANEOUS	TOTAL
SERIOUS				
UNLABELED (15-DAY)	90	125	65	280
LABELED	189	NA	NA	189
NONSERIOUS	243	NA	NA	243
TOTAL	522	125	65	712

There were significantly to the high volume of reports during the first 22 months of marketing was the number of reports classified as "serious" by virtue alone of the "treated with prescription drug" criterion.

A single tabulation of all ADEs reported to FDA during the three yrs, characterized by Body System is submitted (Table 4 vol 11 pages 010-016).

Overall, it is conservatively estimated that 630,000 pts used flec for some period of time during the three yrs ended 12/31/88. That population of pts is the source from which the 712 ADE reports discussed in this section.

In worldwide drug experience reports there were 469 cases "serious" ADEs in which 138 were deaths nearly half of them were related to abnormal cardiac rhythms (Figure 10). Review and analysis of ADE report have reconfirmed the basic safety profile of flec in clinical usage, in the treatment of ventricular and supraventricular arrhythmias.

Tambocor has been approved worldwide and the package insert are similar to that of US labeling pre CAST as of March, 1989.

H. SUMMARY OF EFFICACY DATA

Riker Laboratories, Inc (3M Riker), is seeking Food and Drug Administration (FDA) approval for oral flecainide acetate for the treatment of: 1) PSVT, including (AVNRT), (AVRT) and other SVTs of unspecified mechanism; and 2) (PAF).

There are short-term controlled trials including two trials with concurrent placebo controls and one trial with a dose-response concurrent placebo control; long-term oral therapy trials; and two controlled electrophysiologic trials using oral and/or intravenous (IV) flec.

Short-term trials (R-818-065 and -066) are concurrent placebo control trials to assess the safety and efficacy of flec, at doses up to 400 mg/day, in preventing recurring attacks of symptomatic PSVT. This was a 16-week, double-blind, placebo controlled, randomized crossover study which had three phases: a 4-week Screening Phase; a 3-week Dose Ranging Phase; and a Crossover Phase consisting of two 8-week periods.

During the screening phase, patients documented two attacks of PAT or PAF within 4 wks; at least 1/2 attacks was documented by TTM, the second attack could be by TTM or ECG rhythm strip. Patient-activated telephone transmission of ECGs makes it possible to correlate symptoms with the presence or absence of an underlying attack.

Thirty-four PAT pts, 48 PAF pts completed both placebo and flec treatment periods and were analyzed. The mean age of PAT pts was 50 $\pm$ 15 years; PAF pts was 56 $\pm$ 13 yrs. The median flec dose during treatment was 300 mg per day (range 100 to 400 mg per day).

Combined efficacy results are shown below.

Combined Efficacy Results R-818-065/066
PAT Patients (N=34)

Parameter	Placebo	Flecainide	P-Value
Number (%) of pts with no PSVT events	5 (15%)	27 (79%)	<0.001
Median time to first attack (days)[a]	11	>55	<0.001
Median interval between attacks (days)[a]	12	>55	<0.001

[a]Product-limit estimates for median data were analyzed using the paired Prentice-Wilcoxon test for censored paired data.

Combined Efficacy Results R-818-065/066
PAF Patients (N=48)

Parameter	Placebo	Flecainide	P-Value
Number (%) of pts with no PSVT events	4 (8%)	15 (31%)	0.013
Median time to first attack (days)[a]	3	14.5	<0.001
Median interval between attacks (days)[a]	6.2	27.0	<0.001

In PAT 79% of the pts had no PSVT attacks while receiving flec compared with 15% while receiving placebo ($p < .001$). In addition, the number of pts with at least one PSVT event was 29 on placebo and only 8 on flec ($p < 0.001$). Only 1 pt had an event during flec Rx without having an event during the placebo period. In PAF 31% of the pts had no PAF attacks while receiving flec compared with 8% during placebo Rx ($p = 0.013$).

Both median time to first attack and median interval between attacks are significantly prolonged with flec than placebo Rx ($p < .001$) both PAT and PAF groups. By all efficacy criteria analyzed, flec when compared with placebo significantly reduced or eliminated the recurrence of symptomatic PSVT. This is impressive because the reduction or elimination of symptomatic PSVT was documented by patient-activated TTM transmissions in response to symptomatic attacks. All TTM transmissions were then reviewed and verified by the contract company hired to receive the transmissions, the primary investigator at each study center and by 3M Riker's medical monitor.

R-818-065/066 Transtelephonic Monitoring Results: Forty-nine PAT and 64 PAF pts were included in the analysis of TTM transmissions made during the trials. In PAT pts 443/944 (46.9%) of the calls were asymptomatic (mean HR 79.6 ± 96), and 501 (53.1%) were symptomatic (mean HR 81.0 ± 10.9). Of the 443 asymptomatic call, 6.8% (false negative rate) were associated with an ECG diagnosis of PSVT (mean HR 108 ± 38.7). Over 85% of the symptomatic calls from PAT pts were associated with true PSVT attacks (mean HR 157.6 ± 33.8) and other arrhythmias likely to cause symptoms. Approximately two thirds (62.7%) of the symptomatic calls were related to true PSVT, 22.9% were related to other arrhythmias likely to cause symptoms, and 14.4% (false positive rate) were associate with NSR or other ECG diagnoses considered unlikely to be symptomatic.

In 64 PAF pts, 1061/2375 (44.7%) of the calls were asymptomatic (mean HR 74.7 ± 9.2), and 1314 (55.3%) calls were symptomatic (mean HR 77.4 ± 13.5). Of the 1061 asymptomatic calls 10.6% (false negative rate) were associated with a diagnosis of a PAF attack with mean HR 105.4 ± 25.9. Over 87% of symptomatic calls from PAF pts were associated with true PAF attacks with mean HR 118.2 ± 27.5 and other arrhythmias likely to cause symptoms. Nine hundred nine (69.2%) transmissions documented attacks of true PAF, 18.3% were related to other arrhythmias likely to cause symptoms, and 12.6% (false positive rate) were associated with NSR or other ECG diagnoses considered unlikely to be symptomatic by the 3M Riker medical monitor.

Several symptoms including tachycardia, palpitations, dyspnea, chest pain and dizziness were consistently associated with attacks of PSVT, indicating the reliability of these symptoms as a sign of a PSVT attack with rapid HR. Statistical analysis indicated a significant decrease for tachycardia, palpitations, dyspnea, chest pain, and dizziness for PAT pts during flec Rx.

This analysis of TTM indicates PAT pts' symptoms are associated with their attacks of PSVT, TTM is an effective means of confirming attacks of PSVT, and documents the efficacy of flec in reducing the frequency of symptomatic attacks of PSVT.

Dose-Response Concurrent Placebo Control (R-818-074) was a 20-week, double-blind, placebo-controlled, multicenter, dose-response trial with an initial 4-wk screening phase followed by a dose-response phase consisting of five 4-wk treatment periods.

After qualifying for the study, pts were randomly assigned to one of four different ascending dose Rx sequences. Each treatment sequence consisted of five, 4-wk Rx periods. Four of these periods evaluated oral flec given bid using four ascending dosage regimens (25, 50, 100, and 150 mg bid). A placebo control period was randomly inserted before or during the ascending dosage sequence. Patients recorded paroxysmal supraventricular attacks occurring during each treatment period by TTM or ECG rhythm strip. Patients couls crossover to the next treatment period after four attacks of PAT or PAF, or 4 wks of study drug, whichever occurred first.

Seventy-three pts (PAT 28, PAF 45) were enrolled the study and 45 (PAT 17, PAF 28) completed the study and 42 pts data (PAT 14, PAF 28) were analyzed. An analysis of variance showed a significant ($P < .001$) linear dose-response in the percentage of both PAT and PAF pts remained attack free. The time to first attack and the median interval between attacks and median rate of attacks were significantly increased for 100 and 150 mg bid flecainide when compared to placebo.

LONG TERM TRIALS

All pts participating in these amendments had previously completed the double-blind efficacy studies (R-818-065 and R-818-066) or the double-blind dose-response study (R-818-074) and had received a minimum of 6 mos of uninterrupted open-label flec Rx since completion of those studies. Pts were instructed to continue the same flec dosage they had been receiving during long-term Rx for the duration of the amendment period. During this time, pts were instructed to record all symptomatic attacks of PAT or PAF by TTM and to report all symptoms associated with each attack.

Thirty-two pts (PAT 14, PAF 18) were entered in this chronic study and 30 (PAT 14, PAF 16) completed the study and 26 pts data (PAT 10, PAF 16) were analyzed. Compared to the placebo period of the parent studies, significantly more PAT/PAF pts were free of attacks, had longer interval time between attacks and intervals of time until the first attack. No statistically significant differences were found for any parameters between flec Rxs during short-term studies and chronic efficacy study.

EP studies pre and post IV or oral flec (IND were done in 27 pts and 12/21 (57%) with AVRT ard 4/6 (67%) pts with inducible at baseline were no longer inducible followi.g IV flec. EP study showed that flec had a dramatic depressant effect on retrograde accessory pathway conduction and to a lesser degree of depressant effect on anterograde conduction over the accessory pathway. Because a small number pts were followed with oral flec that comparison of EP results on oral an IV flec could not be made in this study. Similar results were observed on 21 pts in study R-818-065 Amendment A. The study R-818-EG-11 where preselected IV flec EP study repsponders 16/17 pts maintained the drug efficacy with chronic oral Rx.

These clinical controlled studies and EP studies showed oral flec 200-300 mg/day effectively presented recurrence of PSVT due to AVRT, AVNRT, WPW and AFib.

The most commonly reported AEs remained consistent with those known for pts treated with flec for VAs. The incidences in these studies for PAT, PAF, and WPW pts were generally higher, however, than those reported for pts with VAs, probably partially due to many pts were dosed to tolerance rather than efficacy. As expected, numbers of pts reporting AEs increased with increasing doses. AEs generally decreased with increased time on drug. However, the total number of patients under treatment also decreased with time.

Overall, incidences including cardiac AEs, were similar to seen with pts with VAs, with the exception of higher incidences of dyspnea, headache, nausea, and flushing in PAT pts.

Proarrhythmia was observed 1/108 PAT pts, 8/117 PAF pts (one resulted in death), 0/35 WPW pts, 3/14 chronic AFib pts (one sudden death). One PAT pt had possible MI and 1 WPW pt had sinus pause probably preexisting condition.

Incidences of patients discontinuing study participation due to noncardiac AEs were similar for PAT, PAF and WPW patients, ranging from 8% to 14% of pts. Two of 108 (2%) PAT pts d/ced due to cardiac AEs. One of the two cardiac AEs was a proarrhythmic event. No PAT patient died. Discontinuation due to lack of efficacy was 3% for PAT pts.
Ten of 117 (8%) PAF pts d/ced due to cardiac AEs: 2 (2%) for conduction disturbances and 8 (7%) due to proarrhythmic events. One of the proarrhythmic events (1%) resulted in death. Seven percent of PAF pts discontinued due to lack of efficacy.
No WPW patient died or d/ced due to a cardiac AEs or a proarrhythmic event. D/C due to lack of efficacy was 3% for WPW pts.

Independent study R-818-075-01 for chronic AFib was terminated early after 14 pts enrollment due to 3 proarrhythmic events: 1 developed vent flutter/VT immediately after ETT which required DC-cardioversion, 1 sudden death a week after 100 mg tid dosing, 1 self terminated susVT within 15 sec of ending exercise while on digoxin 0.375 mg and flec 150 mg bid for 2 wks. This pt continued the study with a reduced flec dose 100 mg bid.

CHF (new or worsened) was 1/108 PAT pts, 0/117 PAF pts, 3/14 chronic AFib pts.

SUMMARY OF BENEFITS AND RISKS

The efficacy of flec in preventing recurrence of PAT associated symptoms was clearly documented using pt activated TTM. Clearcut efficacy was seen in PAT pts with AVNRT, AVRT, WPW and pts with unspecified mechanisms of arrhythmia. The AEs associated with flec in the treatment of PAT pts were mild, reversible and similar to those seen in VA pts. PAT pts may have highly symptomatic arrhythmias, with syncope, angina, CHF, shock and pulmonary edema as consequences. The risks of flec for PAT pts appear low; the benefits appear worth the low risk.

Although the efficacy of flec in the total elimination of attacks of PAF is not as striking as in PAT, no other drug has shown such clear evidence of efficacy in preventing recurrences of PAF. Notably, pts with complete eradication of episodes of PAF were counted in the analysis, ignoring the pts who were improved but not 100% attack free. PAF pts may benefit from effective treatment of their arrhythmia, because PAF can also cause syncope, angina, CHF, shock and pulmonary edema. Further, PAF pts are at increased risk of stroke, which can be disabling or fatal. PAF pts had more cardiac AEs than PAT pts, including the only pt who died from a possible proarrhythmic effect while on flec in the PAT/PAF clinical trials program. The other

cardiac AEs reported for PAF pts were not life-threatening, and the risks of flec Rx for PAF pts appear to be balanced by benefits. Flec is an effective treatment for PAF, however, the risk may outweigh.

In the WPW subset of pts, efficacy was consistent with the results seen for the major set of PSVT. This remarkable efficacy was seen in pts refractory and potentially life-threatening arrhythmias who were referred to tertiary care centers after failure of standard approaches. No WPW pt in the 3M Riker clinical trials program discontinued flecainide for a cardiac AE. The small number of pts enrolled in each study with this relatively uncommon disorder precluded statistical analysis of this subset. Although the number of pts studied was small, the arrhythmia control was consistent with that seen with PAT and PAF pts overall. Given the highly symptomatic and potentially life-threatening nature of WPW syndrome, the benefits of flec in this subset of SVT pts outweigh the risks.

Flecainide provides a positive benefit/risk equation for supraventricular arrhythmias, representing a major contribution to the therapeutic armamentarium.

RECOMMENDATION

I recommended the approval of flec for the prevention of recurrent PSVT due to AVNRT and AVRT including WPW. However, indications for PSVT be limited to seriously symptomatic pts only and not asymptomatic or trivial symptomatic pts due to its proarrhythmic potential. Chronic flec treatment for prevention of PAFib is debatable.

S.K. Chun 9/15/89

Sughok K. Chun, MD HFD-110

cc: Orig. NDA
HFD-110
HFD-110/CSO
HFD-110/SChun
ml:9/15/89:#0587a

Indication 1: Paroxysmal Supraventricular Tachycardias

Drug: Flecainide Acetate
Route: Oral

Table 1

Controlled Clinical Trials
Table of Studies

Study No. or Report Title, Investigators, Publication	Completion Status, Starting Date	Location, Product Code	Study Design	Treatment, Doses	Duration of Treatment	Patient Population: No. Enrolled	Patient Population: Age Range (mean)	Patient Population: Sex M/F	Location of: Full Report (R) Data Listings (D)	Location of: CRFs
Concurrent Placebo Control										
R-818-065 Multicenter (see Table 5) J Am Cardiac Coll 11(2):77A, 1988	Complete Jan 1985	US, Canada	DB, randomized X-over, placebo-controlled safety and efficacy with open-label, dose-ranging (DR) lead-in to tolerance	Flecainide: DR 50-200 mg bid DB 100-200 mg bid Placebo: bid	 ≤ 3 wks ≤ 8 wks ≤ 8 wks	34	18-78 (48.9)	9/25	(R) Vol 1-2 (D) Vol 21-22	Vol 29, Pg 178 to Vol 31, Pg 196
R-818-066 Multicenter (see Table 6) J Am Cardiac Coll 11(2):77A, 1988	Complete Jan 1985	US	DB, randomized X-over, placebo-controlled safety and efficacy with open-label, dose-ranging (DR) lead-in to tolerance	Flecainide: DR 50-200 mg bid DB 50-200 mg bid Placebo: bid	 ≤ 3 wks ≤ 8 wks ≤ 8 wks	17	22-74 (49.8)	6/11	(R) Vol 3 (D) Vol 23	Vol 31, Pg 197 to Vol 32, Pg 88
Dose-Comparison Concurrent Control										
R-818-074 Multicenter (see Table 7)	Complete Aug 1986	US	DB, randomized X-over, placebo-controlled dose response	Flecainide: 25 mg bid 50 mg bid 100 mg bid 150 mg bid Placebo: bid	 ≤ 4 wks ≤ 4 wks ≤ 4 wks ≤ 4 wks ≤ 4 wks	28	18-65 (44.8)	17/11	(R) Vol 5-6 (D) Vol 24-25	Vol 32, Pg 173 to Vol 36, Pg 188

Table 1 (cont'd)

Indication 1: Paroxysmal Supraventricular Tachycardias

Controlled Clinical Trials
Table of Studies (concluded)

Drug: Flecainide Acetate
Route: Oral

Study No. or Report Title, Investigators, Publication	Completion Status, Starting Date	Location, Product Code	Study Design	Treatment, Doses	Duration of Treatment	Patient Population: No. Enrolled	Patient Population: Age Range (mean)	Patient Population: Sex M/F	Location of: Full Report (R) Data Listings (D)	Location of: CRFs
				Historical Control						
Long-Term Therapy 065/066 Multicenter (see Table 8)	Complete May 1985	US	Open-label, long-term therapy in effectively treated pts who completed studies 065 and 066	Flecainide 50-400 mg/day	1-30 mos	25	18-78 (49.3)	9/16	(R) Vol 7	Vol 29, Pg 371 Vol 30, Pg 1-304 Vol 32, Pg 88
Chronic Efficacy 065/066/074 Multicenter (See Table 9)	Ongoing June 1988	US	Open-label efficacy evaluation during long-term therapy in pts from studies 065, 066, and 074	Flecainide 100-400 mg/day	4 or 8 wks	14	29-67 (56)	6/8	(R) Vol 8 (D) Vol 25	Vol 32, Pg 173
IND Oral Ruffy, R.	Ongoing June 1983	US	Open-label, long-term therapy following EPS testing with IV drug	Flecainide 150-400 mg/day	1 day-45 mos	30	16-71 (39.7)	19/11	(R) Vol 8 (D) Vol 26	Vol 27, Pg 37 to Vol 29, Pg 177
R-818-074 Chronic Use Phase (Multicenter) (see Table 10)	Ongoing Mar 1987	US	Open-label, long-term therapy in effectively treated pts who completed study 074	Flecainide 100-400 mg/day	≤ 1 year	18	18-65 (49.4)	9/9	(R) Vol 9	--
R-818-077 Multicenter (see Table 11)	Ongoing Mar 1988	US	Open-label safety and efficacy study	Flecainide 100-400 mg/day	≤ 1 year	142[a]	unknown		(R) Vol 9	Vol 36, Pg 385

[a] The reported enrollment for this study totals 142 patients. Due to the ongoing status, the number of patients with paroxysmal supraventricular tachycardias and their ages and sexes are unknown at this time.

Table 1 (cont'd)

Indication 2: Paroxysmal Atrial Fibrillation/Flutter

Controlled Clinical Trials
Table of Studies

Drug: Flecainide Acetate
Route: Oral

Study No. or Report Title, Investigators, Publication	Completion Status, Starting Date	Location, Product Code	Study Design	Treatment, Doses	Duration of Treatment	Patient Population: No. Enrolled	Age Range (mean)	Sex M/F	Location of: Full Report (R) Data Listings (D)	CRFs
Concurrent Placebo Control										
R-818-065 Multicenter (see Table 5) J Am Cardiac Coll 11(2):77A,1988	Complete Jan 1985	US, Canada	DB, randomized X-over, placebo-controlled safety and efficacy with open-label, dose-ranging (DR) lead-in to tolerance	Flecainide: DR 50-200 mg bid DB 100-200 mg bid Placebo: bid	 ≤ 3 wks ≤ 8 wks ≤ 8 wks	39	23-73 (56.0)	25/14	(R) Vol 1-2 (D) Vol 21-22	Vol 29, Pg 178 to Vol 31, Pg 196
R-818-066 Multicenter (see Table 6) J am Cardiac Coll 11(2):77A,1988	Complete Jan 1985	US	DB, randomized X-over, placebo-controlled safety and efficacy with open-label, dose-ranging (DR) lead-in to tolerance	Flecainide: DR 50-300 mg bid DB 50-300 mg bid Placebo: bid	 ≤ 3 wks ≤ 8 wks ≤ 8 wks	25	24-83 (59.5)	15/10	(R) Vol 3 (D) Vol 23	Vol 31, Pg 197 to Vol 32, Pg 88
R-818-078 Bhandari, AK Pritchett, ELC Webb, CR	Incomplete Nov 1986	US	Single-blind, placebo-controlled efficacy evaluation during long-term therapy	Flecainide 150 mg bid Placebo: bid	4 wks 4-8 wks	2	63-71 (67.0)	2/0	(R) Vol 9	--
Dose-Comparison Concurrent Control										
R-818-074 Multicenter (see Table 7)	Complete Aug 1986	US	DB, randomized X-over, placebo-controlled dose response	Flecainide: 25 mg bid 50 mg bid 100 mg bid 150 mg bid Placebo: bid	 ≤ 4 wks ≤ 4 wks ≤ 4 wks ≤ 4 wks ≤ 4 wks	45	21-82 (59.8)	27/18	(R) Vol 5-6 (D) Vol 24-25	Vol 32, Pg 173 to Vol 36, Pg 188

Table 8 (Cont'd.)

Controlled Clinical Trials
Table of Studies (Concluded)

Indication 2: Paroxysmal Atrial Fibrillation/Flutter

Drug: Flecainide Acetate
Route: Oral

Study No. or Report Title, Investigators, Publication	Completion Status, Starting Date	Location, Product Code	Study Design	Treatment, Doses	Duration of Treatment	Patient Population: No. Enrolled	Patient Population: Age Range (mean)	Patient Population: Sex M/F	Location of: Full Report (R) Data Listings (D)	Location of: CRFs
				Historical Control						
Long-Term Therapy 065/066 Multicenter (see Table 8)	Complete May 1985	US	Open-label, long-term therapy in effectively treated pts who completed studies 065 and 066	Flecainide 100-600 mg/day	1-32 mos	41	23-83 (56.0)	29/12	(R) Vol 7	Vol 29, Pg 371 Vol 30, Pg 1-304 Vol 32, Pg 88
Chronic Efficacy 065/066/074 Multicenter (See Table 9)	Ongoing June 1988	US	Open-label efficacy evaluation during long-term therapy in pts from studies 065, 066, and 074	Flecainide 100-400 mg/day	4 or 8 wks	18	36-86 (61)	8/10	(R) Vol 8 (D) Vol 25	Vol 32, Pg 173
R-818-074 Chronic Use Phase Multicenter (see Table 10)	Ongoing Mar 1987	US	Open-label, long-term therapy in effectively treated pts who completed study 074	Flecainide 100-400 mg/day	≤ 1 year	28	21-82 (60.5)	15/13	(R) Vol 8 (D) Vol 26	Vol 27, Pg 37 to Vol 29, Pg 177
R-818-077 Multicenter (see Table 11)	Ongoing Mar 1988	US	Open-label safety and efficacy study	Flecainide 100-400 mg/day	≤ 1 year	142[a]	unknown		(R) Vol 9	Vol 36, Pg 385

[a] The reported enrollment for this study totals 142 patients. Due to the ongoing status, the number of patients with paroxysmal atrial fibrillation/flutter and their ages and sexes are unknown at this time.

Table 1 (cont'd)

Indication 1: Paroxysmal Supraventricular Tachycardias

Controlled Clinical Trials
Table of Studies

Drug: Flecainide Acetate
Route: Intravenous

Study No. or Report Title, Investigators, Publication	Completion Status, Starting Date	Location, Product Code	Study Design	Treatment, Doses	Duration of Treatment	Patient Population: No. Enrolled	Patient Population: Age Range (mean)	Patient Population: Sex M/F	Location of: Full Report (R) Data Listings (D)	Location of: CRFs
				Historical Control						
R-818-065, Amendment A Multicenter (see Table 12)	Complete	US, Canada	Open-label study of effects of IV drug on EP measurements	Flecainide 2-3 mg/kg	one dose	16	23-78 (52.2)	3/13	(R) Vol 9	Vol 28, Pg 273 Vol 29, Pg 178 Vol 30, Pg 264
IND IV & Oral EPS Ruffy, R.	Complete June 1983	US	Open-label study of effects of drug on mechanism of arrhythmia before and after flecainide	Flecainide 1-3 mg/kg IV 200-500 mg/day, oral	one dose 1-21 days	30	16-71 (39.7)	19/11	(R) Vol 8 (D) Vol 26	Vol 28, Pg 273
				Historical Control						
R-818-065, Amendment A Multicenter (see Table 12)	Complete	US, Canada	Open-label study of effects of IV drug on EP measurements	Flecainide 2-3 mg/kg	one dose	5	34-64 (53.0)	3/2	(R) Vol 9	Vol 28, Pg 273 Vol 29, Pg 178 Vol 30, Pg 264

Table 2

STUDY R-818-065

List of Principal Investigators and Number of Patients Enrolled by Study Number

Study Number	Investigator	No. of Patients Enrolled Indication 1[a]	Indication 2[b]	Total
R-818-065-01	Barry Alpert, MD	10	11	21
R-818-065-02	Michael Brodsky, MD	2	3	5
R-818-065-04	George Klein, MD	6	2	8
R-818-065-05	Gerald Naccarelli, MD	2	0	2
R-818-065-06	Jeremy Ruskin, MD	1	1	2
R-818-065-07	Paul Troup, MD	1	0	1
R-818-065-08	Al Waldo, MD	5	7	12
R-818-065-09	John Di Marco, MD	0	2	2
R-818-065-10	Anil Bhandari, MD	5	5	10
R-818-065-11	Michael Rosengarten, MD	1	2	3
R-818-065-12	Raymond Woosley, MD	1	2	3
R-818-065-14	Charles Webb, MD	0	4	4
	Total	34	39	73

[a] Indication 1: Paroxysmal supraventricular tachycardias.
[b] Indication 2: Paroxysmal atrial fibrillation/flutter

STUDY R-818-066

List of Principal Investigators and Number of Patients Enrolled by Study Number

Study Number	Investigator	No. of Patients Enrolled Indication 1[a]	Indication 2[b]	Total
R-818-066-01	Jeffrey Anderson, MD	5	10	15
R-818-066-03	William Hart, MD	2	2	4
R-818-066-04	L. David Hillis, MD	3	1	4
R-818-066-05	James Laidlaw, MD	6	3	9
R-818-066-06	Edward Pritchett, MD	0	2	2
R-818-066-07	Rodolphe Ruffy, MD	0	4	4
R-818-066-08	Leonard Horowitz, MD	1	3	4
R-818-066-09	Mark Platt, MD	0	0	0
	Total	17	25	42

Table 2 (cont'd)

STUDY R-818-074

List of Principal Investigators and Number of Patients Enrolled by Study Number

Study Number	Investigator	No. of Patients Enrolled Indication 1[a]	Indication 2[b]	Total
R-818-074-01	Barry Alpert, MD	0	2	2
R-818-074-02	G. Neal Kay, MD	1	4	5
R-818-074-04	Irvin Goldenberg, MD	0	2	2
R-818-074-05	J. Anthony Gomes, MD	3	2	5
R-818-074-06	Thomas Guarnieri, MD	4	4	8
R-818-074-07	Charles Haffajee, MD	2	4	6
R-818-074-08	Morrison Hodges, MD	0	2	2
R-818-074-09	Leonard Christie, Jr., MD	0	3	3
R-818-074-10	Syed Mohiuddin, MD	2	2	4
R-818-074-11	Kenneth Ellenbogen, MD	4	3	7
R-818-074-12	Edward Pritchett, MD	6	0	6
R-818-074-14	Marc Platt, MD Benjamin Rosin, MD	1	5	6
R-818-074-18	Jeffrey Anderson, MD	1	2	3
R-818-074-20	Douglas Zipes, MD	0	2	2
R-818-074-21	James Foster, MD	2	5	7
R-818-074-25	Anil Bhandari, MD	2	1	3
R-818-074-26	Charles Webb, MD	0	2	2
	Total	28	45	73

[a] Indication 1: Paroxysmal supraventricular tachycardias
[b] Indication 2: Paroxysmal atrial fibrillation/flutter

LONG-TERM THERAPY, R-818-065 AND R-818-066

List of Principal Investigators and Number of Patients Who Completed Studies R-818-065 and R-818-066 and Continued on Long-Term Therapy by Study Number

Study Number	Investigator	No. of Patients Enrolled Indication 1[a]	Indication 2[b]	Total
R-818-065-01	Barry Alpert, MD	2	7	9
R-818-065-03	Gerald Naccarelli, MD	2	0	2
R-818-065-06	Jeremy Ruskin, MD	1	1	2
R-818-065-07	Paul Troup, MD	1	0	1
R-818-065-08	Al Waldo, MD	3	3	6
R-818-065-10	Anil Bhandari, MD	2	5	7
R-818-065-12	Raymond Woosley, MD	1	1	2
R-818-065-14	Charles Webb, MD	0	3	3
R-818-066-01	Jeffrey Anderson, MD	5	9	14
R-818-066-03	William Hart, MD	2	2	4
R-818-066-04	L. David Hillis, MD	2	1	3
R-818-066-05	James Laidlaw, MD	3	3	6
R-818-066-06	Edward Pritchett, MD	0	1	1
R-818-066-07	Rodolphe Ruffy, MD	0	3	3
R-818-066-08	Leonard Horowitz, MD	1	2	3
	Total	25	41	66

Table 2 (cont'd)

CHRONIC EFFICACY, STUDIES R-818-065, R-818-066, AND R-818-074

List of Principal Investigators and Number of Patients From Studies R-818-065, R-818-066, and R-818-074 Who Enrolled in the Chronic Efficacy Amendments by Study Number

Study Number	Investigator	No. of Patients Enrolled Indication 1[a]	Indication 2[b]	Total
R-818-065-01	Barry Alpert, MD	1	1	2
R-818-065-14	Charles Webb, MD	0	2	2
R-818-066-01	Jeffrey Anderson, MD	3	3	6
R-818-066-03	William Hart, MD	1	2	3
R-818-066-05	James Laidlaw, MD	0	1	1
R-818-066-06	Edward Prichett, MD	0	1	1
R-818-074-02	G. Neal Kay, MD	0	2	2
R-818-074-05	J. Anthony Gomes, MD	1	0	1
R-818-074-06	Thomas Guarnieri, MD	2	2	4
R-818-074-07	Charles Haffajee, MD	0	1	1
R-818-074-09	Leonard Christie, Jr., MD	0	2	2
R-818-074-11	Kenneth Ellenbogen, MD	3	0	3
R-818-074-12	Edward Pritchett, MD	3	0	3
R-818-074-18	Jeffrey Anderson, MD	0	1	1
	Total	14	18	32

[a] Indication 1: Paroxysmal supraventricular tachycardias
[b] Indication 2: Paroxysmal atrial fibrillation/flutter

TABLE 10

STUDY R-818-074, LONG-TERM THERAPY

List of Principal Investigators and Number of Patients Who Completed Study R-818-074 and Continued on Long-Term Therapy by Study Number

Study Number	Investigator	No. of Patients Enrolled Indication 1[a]	Indication 2[b]	Total
R-818-074-02	G. Neal Kay, MD	0	2	2
R-818-074-05	Irvin Goldenberg, MD	0	1	1
R-818-074-05	J. Anthony Gomes, MD	3	1	4
R-818-074-06	Thomas Guarnieri, MD	3	4	7
R-818-074-07	Charles Haffajee, MD	1	3	4
R-818-074-08	Morrison Hodges, MD	0	2	2
R-818-074-09	Leonard Christie, Jr., MD	0	3	3
R-818-074-10	Syed Mohiuddin, MD	0	1	1
R-818-074-11	Kenneth Ellenbogen, MD	3	0	3
R-818-074-12	Edward Pritchett, MD	5	0	5
R-818-074-14	Marc Platt, MD Benjamin Rosin, MD	1	5	6
R-818-074-18	Jeffrey Anderson, MD	0	1	1
R-818-074-20	Douglas Zipes, MD	0	2	2
R-818-074-21	James Foster, MD	1	3	4
R-818-074-25	Anil Bhandari, MD	1	0	1
	Total	18	28	46

Table 2 (Cont'd)

STUDY R-818-077

List of Principal Investigators and Reported Number of Patients Enrolled by Study Number

Study Number	Investigator	Reported No. of Patients Enrolled[a]
R-818-077-01	Karen Beckman, MD	7
R-818-077-02	William Mandel, MD	10
R-818-077-03	James Porterfield, MD	10
R-818-077-04	Mike Kienzle, MD	10
R-818-077-05	Paul Fenster, MD	3
R-818-077-06	Robert Rinkenberger, MD	8
R-818-077-07	Koonlawee Nademanee, MD	10
R-818-077-08	Mark Josephson, MD Alfred Buxton, MD	10
R-818-077-09	J. Thomas Bigger, MD	3
R-818-077-10	Alberto Interian, MD	4
R-818-077-12	Daniel Wise, MD	11
R-818-077-13	Philip Podrid, MD	3
R-818-077-15	Kelly Anderson, MD	3
R-818-077-16	Charles Haffajee, MD	7
R-818-077-17	Bing Liem, DO	10
R-818-077-18	Edward Shen, MD	10
R-818-077-19	Allen Kadish, MD	10
R-818-077-20	Stephen Schaal, MD	2
R-818-077-21	Masood Akhtar, MD	10
R-818-077-22	Andres Ticzon, MD	1
R-818-077-23	Theodore Wang, MD	0
	Total	142

[a] Due to the ongoing status, the numbers of patients with paroxysmal supraventricular tachycardias and paroxysmal atrial fibrillation/flutter are unknown.

STUDY R-818-065, AMENDMENT A

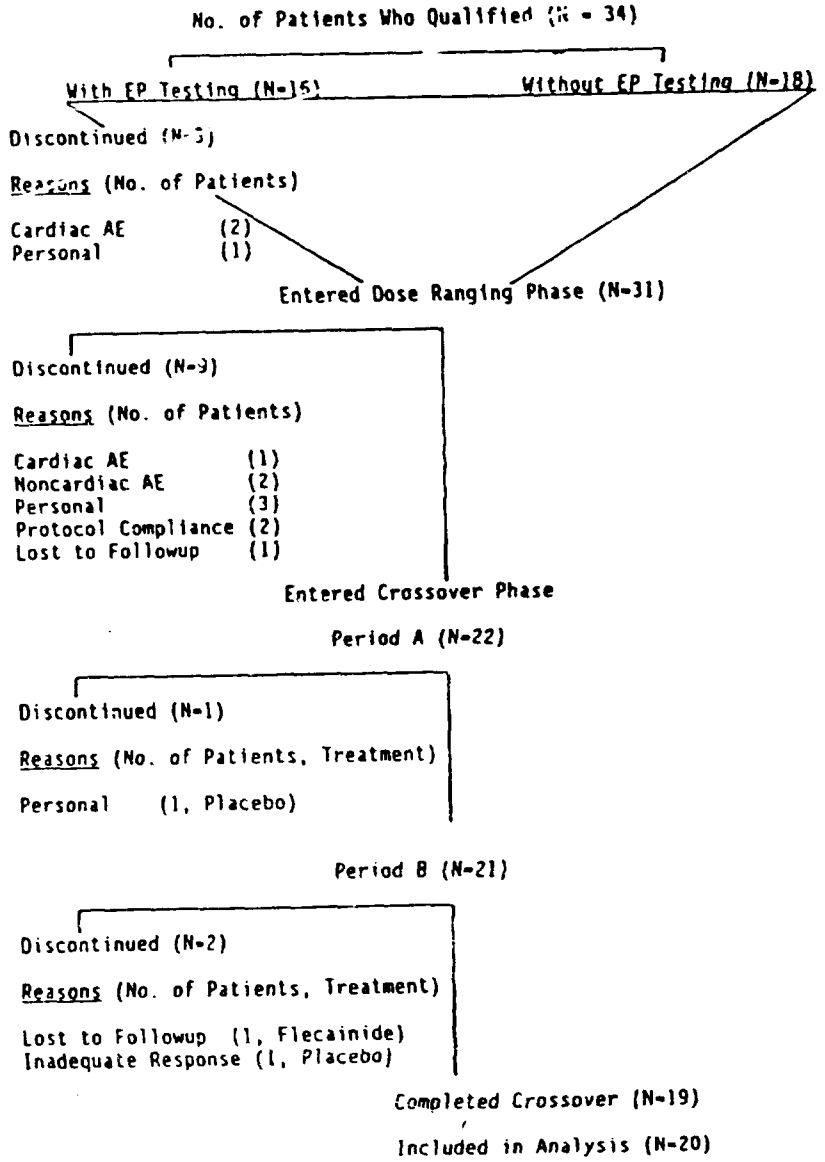
List of Principal Investigators and Number of Patients Who Received Intravenous Flecainide in Amendment A by Study Number

		No. of Patients Enrolled Indication		
Study Number	Investigator	1[a]	2[b]	Total
R-818-065-01	Barry Alpert, MD	8	3	11
R-818-065-04	George Klein, MD	4	0	4
R-818-065-08	Al Waldo, MD	3	2	5
R-818-065-10	Anil Bhandari, MD	1	0	1
	Total	16	5	21

[a] Indication 1: Paroxysmal supraventricular tachycardias
[b] Indication 2: Paroxysmal atrial fibrillation/flutter

Table 3 (R-818-065)

NUMBER OF PATIENTS ENROLLED AND PATIENT ACCOUNTABILITY THROUGHOUT THE STUDY: PAT PATIENTS



NUMBER OF PATIENTS ENROLLED AND PATIENT ACCOUNTABILITY THROUGHOUT THE STUDY: PAF PATIENTS

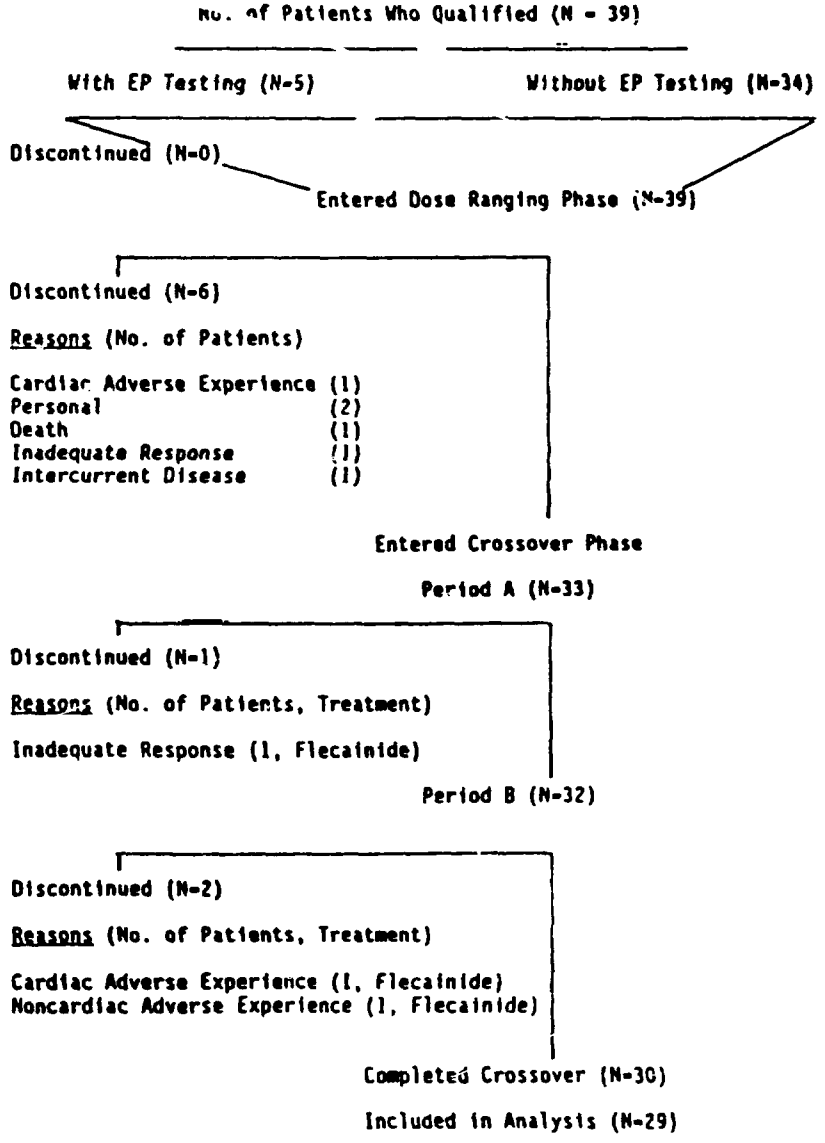


Table 4. (R-818-065)

HISTORICAL SYMPTOMS[a] ASSOCIATED WITH PSVT ATTACKS:
PAT PATIENTS

SYMPTOM[b]	NO. OF PATIENTS REPORTING (%) ALL PATIENTS (N=33)	PATIENTS INCLUDED (N=20)	PATIENTS EXCLUDED[c] (N=13)	COMPARISON[d] P-VALUE
PALPITATION	29 (88%)	18 (90%)	11 (85%)	1.000
ASTHENIA	24 (73%)	13 (65%)	11 (85%)	0.263
DIZZINESS	21 (64%)	13 (65%)	8 (62%)	1.000
FATIGUE	19 (58%)	11 (55%)	8 (62%)	1.000
SYNCOPE	7 (21%)	4 (20%)	3 (23%)	1.000
DYSPNEA	6 (18%)	5 (25%)	1 (8%)	0.364
CHEST PAIN	4 (12%)	1 (5%)	3 (23%)	0.276
TACHYCARDIA	3 (9%)	3 (15%)	0 (0%)	0.261
OTHER[e]	6 (18%)	4 (20%)	2 (15%)	1.000

[a] PATIENTS COULD REPORT MORE THAN ONE SYMPTOM.
[b] WORLD HEALTH ORGANIZATION PREFERRED TERM.
[c] ONE PATIENT DID NOT HAVE INFORMATION COLLECTED REGARDING HISTORICAL SYMPTOMS.
[d] P-VALUE ASSOCIATED WITH THE STATISTICAL COMPARISON OF INCLUDED AND EXCLUDED PATIENTS (SEE APPENDIX III FOR DETAILS).
[e] INCLUDES SYMPTOMS OF ANXIETY, INCREASING SWEATING, NAUSEA, VOMITING, AND ERUCTATION.

HISTORICAL SYMPTOMS[a] ASSOCIATED WITH PSVT ATTACKS:
PAF PATIENTS

SYMPTOM[b]	NO. OF PATIENTS REPORTING (%) ALL PATIENTS (N=39)	PATIENTS INCLUDED (N=29)	PATIENTS EXCLUDED (N=10)	COMPARISON[c] P-VALUE
PALPITATION	34 (87%)	25 (86%)	9 (90%)	1.000
ASTHENIA	26 (67%)	18 (62%)	8 (80%)	0.445
FATIGUE	21 (54%)	14 (48%)	7 (70%)	0.290
DIZZINESS	15 (39%)	10 (35%)	5 (50%)	0.463
DYSPNEA	10 (26%)	7 (24%)	3 (30%)	0.696
TACHYCARDIA	6 (15%)	5 (17%)	1 (10%)	1.000
CHEST PAIN	6 (15%)	5 (17%)	1 (10%)	1.000
NEAR SYNCOPE	3 (8%)	3 (10%)	0 (0%)	0.556
OTHER[d]	8 (21%)	8 (28%)	0 (0%)	0.086

[a] PATIENTS COULD REPORT MORE THAN ONE SYMPTOM.
[b] WORLD HEALTH ORGANIZATION PREFERRED TERM.
[c] P-VALUE ASSOCIATED WITH THE STATISTICAL COMPARISON OF INCLUDED AND EXCLUDED PATIENTS (SEE APPENDIX III FOR DETAILS).
[d] INCLUDED SYMPTOMS OF PARESTHESIA, HYPOESTHESIA, NAUSEA, INCREASED SWEATING, ANXIETY, CONFUSION, ARRHYTHMIA, ABNORMAL VISION, POLYURIA, DYSPEPSIA.

Table 5. (R-818-065)

QUALIFICATION SUMMARY: PAT PATIENTS

DAYS TO SECOND ATTACK IN SCREENING	ALL PATIENTS (N = 34[a])		PATIENTS INCLUDED (N = 20)		PATIENTS EXCLUDED (N = 14[a])	
	N	%	N	%	N	%
2 - 7	11	(32)	5	(25)	6	(43)
8 - 14	5	(15)	3	(15)	2	(14)
15 - 21	8	(24)	7	(35)	1	(7)
22 - 28	2	(6)	1	(5)	1	(7)
>28	2	(6)	1[b]	(5)	1[c]	(7)
TOTAL	28	(82)	17[d]	(85)	11[e]	(85)
MEAN ± SD[f]			13.9 ± 8.2		11.4 ± 12.9	

[a] THE PATIENT WHO DISCONTINUED AFTER EP TESTING NEVER RECEIVED A TRANSTELEPHONIC MONITOR.
[b] PATIENT HAD TWO ATTACKS IN 31 DAYS.
[c] PATIENT HAD TWO ATTACKS IN 43 DAYS.
[d] THREE PATIENTS HAD ONLY ONE ATTACK.
[e] ONE PATIENT HAD ONLY ONE ATTACK; ONE HAD TWO ATTACKS, BUT BOTH WERE RECORDED ON THE SAME DAY.
[f] P-VALUE COMPARISON OF INCLUDED AND EXCLUDED PATIENTS, P < 0.532.

QUALIFICATION SUMMARY: PAF PATIENTS

DAYS TO SECOND ATTACK IN SCREENING	ALL PATIENTS (%) (N = 39)		PATIENTS INCLUDED (N = 29)		PATIENTS EXCLUDED (N = 10)	
	N	%	N	%	N	%
2 - 7	26	(67)	18	(62)	8	(80)
8 - 14	5	(13)	4	(14)	1	(10)
15 - 21	6	(15)	5	(17)	1	(10)
22 - 28	1	(3)	1	(3)	0	(0)
>28	1[a]	(3)	1	(3)	0	(0)
TOTAL	39	(100)	29	(100)	10	(100)
MEAN ± SD[b]			9.2 ± 7.4		6.3 ± 6.0	

[a] PATIENT HAD TWO ATTACKS IN 29 DAYS.
[b] P-VALUE OF T-TEST COMPARING INCLUDED AND EXCLUDED PATIENTS, P < 0.257.

Table 6 (R818-065)

PSVT ATTACK SYMPTOMS EXPERIENCED
DURING SCREENING: PAT PATIENTS

SYMPTOMS REPORTED WHO[a] PREFERRED TERM	NO. OF PATIENTS REPORTING ALL (%) (N = 33)	INCLUDED (%) (N = 20)	EXCLUDED (%) (N = 13)
TACHYCARDIA	24 (73)	16 (80)	8 (62)
PALPITATION	14 (42)	9 (45)	5 (38)
DYSPNEA	9 (27)	8 (40)	1 (8)
DIZZINESS	7 (21)	5 (25)	2 (15)
ASTHENIA	5 (15)	4 (20)	1 (8)
FATIGUE	6 (18)	4 (20)	2 (15)
HEADACHE	3 (9)	2 (10)	1 (8)
CHEST PAIN	4 (12)	2 (10)	2 (15)
SWEATING INCREASED	1 (3)	1 (5)	0 (0)
MYALGIA	1 (3)	1 (5)	0 (0)
ANXIETY	1 (3)	1 (5)	0 (0)
SOMNOLENCE	1 (3)	1 (5)	0 (0)
VOMITING	1 (3)	1 (5)	0 (0)
TACHYCARDIA SUPRAVENTRICULAR	2 (6)	1 (5)	1 (8)
DYSPEPSIA	1 (3)	1 (5)	0 (0)
NAUSEA	2 (6)	1 (5)	1 (8)
EDEMA	1 (3)	1 (5)	0 (0)
ARRHYTHMIA	1 (3)	1 (5)	0 (0)
CHEST PAIN SUBSTERNAL	1 (3)	1 (5)	0 (0)
HYPOESTHESIA	2 (6)	0 (0)	2 (15)
TREMOR	1 (3)	0 (0)	1 (8)
SYNCOPE	1 (3)	0 (0)	1 (8)
PAIN	1 (3)	0 (0)	1 (8)

PSVT ATTACK SYMPTOMS EXPERIENCED
DURING SCREENING: PAF PATIENTS

SYMPTOMS REPORTED WHO[a] PREFERRED TERM	NO. OF PATIENTS REPORTING ALL (%) (N = 39)	INCLUDED (%) (N = 29)	EXCLUDED (%) (N = 10)
PALPITATION	26 (67)	19 (66)	7 (70)
TACHYCARDIA	14 (36)	10 (34)	4 (40)
DYSPNEA	10 (26)	7 (24)	3 (30)
ASTHENIA	7 (18)	5 (17)	2 (20)
FATIGUE	5 (13)	5 (17)	0 (0)
DIZZINESS	7 (18)	4 (14)	3 (30)
ARRHYTHMIA	5 (13)	4 (14)	1 (10)
FIBRILLATION CARDIAC	5 (13)	4 (14)	1 (10)
CHEST PAIN	4 (10)	4 (14)	0 (0)
SWEATING INCREASED	1 (3)	1 (3)	0 (0)
CONFUSION	1 (3)	1 (3)	0 (0)
PARESTHESIA	1 (3)	1 (3)	0 (0)
AGITATION	1 (3)	1 (3)	0 (0)
ANXIETY	2 (5)	1 (3)	1 (10)
DEPRESSION	1 (3)	1 (3)	0 (0)
NERVOUSNESS	1 (3)	1 (3)	0 (0)
SYNCOPE	1 (3)	1 (3)	0 (0)
DYSPEPSIA	1 (3)	1 (3)	0 (0)
FIBRILLATION ATRIAL	1 (3)	1 (3)	0 (0)
LARYNGISMUS	1 (3)	1 (3)	0 (0)
PAIN	1 (3)	1 (3)	0 (0)
DYSPHORIA	1 (3)	1 (3)	0 (0)
FLATULENCE	1 (3)	0 (0)	1 (10)
HEADACHE	1 (3)	0 (0)	1 (10)
FLUSHING	1 (3)	0 (0)	1 (10)

[a]WORLD HEALTH ORGANIZATION

Table 7 (R818-065)

PATIENT EXPOSURE TO VARIOUS DOSAGE LEVELS OF FLECAINIDE DURING THE DOSE RANGING AND INITIAL DOSE FOR CROSSOVER PHASE: PAT PATIENTS

PAT PATIENTS

TOTAL DAILY DOSE	DOSE RANGING N	DOSE RANGING %	INITIAL DOSE[a] CROSSOVER PHASE N	INITIAL DOSE[a] CROSSOVER PHASE %
100 MG/DAY (1 TAB/DAY)	1	3.2%	0	0.0%
200 MG/DAY (2 TABS/DAY)	31	100.0%	6	27.3%
250 MG/DAY (2 ½ TABS/DAY)	1	3.2%	0	0.0%
300 MG/DAY (3 TABS/DAY)	29	93.5%	8	36.4%
400 MG/DAY (4 TABS/DAY)	21	67.7%	8	36.4%
TOTAL NO. OF PATIENTS	31		22	

[a]TEN PATIENTS STARTED THE CROSSOVER PHASE AT THE MAXIMUM DOSAGE LEVEL THEY RECEIVED DURING THE DOSE RANGING PHASE (EIGHT AT 400 MG/DAY, TWO AT 300 MG/DAY). TWELVE PATIENTS STARTED AT A LOWER DOSAGE LEVEL THAN THE MAXIMUM RECEIVED DURING DOSE RANGING.

PATIENT EXPOSURE TO VARIOUS DOSAGE LEVELS OF FLECAINIDE DURING THE DOSE RANGING AND INITIAL DOSE FOR CROSSOVER PHASE: PAF PATIENTS

PAF PATIENTS

TOTAL DAILY DOSE	DOSE RANGING N	DOSE RANGING %	INITIAL DOSE[a] CROSSOVER PHASE N	INITIAL DOSE[a] CROSSOVER PHASE %
100 MG/DAY (1 TAB/DAY)	1	2.6%	1	3.0%
200 MG/DAY (2 TABS/DAY)	39	100.0%	9	27.3%
300 MG/DAY (3 TABS/DAY)	37	94.9%	12	36.4%
400 MG/DAY (4 TABS/DAY)	33	84.6%	11	33.3%
TOTAL NO. OF PATIENTS	39		33	

[a]OF THE 33 PATIENTS WHO ENTERED THIS PHASE, 13 STARTED AT THE MAXIMUM DOSAGE LEVEL THEY RECEIVED DURING THE DOSE RANGING (11 AT 400 MG/DAY AND TWO AT 200 MG/DAY) PHASE OF THE TRIAL AND 20 STARTED AT A LOWER DOSAGE REGIMEN.

Table 8A (R-818-065)

NUMBER OF ATTACKS DURING CROSSOVER PHASE
PAT PATIENTS
N = 20

NUMBER OF ATTACKS	NUMBER OF PATIENTS	
	PLACEBO	FLECAINIDE
0	4	16
1	4	3
2	1	1
3	1	0
4	6	0
5	2	0
6	1	0
7	1	0

NUMBER OF ATTACKS DURING CROSSOVER PHASE
PAF PATIENTS
N = 29

NUMBER OF ATTACKS	NUMBER OF PATIENTS	
	PLACEBO	FLECAINIDE
0	4	9
1	4	1
2	4	8
3	2	2
4	6	5
5	5	4
6	4	0

Table 8B (R-818-065)

EFFICACY RESULTS: PAT PATIENTS (N=20)

PARAMETER		PLACEBO	FLECAINIDE	P-VALUE
NUMBER OF PATIENTS WITH NO ATTACKS		4	16	< 0.001[a]
TIME TO FIRST ATTACK (DAYS)	MEAN ± SE[b]	>12.7 ± 2.2	>35.0 ± 2.2	< 0.001
	MEDIAN	11.5	>55[c]	
INTERVAL BETWEEN ATTACKS (DAYS)	MEAN ± SE[b]	>21.2 ± 4.6	>50.9 ± 3.3	< 0.001
	MEDIAN	12.8	>55[c]	
RATE OF ATTACKS (ATTACKS/DAY)	MEAN ± SE[d]	0.21 ± 0.078	0.03 ± 0.008	0.035
	RANGE	(0.02 - 1.33)	(0.02 - 0.17)	
VENTRICULAR RATE FOR PATIENTS WITH ATTACKS IN BOTH PERIODS (BEATS/MIN) N=4	MEAN ± SE[d,e]	178 ± 22	140 ± 22	
	RANGE	(125-225)	(92-195)	

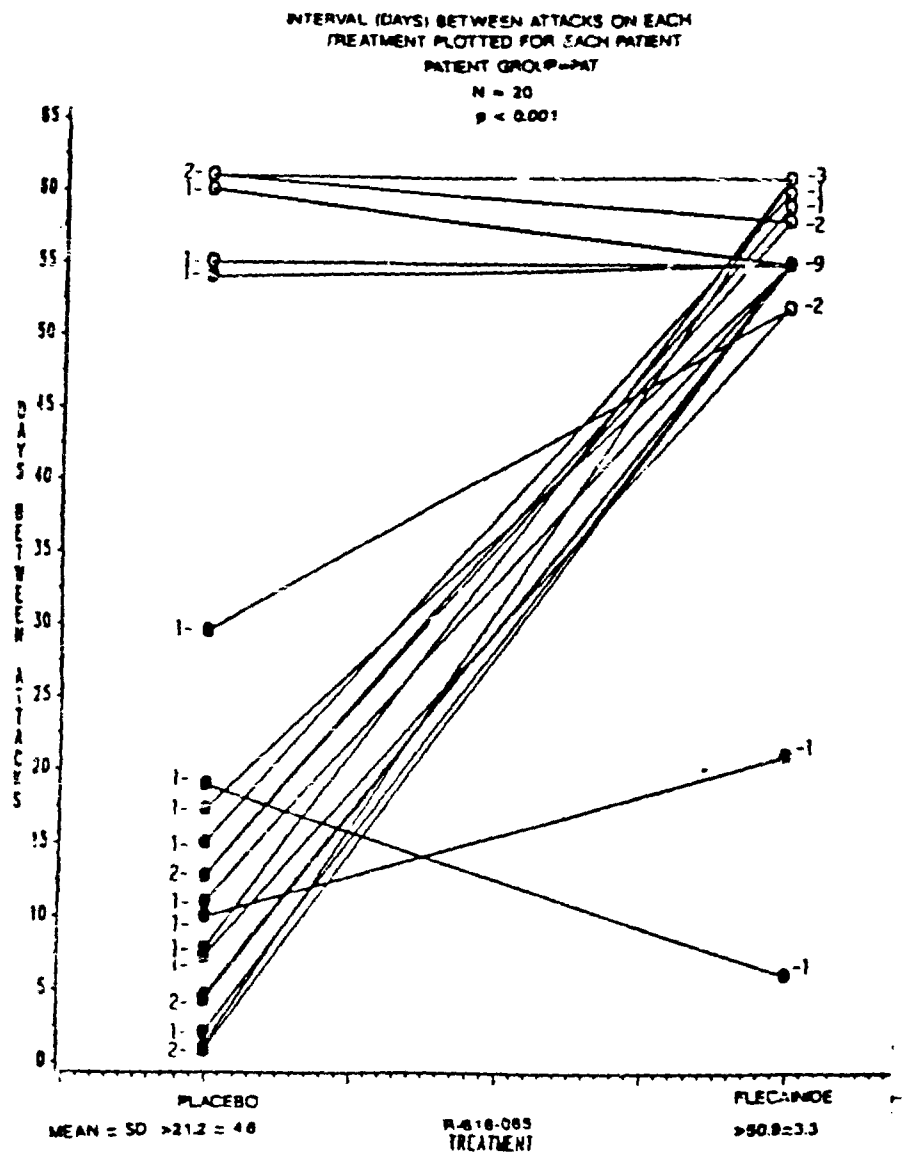
[a] P-VALUE FROM MCNEMAR'S TEST.
[b] PRODUCT-LIMIT ESTIMATES FOR MEAN, STANDARD ERROR OF THE MEAN AND MEDIAN DATA WERE ANALYZED USING THE PAIRED PRENTICE-WILCOXON TEST FOR CENSORED PAIRED DATA.
[c] ACTUAL PRODUCT-LIMIT ESTIMATE COULD NOT BE DETERMINED. ESTIMATE BASED ON THE MEDIAN TREATMENT DURATION. ONLY 20% OF PAT PATIENTS HAD ATTACKS WHILE RECEIVING FLECAINIDE.
[d] SE = STANDARD ERROR OF THE MEAN = STD DEV /√n
[e] NOT SUFFICIENT DATA TO STATISTICALLY ANALYZE.

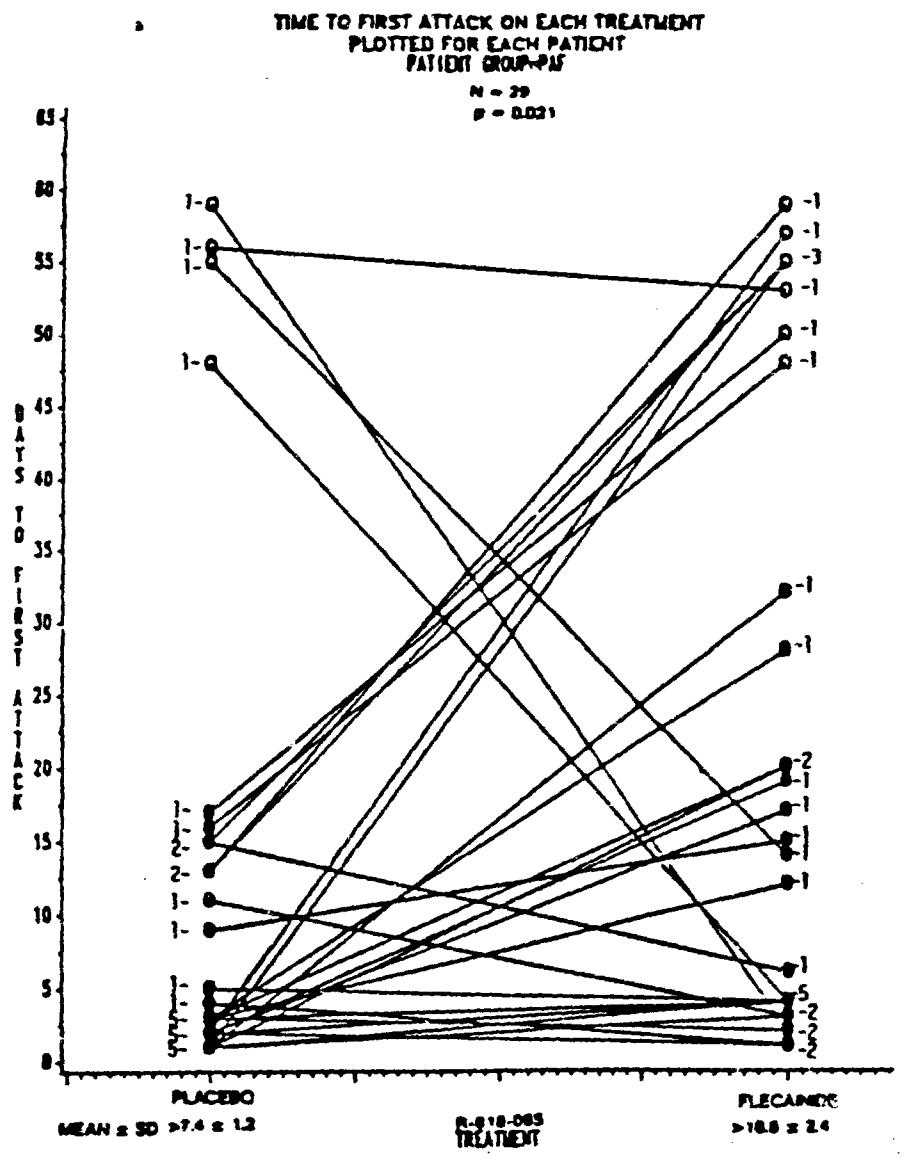
EFFICACY RESULTS: PAF PATIENTS (N=29)

PARAMETER		PLACEBO	FLECAINIDE	P-VALUE
NUMBER OF PATIENTS WITH NO ATTACKS		4	9	0.228[a]
TIME TO FIRST ATTACK (DAYS)	MEAN ± SE[b]	>7.4 ± 1.2	>16.6 ± 2.4	0.021
	MEDIAN	3.0	15.0	
INTERVAL BETWEEN ATTACKS (DAYS)	MEAN ± SE[b]	>17.3 ± 3.7	30.6 ± 4.3	0.003
	MEDIAN	6.3		
RATE OF ATTACKS (ATTACKS/DAY)	MEAN ± SE[c]	0.23 ± 0.045	0.09 ± 0.021	0.009
	RANGE	(0.02 - 1.00)	(0.02 - 0.57)	
VENTRICULAR RATE FOR PATIENTS WITH ATTACKS IN BOTH PERIODS (BEATS/MIN) N=17	MEAN ± SE[c]	124 ± 5	116 ± 4	0.015
	RANGE	(89-175)	(89-150)	

[a] P-VALUE FROM MCNEMAR'S TEST.
[b] PRODUCT-LIMIT ESTIMATES FOR MEAN, STANDARD ERROR OF THE MEAN AND MEDIAN DATA WERE ANALYZED USING THE PAIRED PRENTICE-WILCOXON TEST FOR CENSORED PAIRED DATA.
[c] SE = STANDARD ERROR OF THE MEAN = STD DEV /√n

Figure 1 (R-818-065

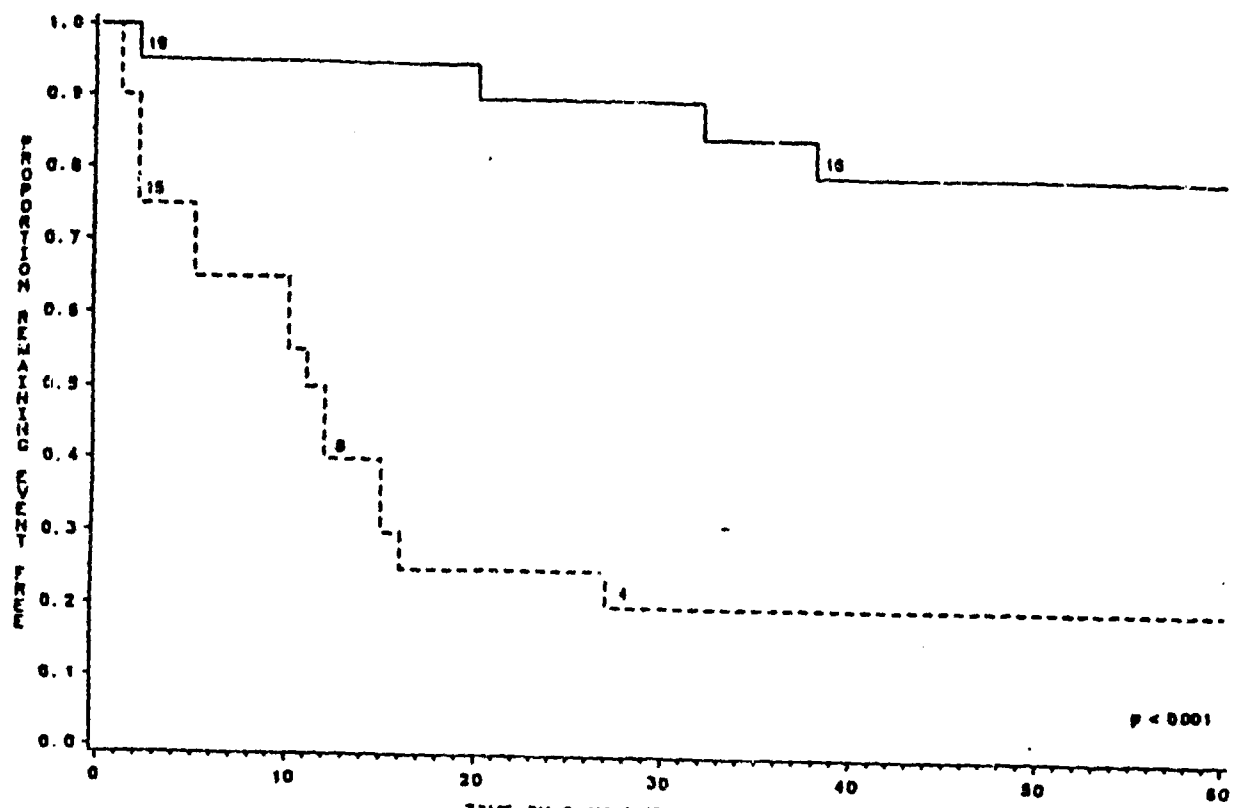




● OBSERVED
○ CENSORED – no attack during the study period.

Figure 2.(R-818-065)

Time to First Attack For PAT Patients Who Received Both Flecainide and Placebo in Crossover Fashion Study R-818-065 - N=20



Time to First Attack For PAF Patients Who Received Both Flecainide and Placebo in Crossover Fashion Study R-818-065 - N=29

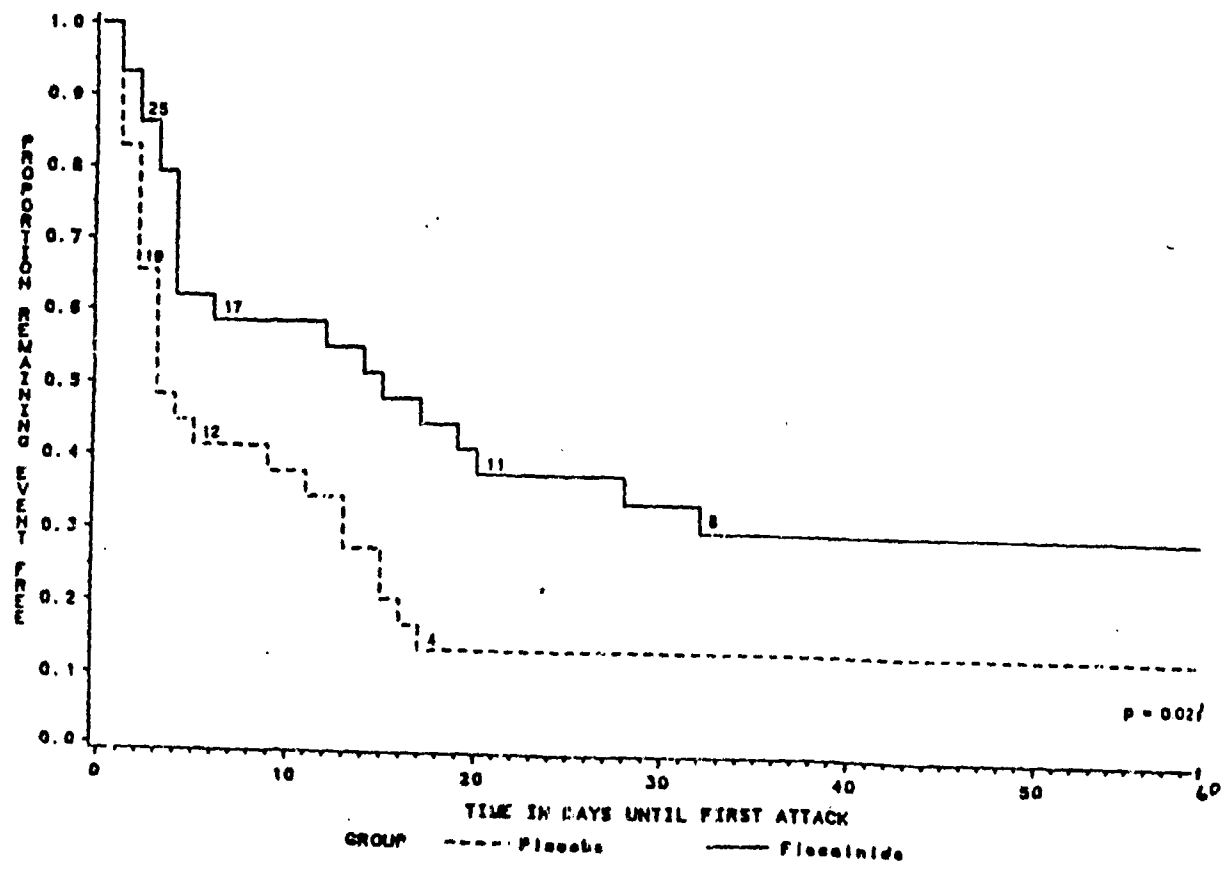
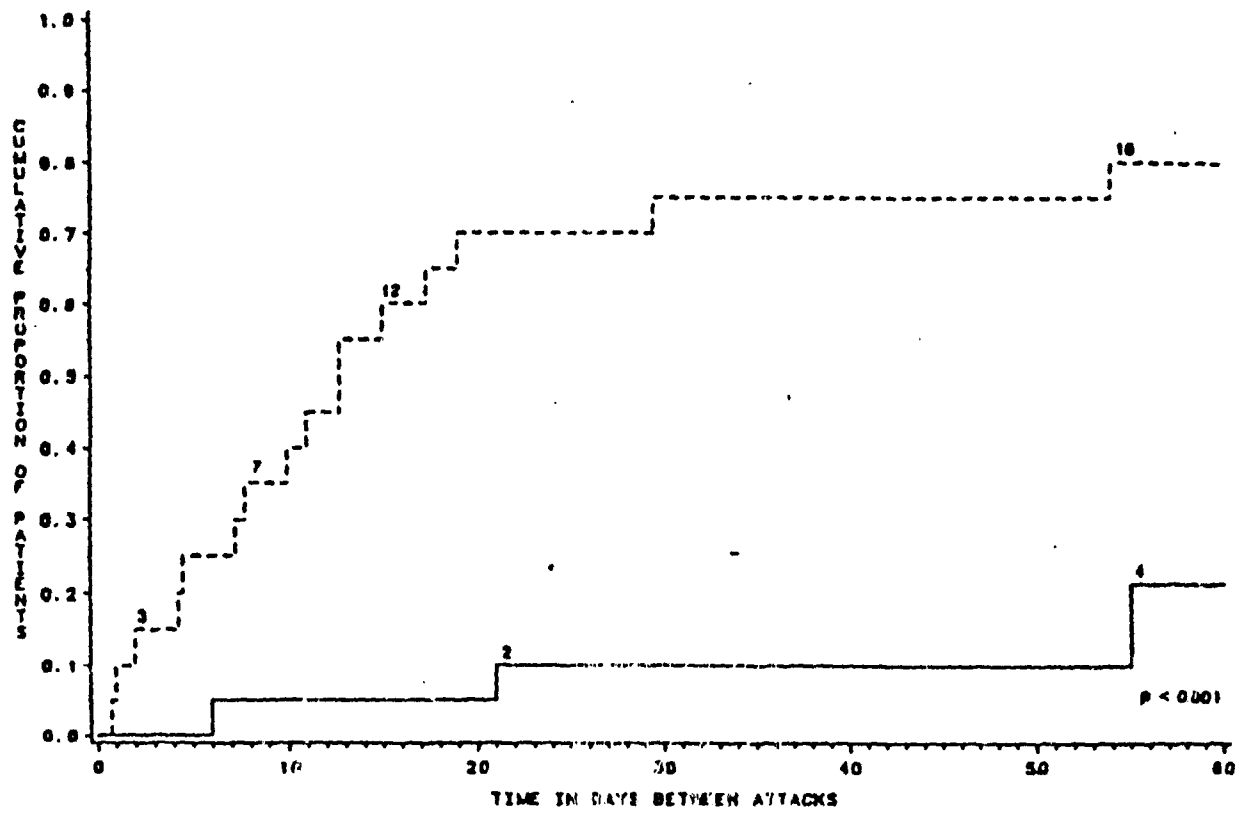


Figure 3 (R-818-065)

Interval Between Attacks For PAT Patients Who Received Both Flecainide and Placebo in Crossover Fashion
Study R-818-065 - N=20



Interval Between Attacks For PAF Patients Who Received Both Flecainide and Placebo in Crossover Fashion
Study R-818-065 - N=29

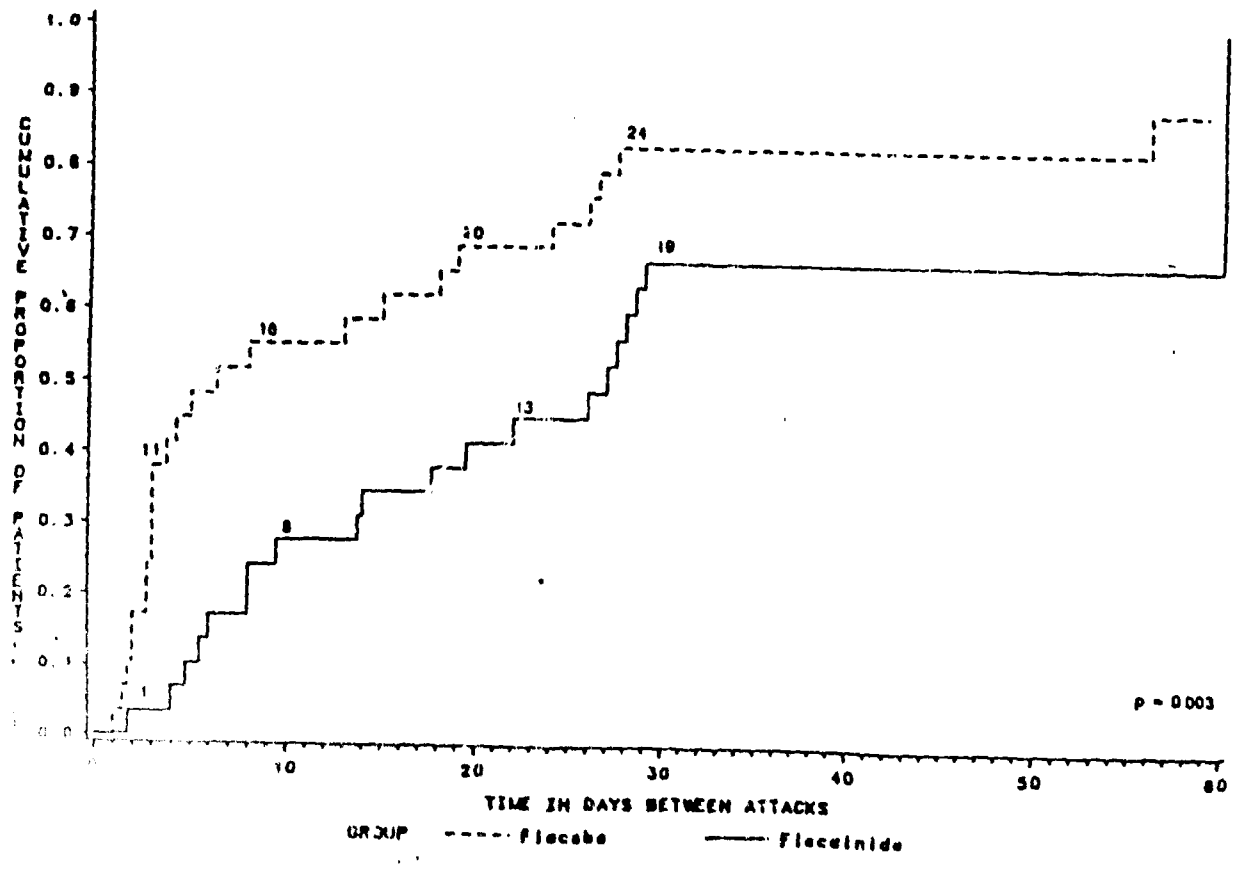


Table 9. (R-818-065)

[a]
PSVT ATTACK SYMPTOMS[a] EXPERIENCED
DURING PLACEBO OR FLECAINIDE THERAPY: PAT PATIENTS

SYMPTOMS REPORTED WHO[b] PREFERRED TERM	NO. OF PATIENTS REPORTING (%) PLACEBO (N[c] = 16)	FLECAINIDE (N[c] = 4)
TACHYCARDIA	11 (69)	3 (75)
DYSPNEA	8 (50)	2 (50)
PALPITATION	8 (50)	1 (25)
CHEST PAIN	7 (44)	1 (25)
DIZZINESS	4 (25)	0 (0)
FATIGUE	3 (19)	1 (25)
HEADACHE	3 (19)	0 (0)
ASTHENIA	3 (19)	0 (0)
TACHYCARDIA SUPRAVENTRICULAR	2 (13)	0 (0)
NAUSEA	2 (13)	0 (0)
SWEATING INCREASED	0 (0)	1 (25)
ARRHYTHMIA	1 (6)	0 (0)
PHARYNGITIS	1 (6)	0 (0)
BACK PAIN	1 (6)	0 (0)
DYSPHORIA	1 (6)	0 (0)

[a]DATA COMPILED FROM DOCUMENTED PSVT ATTACKS.
[b]WORLD HEALTH ORGANIZATION
[c]NUMBER OF PATIENTS HAVING DOCUMENTED ATTACKS.

PSVT ATTACK SYMPTOMS[a] EXPERIENCED
DURING PLACEBO OR FLECAINIDE THERAPY: PAF PATIENTS

SYMPTOMS REPORTED WHO[b] PREFERRED TERM	NO. OF PATIENTS REPORTING (%) PLACEBO (N[c] = 25)	FLECAINIDE (N[c] = 20)
PALPITATION	18 (72)	12 (60)
DYSPNEA	9 (36)	6 (30)
TACHYCARDIA	6 (24)	6 (30)
CHEST PAIN	6 (24)	5 (25)
DIZZINESS	4 (16)	4 (20)
FATIGUE	5 (20)	1 (5)
ARRHYTHMIA	3 (12)	2 (10)
ASTHENIA	3 (12)	2 (10)
PARESTHESIA	2 (8)	1 (5)
FIBRILLATION CARDIAC	3 (12)	0 (0)
PAIN	2 (8)	1 (5)
TREMOR	1 (4)	1 (5)
ANXIETY	1 (4)	1 (5)
NAUSEA	1 (4)	1 (5)
MICTURITION FREQUENCY	1 (4)	1 (5)
MYALGIA	0 (0)	1 (5)
HEADACHE	0 (0)	1 (5)
IMPOTENCE	1 (4)	0 (0)
NERVOUSNESS	1 (4)	0 (0)
PALLOR	0 (0)	1 (5)
DYSPEPSIA	1 (4)	0 (0)
LARYNGISMUS	0 (0)	1 (5)
DYSPHORIA	0 (0)	1 (5)

[a]DATA COMPILED FROM DOCUMENTED PSVT ATTACKS.
[b]WORLD HEALTH ORGANIZATION
[c]NUMBER OF PATIENTS HAVING DOCUMENTED ATTACKS.

Table 10. (R-818-065)

AVERAGE TROUGH[a] PLASMA FLECAINIDE LEVELS: PAT PATIENTS[b]

PATIENTS INCLUDED IN EFFICACY ANALYSIS	TOTAL DAILY DOSE (MG)	DOSE RANGING (mcg/mL) MEAN ± SD	N	RANGE	CROSSOVER (mcg/mL) MEAN ± SD	N	RANGE
N = 20	200	---	-	---	0.463 ± 0.131	3	0.36 - 0.61
	300	0.820	1	0.82	0.396 ± 0.253	5	0.10 - 0.77
	400	0.874 ± 0.481	5	0.15 - 1.45	0.970 ± 0.594	2	0.55 - 1.39
	ALL PATIENTS	0.865 ± 0.431	6	0.15 - 1.45	0.531 ± 0.355	10	0.10 - 1.39

ALL PATIENTS[b]	TOTAL DAILY DOSE (MG)	MEAN ± SD	N	RANGE	MEAN ± SD	N	RANGE
N = 31	200	---	-	---	0.463 ± 0.131	3	0.36 - 0.61
	300	0.820	1	0.82	0.396 ± 0.253	5	0.10 - 0.77
	400	0.817 ± 0.45	6	0.15 - 1.45	0.970 ± 0.594	2	0.55 - 1.39
	ALL PATIENTS	0.817 ± 0.41	7	0.15 - 1.45	0.531 ± 0.355	10	0.10 - 1.39

AVERAGE TROUGH[a] PLASMA FLECAINIDE LEVELS: PAF PATIENTS

PATIENTS INCLUDED IN EFFICACY ANALYSIS	TOTAL DAILY DOSE (MG)	DOSE RANGING (mcg/mL) MEAN ± SD	N	RANGE	CROSSOVER (mcg/mL) MEAN ± SD	N	RANGE
N = 29	200	0.390	1	0.39	0.478 ± 0.170	4	0.31 TO 0.70
	300	0.280	1	0.28	0.655 ± 0.233	2	0.49 TO 0.82
	400	0.675 ± 0.238	12	0.16 - 1.06	0.645 ± 0.177	2	0.52 TO 0.77
	ALL PATIENTS	0.626 ± 0.252	14	0.16 - 1.06	0.564 ± 0.182	8	0.31 TO 0.82

ALL PATIENTS[b]	TOTAL DAILY DOSE (MG)	MEAN ± SD	N	RANGE	MEAN ± SD	N	RANGE
N = 39	200	0.390	1	0.39	0.478 ± 0.170	4	0.31 - 0.70
	300	0.670 ± 0.339	3	0.28 - 0.89	0.655 ± 0.233	2	0.49 - 0.82
	400	0.642 ± 0.257	13	0.16 - 1.06	0.637 ± 0.126	3	0.52 - 0.77
	ALL PATIENTS	0.632 ± 0.260	17	0.16 - 1.06	0.570 ± 0.171	9	0.31 - 0.82

[a]TROUGH IS DEFINED FOR PURPOSES OF THIS ANALYSIS TO BE THOSE SAMPLES TAKEN 8 TO 16 HOURS AFTER THE LAST DOSE OF FLECAINIDE. OVERALL, ONLY 40% (18/45) OF THE SAMPLES MET THIS CRITERIA.
[b]ALL PATIENTS WHO RECEIVED FLECAINIDE IN EITHER THE DOSE RANGING OR CROSSOVER PHASE OF THE TRIAL.

Table 11 (R818-065)

SUMMARY OF IV FLECAINIDE RESULTS AND COMPARISON TO ORAL EFFICACY: PAT PATIENTS

SITE	PATIENT NUMBER	IV FLECAINIDE RESULTS[a]	ORAL RESULTS NO. OF ATTACKS/DAYS PLACEBO	ORAL RESULTS NO. OF ATTACKS/DAYS FLECAINIDE	ADVERSE EXPERIENCES IV ONLY	REASON DISCONTINUED/ STUDY PHASE
01	001	EFFECTIVE[b]	-	-	FIBRILLATION VENTRICULAR	WORSENED AND NEW ARRHYTHM
01	002	NONEFFECTIVE	1/10	1/21	NONE	
01	003	NONEFFECTIVE	5/54	0/58	NONE	
01	004	NONEFFECTIVE			NONE	PERSONAL/DOSE RANGING
01	006	NONEFFECTIVE			NONE	NCAE[c]/DOSE RANGING
01	007	EFFECTIVE			NONE	NCAE/DOSE RANGING
01	008	NONEFFECTIVE			NONE	PERSONAL/DOSE RANGING
01	009	NONEFFECTIVE	[d]	[d]	NONE	PERSONAL/CROSSOVER
04	003	EFFECTIVE	1/11	1/55	DIZZINESS	
04	004	EFFECTIVE	4/17	0/54	NONE	
04	005	EFFECTIVE	1/54	0/54	DIZZINESS, HEADACHE	
04	006	EFFECTIVE			NONE	PERSONAL/EP
08	002	EFFECTIVE	5/4	0/61	NONE	
08	003	NONEFFECTIVE			TACHYCARDIA SUPRAVENTRICULAR	WORSENED ARRHYTHMIA/EP
08	005	NA[e]	4/8	0/54	NONE	
10	004	EFFECTIVE	5/126	[d]	NONE	LTF[f]/CROSSOVER

[a]THE INVESTIGATOR CHECKED "EFFECTIVE" OR "NONEFFECTIVE" IN THE PATIENT'S CASE REPORT FORM.
[b]FLECAINIDE SUPPRESSED SVT, BUT INDUCED VENTRICULAR FIBRILLATION.
[c]NCAE: NONCARDIAC ADVERSE EXPERIENCE.
[d]PATIENT DISCONTINUED DURING CROSSOVER PHASE, AND NO EFFICACY DATA WERE COLLECTED FOR THIS TREATMENT.
[e]NA: ARRHYTHMIA WAS NOT INDUCIBLE AT BASELINE.
[f]LTF: LOST TO FOLLOW-UP.

SUMMARY OF IV FLECAINIDE RESULTS AND COMPARISON TO ORAL EFFICACY: PAF PATIENTS

SITE	PATIENT NUMBER	IV FLECAINIDE RESULTS[a]	ORAL RESULTS NO. OF ATTACKS/DAYS PLACEBO	ORAL RESULTS NO. OF ATTACKS/DAYS FLECAINIDE	ADVERSE EXPERIENCES IV ONLY	REASON DISCONTINUED/ STUDY PHASE
01	106	EFFECTIVE	3/19	0/47	NONE	
01	107	NONEFFECTIVE	5/12	2/39	NONE	
01	108	EFFECTIVE	[b]	1/13	NONE	INADEQUATE RESPONSE/CROSSOVER PHASE
08	102	NA[c]	5/12	4/19	NONE	
08	103	EFFECTIVE	1/24	0/54	NONE	

[a]THE INVESTIGATOR CHECKED "EFFECTIVE" OR "NONEFFECTIVE" IN THE PATIENT'S CASE REPORT FORM.
[b]PATIENT DISCONTINUED IN PERIOD A ON FLECAINIDE, NO PLACEBO DATA.
[c]ARRHYTHMIA WAS NOT INDUCIBLE AT BASELINE.

Table 12 (R-818-065)

OVERALL FREQUENCY OF REPORTED CARDIAC ADVERSE EXPERIENCES WHILE ON ORAL FLECAINIDE

CARDIAC ADVERSE EXPERIENCE	NO. OF PATIENTS ALL N=70 (%)	PAT N=31	PAF N=39
PROARRHYTHMIC EVENTS[a]	2 (2.9%)	0	2
CONDUCTION DISTURBANCE	2 (2.9%)	0	2
MI	1 (1.4%)	1	0
DEATH	1 (1.4%)	0	1
CHF	0 (0%)	0	0

[a]INCLUDES ONE PATIENT ALSO REPORTED UNDER DEATH.

PATIENT LISTING OF REPORTED CARDIAC ADVERSE EXPERIENCES WHILE RECEIVING ORAL FLECAINIDE THERAPY

CAE	PATIENT GROUP	SITE/PATIENT NO.	PERIOD: TREATMENT	EVENT
PROARRHYTHMIC[a] EVENT	PAF	12/102	P:FLECAINIDE	PROLONGED SVT
CONDUCTION DISTURBANCE	PAF	01/103	WEEK 3 DOSE RANGING: FLECAINIDE	PRESYNCOPAL: 1° AVB, IVCD, PR=0.3, QRS=0.16
	PAF	14/103	WEEKS 1&2 DOSE RANGING: FLECAINIDE	QUESTIONABLE SINUS PAUSE HR=44, DRUG TEMPORARILY STOPPED FOR BRADYCARDIA
MI	PAT	08/001	WEEK 2 DOSE RANGING: FLECAINIDE	POSSIBLE MI
DEATH[a]	PAF	09/101	WEEK 2 DOSE RANGING: FLECAINIDE	SUDDEN DEATH: POSSIBLE SUBENDOCARDIAL MI
CHF		NONE REPORTED		

[a]THE PATIENT WHO DIED IS ALSO COUNTED AS A PROARRHYTHMIC EVENT.

Table 13 (R-818-066)

QUALIFICATION SUMMARY: PAT PATIENTS

DAYS TO SECOND ATTACK IN SCREENING	ALL PATIENTS (N = 17)		PATIENTS INCLUDED (N = 14)		PATIENTS EXCLUDED (N = 3)	
	N	%	N	%	N	%
2 - 7	12	70.6%	11	78.6%	1	33.3%
8 - 14	3	17.6%	2	14.3%	1	33.3%
15 - 21	1	5.9%	1	7.1%	0	0.0%
22 - 28	1	5.9%	0	0.0%	1	33.3%
TOTAL	17	100.0%	14	100.0%	3	100.0%
MEAN ± SD[a]			6.4 ± 4.4		14.0 ± 11.5	

[a]p-VALUE COMPARISON OF INCLUDED AND EXCLUDED PATIENTS, P = 0.062.

QUALIFICATION SUMMARY: PAF PATIENTS

DAYS TO SECOND ATTACK IN SCREENING	ALL PATIENTS (N = 25)		PATIENTS INCLUDED (N = 19)		PATIENTS EXCLUDED (N = 6)	
	N	%	N	%	N	%
2 - 7	14	56.0%	10	52.6%	4	66.7%
8 - 14	7	28.0%	6	31.6%	1	16.7%
15 - 21	2	8.0%	2	10.5%	0	0.0%
22 - 28	1	4.0%	1	5.3%	0	0.0%
TOTAL	24[a]	96.0%	19	100.0%	5[a]	83.3%
MEAN ± SD[b]			8.3 ± 5.8		6.2 ± 3.1	

[a]ONE PATIENT HAD ONLY ONE ATTACK.
[b]p-VALUE OF T-TEST COMPARING INCLUDED AND EXCLUDED PATIENTS, P = 0.455.

Table 14 (R-818-066)

NUMBER OF PATIENTS ENROLLED AND PATIENT ACCOUNTABILITY
THROUGHOUT THE STUDY: PAT PATIENTS

No. of Patients Who Qualified (N-17)

Entered Dose Ranging Phase (N-17)

Discontinued (N = 2)

Reasons (No. of Patients)
Inadequate Response (1)
Personal (1)

Entered Crossover Phase (N = 15)
Entered Period A (N = 15)

Discontinued (N = 1)

Reasons (No. of Patients, Treatment)
Noncardiac AE (1, Flecainide)

Entered Period B (N = 14)

Discontinued (N = 0)

Completed Crossover (N = 14)

Included in Analysis (N = 14)

NUMBER OF PATIENTS ENROLLED AND PATIENT ACCOUNTABILITY
THROUGHOUT THE STUDY: PAF PATIENTS

No. of Patients Who Qualified (N = 25)

Entered Dose Ranging Phase (N = 25)

Discontinued (N = 3)

Reasons (No. of Patients)
Cardiac Adverse Experience (3)

Entered Crossover Phase (N = 22)
Entered Period A (N = 22)

Discontinued (N = 1)

Reasons (No. of Patients, Treatment)
Noncardiac
Adverse Experience (1, Flecainide)

Entered Period B (N = 21)

Discontinued (N = 0)

Completed Crossover (N = 21)

Included in Analysis (N =19)

Table 15. (R-818-066)

HISTORICAL SYMPTOMS[a] ASSOCIATED WITH PSVT ATTACKS: PAT PATIENTS

SYMPTOM[c]	NO. OF PATIENTS REPORTING: ALL PATIENTS (N=17) N	%	PATIENTS INCLUDED (N=14) N	%	PATIENTS EXCLUDED (N=3) N	%	COMPARISON (P-VALUE)[b]
PALPITATIONS	16	94.1%	13	92.9%	3	100.0%	1.000
DIZZINESS	13	76.5%	10	71.4%	3	100.0%	0.541
ASTHENIA	11	64.7%	9	64.3%	2	66.7%	1.000
FATIGUE	9	52.9%	7	50.0%	2	66.7%	1.000
DYSPNEA	6	35.3%	6	42.9%	0	0.0%	0.515
SYNCOPE	6	35.3%	5	35.7%	1	33.3%	0.728
CHEST PAIN	4	23.5%	4	28.6%	0	0.0%	0.541
OTHER SYMPTOMS[d]	6	35.3%	5	35.7%	1	33.3%	1.000

[a] A PATIENT COULD REPORT MORE THAN ONE SYMPTOM.
[b] P-VALUE ASSOCIATED WITH THE STATISTICAL COMPARISON OF PATIENTS INCLUDED AND EXCLUDED FROM THE EFFICACY ANALYSIS, SEE APPENDIX III FOR FURTHER DETAILS.
[c] WORLD HEALTH ORGANIZATION PREFERRED TERM.
[d] OTHER SYMPTOMS REPORTED WERE HEADACHE, NAUSEA, PARESTHESIA, ANXIETY, SWEATING INCREASED, AND PULSUS MAGNUS.

HISTORICAL SYMPTOMS[a] ASSOCIATED WITH PSVT ATTACKS: PAF PATIENTS

SYMPTOM[c]	NO. OF PATIENTS REPORTING (%): ALL PATIENTS (N=25) N	%	PATIENTS INCLUDED (N=19) N	%	PATIENTS EXCLUDED (N=6) N	%	COMPARISON (P-VALUE)[b]
PALPITATIONS	22	88.0%	18	94.7%	4	66.7%	0.133
ASTHENIA	11	44.0%	8	42.1%	3	50.0%	1.000
CHEST PAIN	8	32.0%	7	36.8%	1	16.7%	0.624
DYSPNEA	6	24.0%	6	31.6%	0	0.0%	0.279
DIZZINESS	5	20.0%	4	21.1%	1	16.7%	1.000
SYNCOPE	2	8.0%	2	10.5%	0	0.0%	1.000
TACHYCARDIA	0	0.0%	0	0.0%	0	0.0%	---
FATIGUE	6	24.0%	5	26.3%	1	16.7%	1.000
OTHER SYMPTOMS[d]	14	56.0%	11	57.9%	3	50.0%	1.000

[a] A PATIENT COULD REPORT MORE THAN ONE SYMPTOM.
[b] P-VALUE ASSOCIATED WITH THE STATISTICAL COMPARISON OF PATIENTS INCLUDED AND EXCLUDED FROM THE EFFICACY ANALYSIS, SEE APPENDIX III FOR FURTHER DETAILS.
[c] WORLD HEALTH ORGANIZATION PREFERRED TERM.
[d] OTHER SYMPTOMS REPORTED WERE SWEATING INCREASED, ANXIETY, PAIN, HEADACHE, HYPOESTHESIA, PARESTHESIA, APPETITE INCREASED, NERVOUSNESS, SOMNOLENCE, ANGINA PECTORIS, POLYURIA, MALAISE, AND LARYNGISMUS.

Table 16. (LR-818-066)

PATIENT EXPOSURE TO VARIOUS DOSAGE LEVELS
OF FLECAINIDE DURING THE DOSE RANGING
AND INITIAL DOSE FOR CROSSOVER PHASE: PAT PATIENTS

PAT PATIENTS

TOTAL DAILY DOSE (MG)	DOSE RANGING N	DOSE RANGING %	INITIAL DOSE[a] CROSSOVER PHASE N	INITIAL DOSE[a] CROSSOVER PHASE %
100 (1 Tab/Day)	1	5.9%	1	6.7%
200 (2 Tabs/Day)	17	100.0%	2	13.3%
300 (3 Tabs/Day)	15	88.2%	7	46.7%
400 (4 Tabs/Day)	11	64.7%	5	33.3%
TOTAL NO. OF PATIENTS	17		15	

[a]SEVEN PATIENTS STARTED THE CROSSOVER PHASE AT THE MAXIMUM DOSAGE LEVEL THEY RECEIVED DURING THE DOSE RANGING PHASE (FIVE AT 400 MG/DAY; TWO AT 300 MG/DAY). EIGHT PATIENTS STARTED AT A LOWER DOSAGE LEVEL . AN THE MAXIMUM RECEIVED DURING DOSE RANGING.

PATIENT EXPOSURE TO VARIOUS DOSAGE LEVELS
OF FLECAINIDE DURING THE DOSE RANGING
AND INITIAL DOSE FOR CROSSOVER PHASE: PAF PATIENTS

PAF PATIENTS

TOTAL DAILY DOSE (MG)	DOSE RANGING N	DOSE RANGING %	INITIAL DOSE[a] CROSSOVER PHASE N	INITIAL DOSE[a] CROSSOVER PHASE %
100 (1 Tab/Day)	1	4.0%	1	4.5%
200 (2 Tabs/Day)	25	100.0%	2	9.1%
300 (3 Tabs/Day)	23	92.0%	9	40.9%
400 (4 Tabs/Day)	18	72.0%	9	40.9%
500 (5 Tabs/Day)	1	4.0%	0	0.0%
600 (6 Tabs/Day)	1	4.0%	1	4.5%
TOTAL NO. OF PATIENTS	25		22	

[a]TWELVE PATIENTS STARTED THE CROSSOVER PHASE AT THE MAXIMUM DOSAGE LEVEL THEY RECEIVED DURING THE DOSE RANGING PHASE (ONE AT 600 MG/DAY; NINE AT 400 MG/DAY; AND TWO AT 300 MG/DAY). TEN PATIENTS STARTED AT A LOWER DOSAGE LEVEL.

TABLES

Table 17 A (R-818-066)

NUMBER OF ATTACKS DURING CROSSOVER PHASE
PAT PATIENTS
N = 14

NUMBER OF ATTACKS	NUMBER OF PATIENTS PLACEBO	NUMBER OF PATIENTS FLECAINIDE
0	1	10
1	2	3[a]
2	2	0
3	2	0
4	5	0
5	1	0
6	1	1

NUMBER OF ATTACKS DURING CROSSOVER PHASE
PAF PATIENTS
N = 19

NUMBER OF ATTACKS	NUMBER OF PATIENTS PLACEBO	NUMBER OF PATIENTS FLECAINIDE
0	0	5
1	2	2
2	0	4
3	7	1
4	8	3
5	1	0
6	0	1
7	1	2

[a]PATIENT 006, CENTER 05 HAD THEIR ONLY ATTACK ON FLECAINIDE AFTER 60 DAYS OF THERAPY. THIS PATIENT WAS CONSIDERED ATTACK FREE IN THE PRIMARY EFFICACY ANALYSES.

Table 17 B (R-818-066)

EFFICACY RESULTS: PAT PATIENTS (N=14)

PARAMETER		PLACEBO	FLECAINIDE	P-VALUE[a]
NUMBER OF PATIENTS WITH NO ATTACKS		1	11	0.002
TIME TO FIRST ATTACK (DAYS)	MEAN ± SE[b] MEDIAN	>15.2 ± 4.9 9.5	>22.0 ± 1.8 >61[c]	0.001
INTERVAL BETWEEN ATTACKS (DAYS)	MEAN ± SE[b] MEDIAN	>18.5 ± 5.4 7.3	>51.3 ± 4.2 >61[c]	0.001
RATE OF ATTACKS (ATTACKS/DAY)	MEAN ± SE[d] RANGE	0.23 ± 0.07 0.02-0.75	0.03 ± 0.01 0.02-0.22	0.013
VENTRICULAR RATE FOR PATIENTS WITH ATTACKS IN BOTH PERIODS (BEATS/MIN) N=3	MEAN ± SE RANGE	177 ± 10 167-197	150 ± 13 124-167	---[e]

[a]P-VALUE FROM MCNEMAR'S TEST.
[b]PRODUCT-LIMIT ESTIMATES FOR MEAN, STANDARD ERROR OF THE MEAN AND MEDIAN DATA WERE ANALYZED USING THE PAIRED PRENTICE-WILCOXON TEST FOR CENSORED PAIRED DATA.
[c]ACTUAL PRODUCT-LIMIT ESTIMATE COULD NOT BE DETERMINED. ESTIMATE BASED ON THE MEDIAN TREATMENT DURATION. ONLY 21% OF PAT PATIENTS HAD ATTACKS WHILE RECEIVING FLECAINIDE.
[d]SE = STANDARD ERROR OF THE MEAN = STD DEV/√N
DATA WERE ANALYZED USING ANALYSIS OF VARIANCE METHODS FOR A TWO PERIOD CROSSOVER DESIGN.
[e]NO ANALYSIS, INSUFFICIENT DATA.

EFFICACY RESULTS: PAF PATIENTS (N=19)

PARAMETER		PLACEBO	FLECAINIDE	P-VALUE[a]
NUMBER OF PATIENTS WITH NO ATTACKS		0	6	0.031
TIME TO FIRST ATTACK (DAYS)	MEAN ± SE[b] MEDIAN	6.3 ± 1.6 3.0	>18.3 ± 3.6 10.0	0.008
INTERVAL BETWEEN ATTACKS (DAYS)	MEAN ± SE[b] MEDIAN	10.2 ± 3.1 6.0	>31.7 ± 4.9 29.0	0.001
RATE OF ATTACKS (ATTACKS/DAY)	MEAN ± SE[c] RANGE	0.30 ± 0.06 0.02 - 1.00	0.07 ± 0.02 0.02 - 0.33	0.003
VENTRICULAR RATE FOR PATIENTS WITH ATTACKS IN BOTH PERIODS (BEATS/MIN) N=13	MEAN ± SE[c] RANGE	125 ± 7 83-153	121 ± 6 81-150	0.455

[a]P-VALUE FROM MCNEMAR'S TEST.
[b]PRODUCT-LIMIT ESTIMATES FOR MEAN, STANDARD ERROR OF THE MEAN AND MEDIAN DATA WERE ANALYZED USING THE PAIRED PRENTICE-WILCOXON TEST FOR CENSORED PAIRED DATA.
[c]SE = STANDARD ERROR OF THE MEAN = STD DEV/√N. DATA WERE ANALYZED USING ANALYSIS OF

Figure 4 (CR-818-066)

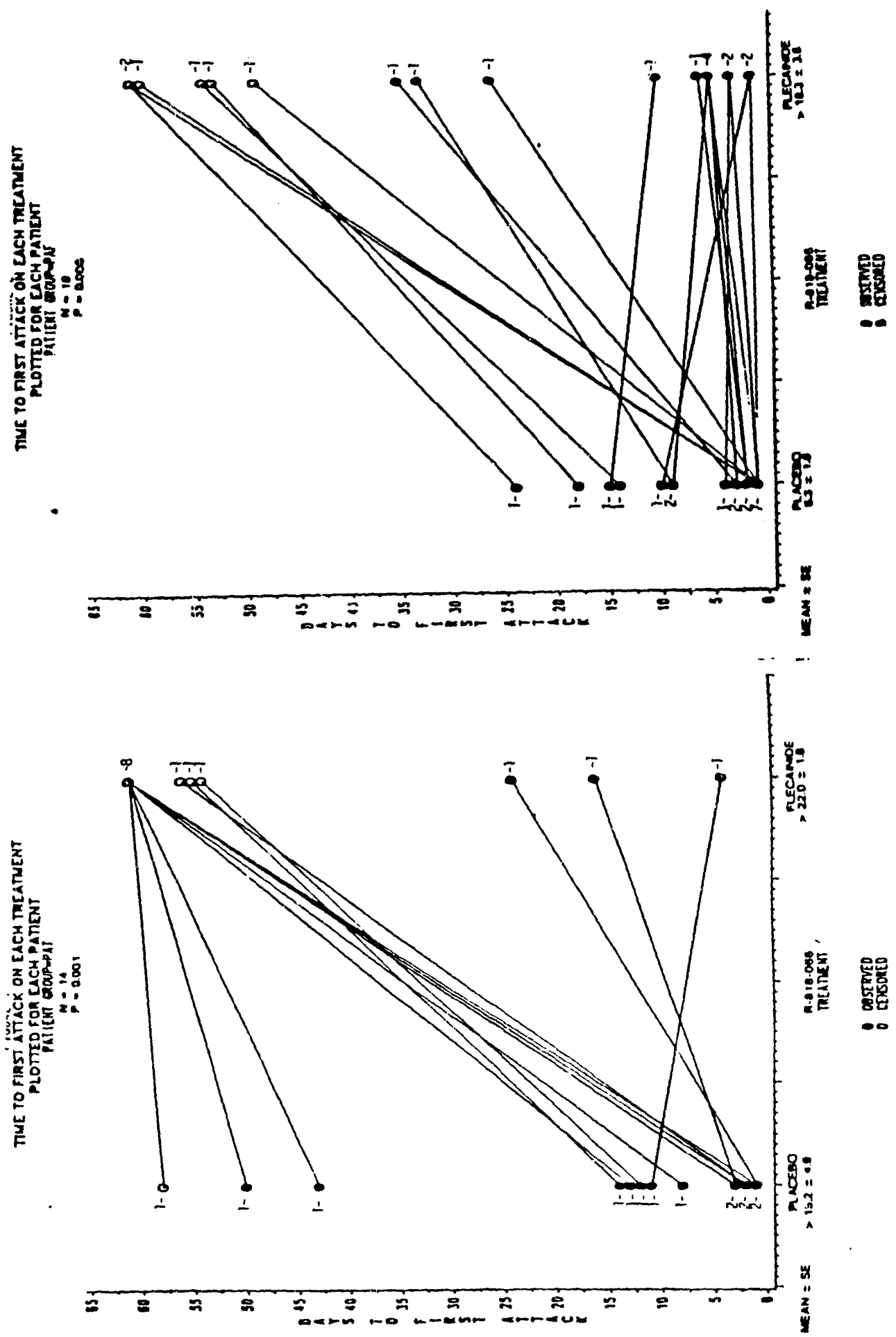
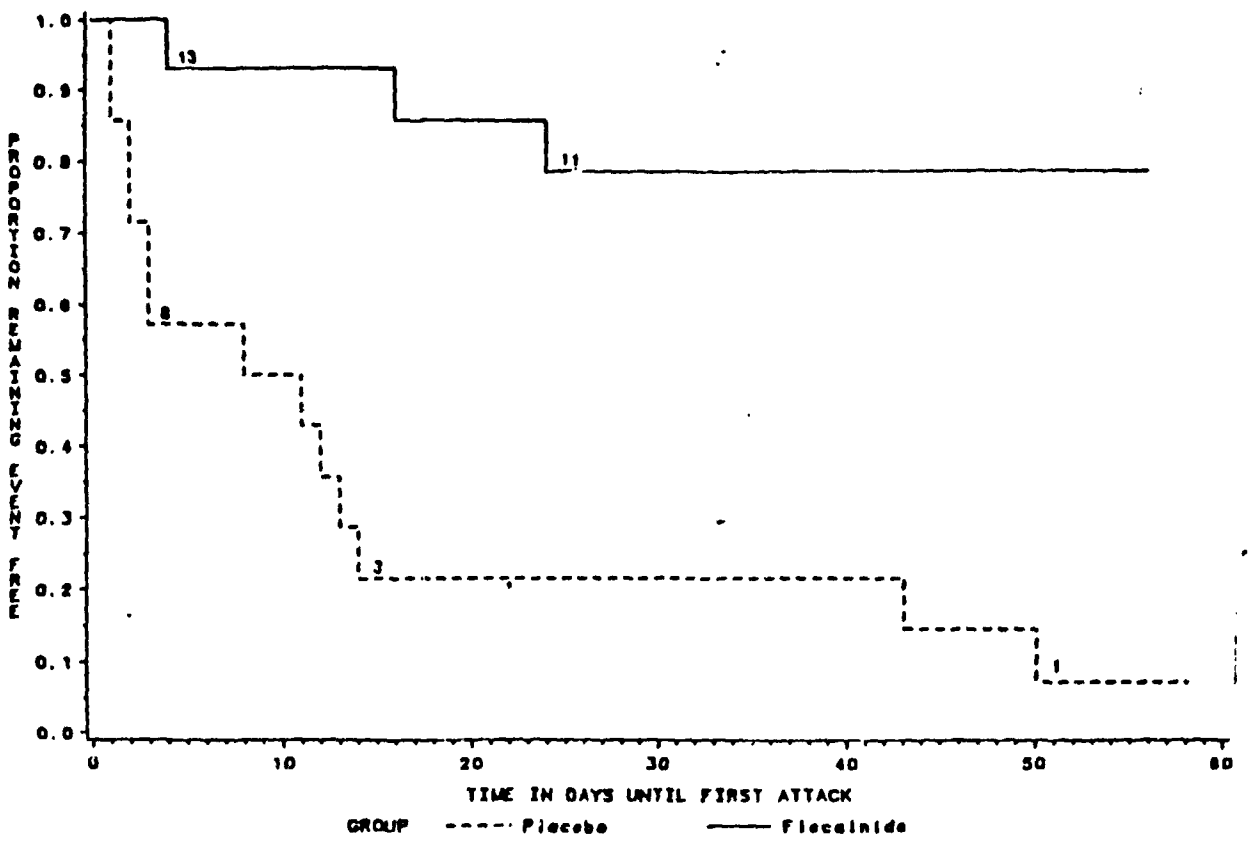


Figure 5. (R818-066)

Time to First Attack For PAT Patients Who Received
Both Flecainide and Placebo in Crossover Fashion
Study R-818-066 - N=14



Time to First Attack For PAF Patients Who Received
Both Flecainide and Placebo in Crossover Fashion
Study R-818-066 - N=19

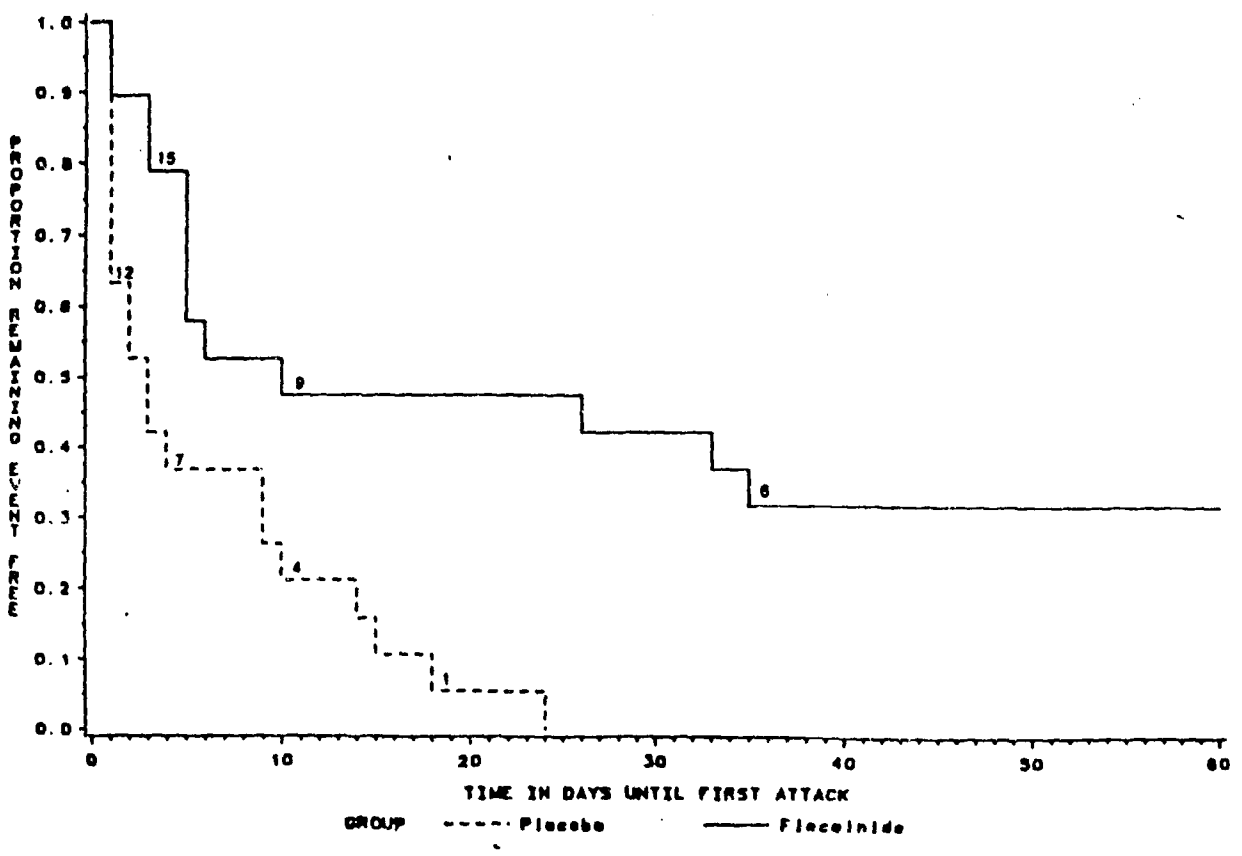
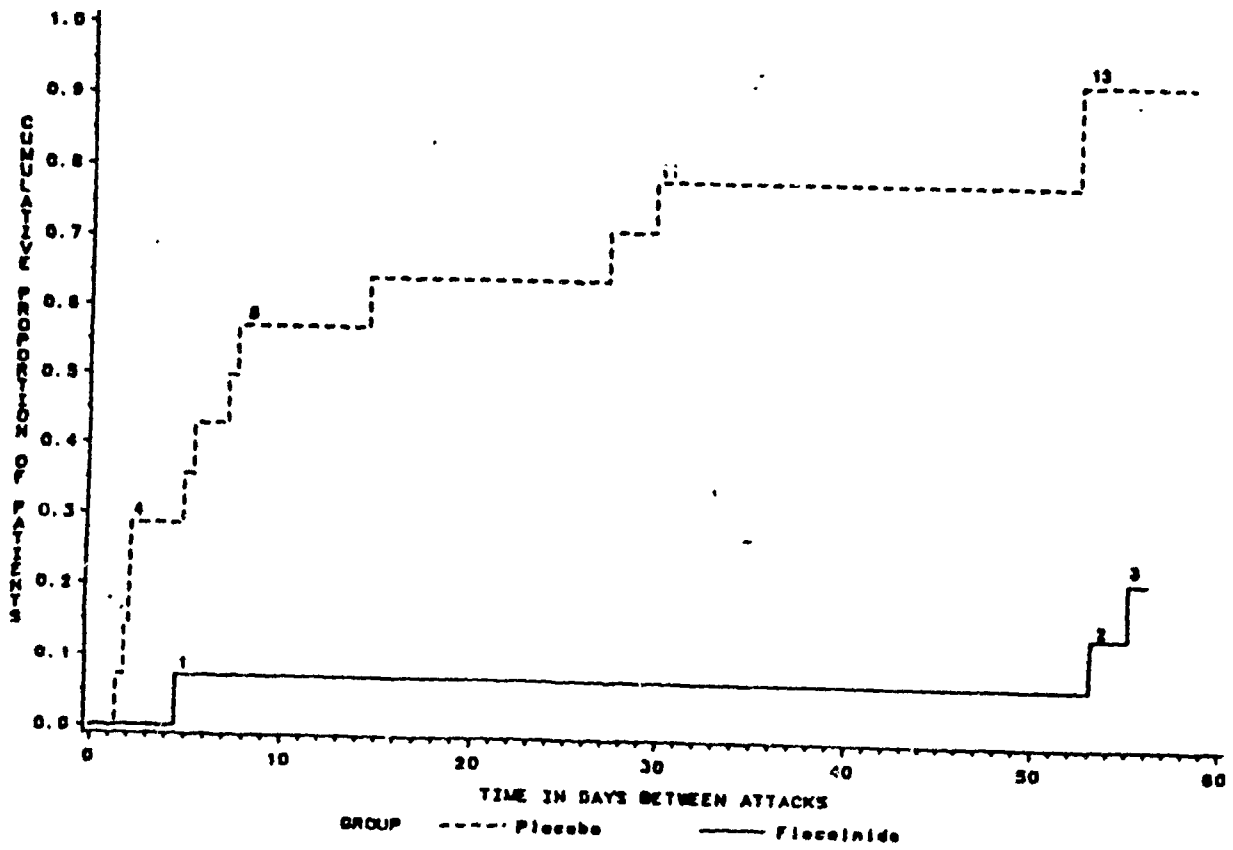


Figure 6. (R818-066)

Interval Between Attacks For PAT Patients Who Received Both Flecainide and Placebo in Crossover Fashion
Study R-818-066 – N=14



Interval Between Attacks For PAF Patients Who Received Both Flecainide and Placebo in Crossover Fashion
Study R-818-066 – N=19

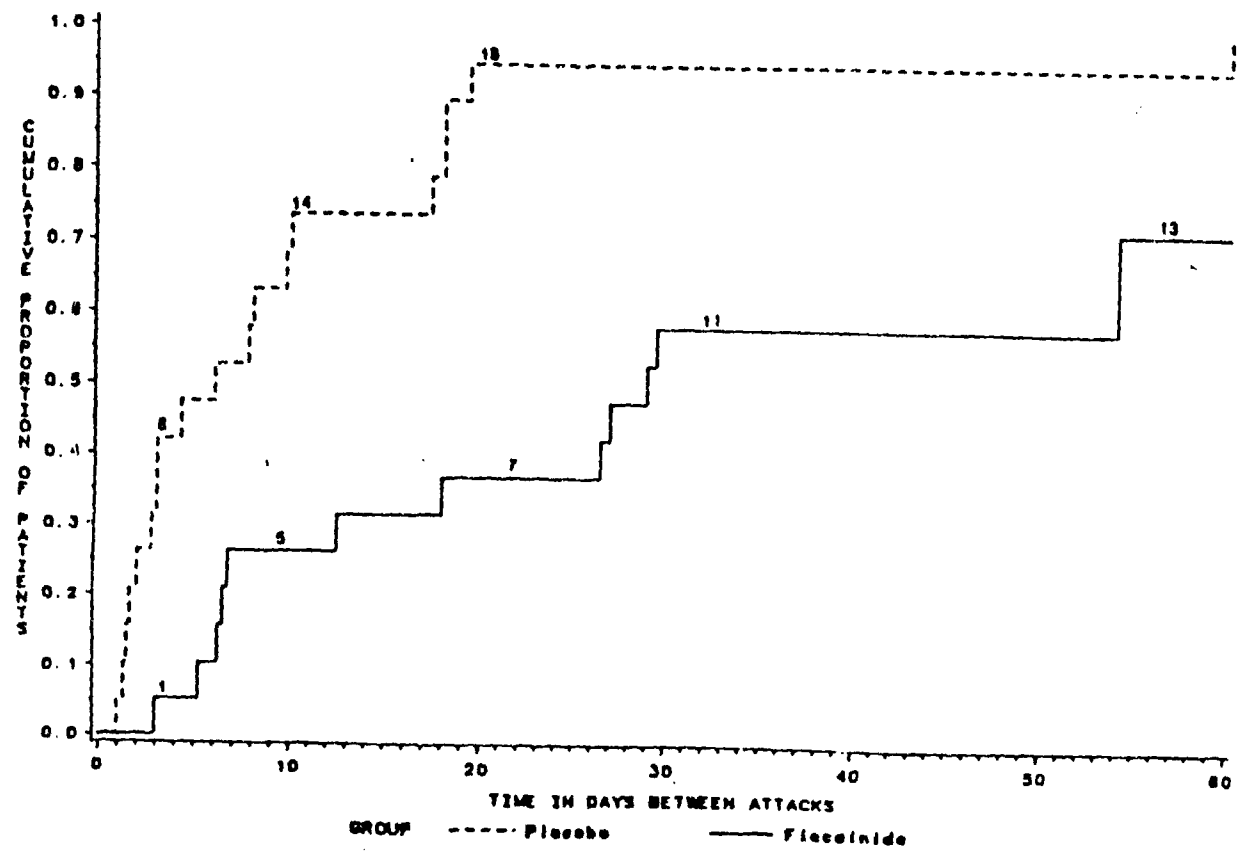


Table 1B (R818-066)

PSVT ATTACK SYMPTOMS[a] EXPERIENCED
DURING PLACEBO OR FLECAINIDE THERAPY: PAT PATIENTS

SYMPTOMS REPORTED WHO[b] PREFERRED TERM	NO. OF PATIENTS REPORTING PLACEBO (N[c] = 13)		FLECAINIDE (N[c] = 3)	
	N	%	N	%
TACHYCARDIA	8	61.5%	3	100.0%
PALPITATION	6	46.2%	1	33.3%
DYSPNEA	4	30.8%	0	0.0%
DIZZINESS	3	23.1%	0	0.0%
HEADACHE	3	23.1%	0	0.0%
NAUSEA	2	15.4%	1	33.3%
ASTHENIA	3	23.1%	0	0.0%
CHEST PAIN	2	15.4%	0	0.0%
FATIGUE	2	15.4%	0	0.0%
SWEATING INCREASED	1	7.7%	0	0.0%
AGITATION	1	7.7%	0	0.0%
FLUSHING	1	7.7%	0	0.0%
MOUTH DRY	0	0.0%	1	33.3%
TACHYCARDIA SUPRAVENTRICULAR	1	7.7%	0	0.0%
VISION ABNORMAL	1	7.7%	0	0.0%
DYSPNEA	1	7.7%	0	0.0%
LARYNGISMUS	1	7.7%	0	0.0%
MALAISE	1	7.7%	0	0.0%
PAIN	1	7.7%	0	0.0%

[a]DATA COMPILED FROM DOCUMENTED PSVT ATTACKS.
[b]WORLD HEALTH ORGANIZATION.
[c]NUMBER OF PATIENTS HAVING DOCUMENTED ATTACKS.

PSVT ATTACK SYMPTOMS[a] EXPERIENCED
DURING PLACEBO OR FLECAINIDE THERAPY: PAF PATIENTS

SYMPTOMS REPORTED WHO PREFERRED TERM	NO. OF PATIENTS REPORTING PLACEBO (N[c] = 19)		FLECAINIDE (N[c] = 13)	
	N	%	N	%
PALPITATION	14	73.7%	9	69.2%
DYSPNEA	7	36.8%	4	30.8%
CHEST PAIN	7	36.8%	1	7.7%
TACHYCARDIA	3	15.8%	4	30.8%
DIZZINESS	4	21.0%	2	15.4%
ARRHYTHMIA	2	10.5%	4	30.8%
FIBRILLATION CARDIAC	3	15.8%	2	15.4%
ASTHENIA	4	21.0%	1	7.7%
NERVOUSNESS	3	15.8%	1	7.7%
SWEATING INCREASED	2	10.5%	1	7.7%
FATIGUE	2	10.5%	1	7.7%
ANXIETY	1	5.3%	1	7.7%
MALAISE	0	0.0%	2	15.4%
SKIN COLD CLAMMY	1	5.3%	1	7.7%
MYALGIA	1	5.3%	0	0.0%
CONFUSION	1	5.3%	0	0.0%
HEADACHE	1	5.3%	0	0.0%
PARESTHESIA	1	5.3%	0	0.0%
TREMOR	1	5.3%	0	0.0%
FLUSHING	1	5.3%	0	0.0%
BRADYCARDIA	0	0.0%	1	7.7%
NAUSEA	0	0.0%	1	7.7%
COUGHING	1	5.3%	0	0.0%
PHARYNGITIS	0	0.0%	1	7.7%
PAIN	1	5.3%	0	0.0%

[a]DATA COMPILED FROM DOCUMENTED PSVT ATTACKS.
[b]WORLD HEALTH ORGANIZATION.
[c]NUMBER OF PATIENTS HAVING DOCUMENTED ATTACKS.

Table 19 (R818-066)

AVERAGE TROUGH[a] PLASMA FLECAINIDE LEVELS: PAT PATIENTS[b]

PATIENTS INCLUDED IN EFFICACY ANALYSIS N = 14	TOTAL DAILY DOSE (MG)	DOSE RANGING (mcg/mL) MEAN + SD	N	RANGE	CROSSOVER (mcg/mL) MEAN + SD	N	RANGE
	100	0.900	1	0.90	0.110	1	0.11
	300	0.430	1	0.43	0.596 ± 0.147	5	0.39 - 0.74
	400	0.710 ± 0.260	6	0.36 - 1.01	0.620 ± 0.134	3	0.47 - 0.73
	OVERALL	0.698 ± 0.254	8	0.36 - 1.01	0.550 ± 0.206	9	0.11 - 0.74

ALL PATIENTS[b] N=17	TOTAL DAILY DOSE (mg)	MEAN + SD	N	RANGE	MEAN + SD	N	RANGE
	100	0.900	1	0.90	0.110	1	0.11
	300	0.430	1	0.43	0.596 ± 0.147	5	0.39 - 0.74
	400	0.760 ± 0.271	7	0.36 - 1.06	0.620 ± 0.134	3	0.47 - 0.73
	OVERALL	0.739 ± 0.266	9	0.36 - 1.06	0.550 ± 0.206	9	0.11 - 0.74

[a]TROUGH IS DEFINED FOR PURPOSES OF THIS ANALYSIS TO BE THOSE SAMPLES TAKEN 8 TO 16 HOURS AFTER THE LAST DOSE OF FLECAINIDE. OVERALL, ONLY 64.3% (18/28) OF THE SAMPLES MET THIS CRITERIA.
[b]ALL PATIENTS WHO RECEIVED FLECAINIDE IN EITHER THE DOSE RANGING OR CROSSOVER PHASE OF THE TRIAL.

AVERAGE TROUGH[a] PLASMA FLECAINIDE LEVELS: PAF PATIENTS[b]

PATIENTS INCLUDED IN EFFICACY ANALYSIS N = 19	TOTAL DAILY DOSE (MG)	DOSE RANGING (mcg/mL) MEAN + SD	N	RANGE	CROSSOVER (mcg/mL) MEAN + SD	N	RANGE
	100	0.240	1	0.24	--	-	--
	200	--	-	--	0.810 ± 0.468	3	0.53 - 1.35
	250	--	-	--	0.860	1	0.86
	300	--	-	--	0.670 ± 0.256	5	0.44 - 1.10
	400	0.914 ± 0.268	7	0.43 - 1.16	0.513 ± 0.170	3	0.41 - 0.71
	OVERALL	0.830 ± 0.344	8	0.24 - 1.16	0.682 ± 0.290	12	0.41 - 1.35

ALL PATIENTS[b] N=25	TOTAL DAILY DOSE (mg)	MEAN + SD	N	RANGE	MEAN + SD	N	RANGE
	100	0.240	1	0.24	--	-	--
	200	--	-	--	0.810 ± 0.468	3	0.53 - 1.35
	250	--	-	--	0.860	1	0.86
	300	1.020	1	1.02	0.785 ± 0.363	6	0.44 - 1.36
	400	0.896 ± 0.261	9	0.43 - 1.16	0.513 ± 0.170	3	0.41 - 0.71
	OVERALL	0.847 ± 0.311	11	0.24 - 1.16	0.734 ± 0.335	13	0.41 - 1.36

[a]TROUGH IS DEFINED FOR PURPOSES OF THIS ANALYSIS TO BE THOSE SAMPLES TAKEN 8 TO 16 HOURS AFTER THE LAST DOSE OF FLECAINIDE. OVERALL, 65.0% (26/40) OF THE SAMPLES MET THIS CRITERIA.
[b]ALL PATIENTS WHO RECEIVED FLECAINIDE IN EITHER THE DOSE RANGING OR CROSSOVER PHASE OF THE TRIAL.

Table 20 (R-818-066)

OVERALL FREQUENCY OF REPORTED CARDIAC ADVERSE EXPERIENCES WHILE ON FLECAINIDE THERAPY

CARDIAC ADVERSE EXPERIENCE	NO. OF PATIENTS ALL (N=42)[a] N	%	PAT (N=17)[a] N	%	PAF (N=25)[a] N	%
PROARRHYTHMIC EVENTS	2	4.8%	0	0.0%	2	8.0%
CONDUCTION DISTURBANCE	2	4.8%	1	5.9%	1	4.0%
MI	0	0.0%	0	0.0%	0	0.0%
DEATH	0	0.0%	0	0.0%	0	0.0%
CHF	0	0.0%	0	0.0%	0	0.0%

[a]NUMBER OF PATIENTS AT RISK

Table 21 (R-818-066)

PATIENT LISTING OF REPORTED CARDIAC ADVERSE EXPERIENCES (CAES) WHILE RECEIVING FLECAINIDE THERAPY

CAE	PATIENT GROUP	SITE/PATIENT NO.	PERIOD: TREATMENT	EVENT
PROARRHYTHMIC EVENT	PAF	07/102	WEEK 2 DOSE RANGING: FLECAINIDE	INCREASE IN NUMBER AND DURATION OF ATTACKS
	PAF	08/102	WEEK 1 DOSE RANGING: FLECAINIDE	PROLONGED PSVT
CONDUCTION DISTURBANCE	PAT	01/002	WEEKS 1 AND 2 DOSE RANGING: FLECAINIDE	SINUS PAUSE FOLLOWED BY JUNCTIONAL ESCAPE BEATS
	PAF	01/108	WEEK 2 DOSE RANGING: FLECAINIDE	BRADYCARDIA TREATED WITH ATROPINE AND EPINEPHRINE RESULTING IN VT.
MI		NONE REPORTED		
DEATH		NONE REPORTED		
CHF		NONE REPORTED		

Table 22 (R-818-066)

FREQUENCY OF ADVERSE EXPERIENCES REPORTED DURING DOSE RANGING: PAT PATIENTS

BODY SYSTEM	WHO[a] PREFERRED TERM	NO. OF PATIENTS	(%) PERCENT
	NONE	4	23.5
AUTONOMIC NERVOUS SYSTEM DISORDERS	DRY MOUTH	1	5.9
BODY AS A WHOLE - GENERAL DISORDERS	HEADACHE	4	23.5
	FATIGUE	1	5.9
CARDIOVASCULAR DISORDERS, GENERAL	HYPOTENSION	1	5.9
CENTR & PERIPH NERV SYST DISORDERS	DIZZINESS	5	29.4
	VERTIGO	1	5.9
	PARESTHESIA	1	5.9
	ATAXIA	1	5.9
	TREMOR	1	5.9
GASTROINTESTINAL SYSTEM DISORDERS	NAUSEA	1	5.9
HEART RATE AND RHYTHM DISORDERS	PALPITATION	1	5.9
PSYCHIATRIC DISORDERS	SOMNOLENCE	2	11.8
	ANXIETY	1	5.9
	LIBIDO DECREASED	1	5.9
VISION DISORDERS	VISION ABNORMAL	8	47.1
	EYE ABNORMALITY	3	17.6
	VISUAL FIELD DEFECT	1	5.9
TOTAL NUMBER OF PATIENTS REPORTING ONE OR MORE ADVERSE EXPERIENCES		13	76.5
TOTAL NUMBER OF PATIENTS		17	

FREQUENCY OF ADVERSE EXPERIENCES REPORTED DURING DOSE RANGING: PAF PATIENTS

BODY SYSTEM	WHO[a] PREFERRED TERM	NO. OF PATIENTS	(%) PERCENT
	NONE	3	12.0
AUTONOMIC NERVOUS SYSTEM DISORDERS	SALIVA ALTERED	1	4.0
	FLUSHING	1	4.0
BODY AS A WHOLE - GENERAL DISORDERS	HEADACHE	3	12.0
	FATIGUE	3	12.0
	CHEST PAIN	1	4.0
	EDEMA	1	4.0
CENTR & PERIPH NERV SYST DISORDERS	DIZZINESS	10	40.0
	ATAXIA	2	8.0
	TWITCHING	1	4.0
	TREMOR	4	16.0
GASTROINTESTINAL SYSTEMS DISORDERS	NAUSEA	4	16.0
	DIARRHEA	3	12.0
HEART RATE AND RHYTHM DISORDERS	PALPITATION	1	4.0
PSYCHIATRIC DISORDERS	NERVOUSNESS	1	4.0
	EUPHORIA	1	4.0
	LIBIDO DECREASED	1	4.0
	SOMNOLENCE	1	4.0
	DYSPHORIA	1	4.0
SKIN AND APPENDAGES DISORDERS	PHOTOSENSITIVITY	1	4.0
	URTICARIA	1	4.0
VISION DISORDERS	VISION ABNORMAL	13	52.0
	DIPLOPIA	1	4.0
	EYE ABNORMALITY	1	4.0
TOTAL NUMBER OF PATIENTS REPORTING ONE OR MORE ADVERSE EXPERIENCES		22	88.0
TOTAL NUMBER OF PATIENTS		25	

[a]WORLD HEALTH ORGANIZATION

Table 23 (R-818-065/066) TTM

Demographics and Associated Cardiac Disorders

PAT Patients

	All Patients[a]		Efficacy Analysis[b]	
Total No. of Patients	49		34	
Sex				
Male	15	30.6%	11	32.4%
Female	34	69.4%	23	67.6%
Age (yrs)				
Mean ± SD	49.8 ± 14.8		50.1 ± 15.0	
Range	(18-78)		(18-78)	
Associated Cardiac[c] Disorders				
None	22	44.9%	14	41.2%
Atherosclerosis	3	6.1%	1	2.9%
Mitral Valve Prolapse	12	24.5%	8	23.5%
Rheumatic Heart Disease	4	8.2%	3	8.8%
Hypertension	10	20.4%	7	20.6%
Cardiomegaly	6	12.2%	4	11.8%
Conduction Disturbance	3	6.1%	3	8.8%
Cardiomyopathy	0	0.0%	0	0.0%
CHF (Class I or II)	1	2.0%	0	0.0%
Sinus Node Disease	0	0.0%	0	0.0%

Demographics and Associated Cardiac Disorders

PAF Patients

	All Patients[a]		Efficacy Analysis[b]	
Total No. of Patients	64		48	
Sex				
Male	40	62.5%	30	62.5%
Female	24	37.5%	18	37.5%
Age (yrs)				
Mean ± SD	57.4 ± 13.0		56.4 ± 13.3	
Range	(23-83)		(23-83)	
Associated Cardiac[c] Disorders				
None	19	29.7%	12	25.0%
Atherosclerosis	18	28.1%	14	29.2%
Mitral Valve Prolapse	5	7.8%	4	8.3%
Rheumatic Heart Disease	1	1.5%	1	2.1%
Hypertension	24	37.5%	18	37.5%
Cardiomegaly	6	9.4%	5	10.4%
Conduction Disturbance	5	7.8%	3	6.3%
Cardiomyopathy	1	1.5%	1	2.1%
CHF (Class I or II)	6	9.4%	4	8.3%
Sinus Node Disease	2	3.1%	1	2.1%

[a] Those patients who received a TTM and qualified for entrance into the R-818-065 and R-818-066 trials.
[b] Those patients who were included in the efficacy analyses - see Sponsor's Clinical Reports.
[c] A patient could have more than one reported cardiac disorder.

Table 24 (R-818-065/066)
TTM

Listing of ECG Diagnoses Classified
by Medical Monitor as Representing PSVT

ECG Diagnosis	Frequency (#)
Atrial Fib/Flutter	25
Atrial Fibrillation	892
Atrial Flutter	126
Atrial Tachycardia	7
Junctional Tach.	1
Paroxysmal A-Fib	33
Paroxysmal Atrial Tach.	20
PSVT	25
Supraventricular Tach.	305

Number of occurrences in database.

Table 25 (R-818-065/066)

Listing of ECG Diagnoses Classified by
Medical Monitor as Representing Other
Symptomatic Rhythm Disorders

ECG Diagnosis	Frequency (#)
Accelerated IVR	1
APC (Paired)	1
APC's	349
Atrial Bigeminy	9
Bradycardia	63
Cardiac Arrest	1
Idioventricular Rhythm	8
Junct. Escape Beat	11
Junctional (Nodal) Rhythm	5
Malfunctioning Pacemaker	1
Occ. Spontaneous Beats	1
Premature Aberrant Beats	33
Salvo's (3-4 Beats)	24
Sinus Bradycardia	76
Sinus Pause	16
Sinus Tachycardia	181
SPC	39
SPC's Conducted Aberrant	13
Ventricular Bigeminy	3
Ventricular Escape Beat	4
Ventricular Tachycardia	3
VPC (Interpolated)	2
VPC's	356
VPC's (Multiform)	71
VPC's (Paired)	50
W.A.P.	9
Wandering Pacemaker	10
Wide Complex Tachycardia	27

#: Number of occurrences in database.

Table 26 (2-818-065/066) TTM

Overall Association of Symptoms and Diagnosis of PSVT Attacks Based on Transtelephonic Monitoring Calls

PAT Patients

Diagnosis[a]	Calls With Symptoms N	Calls With Symptoms %	Calls Without Symptoms N	Calls Without Symptoms %	All Calls N	All Calls %
Normal Rhythm	72	14.4%	297	67 0%	369	39.1%
PSVT Attack[b]	314	62.7%	30	6.8%	344	36.4%
Other[c] Symptomatic Rhythm Disorders	115	22.9%	116	26.2%	231	24.5%
Total	501		443		944	
% of Total	53.1%		46.9%		100.0%	

[a]Statistically significant association between calls with and without symptoms and the presence or absence of symptomatic ECG diagnoses; Chi square = 369.5, df = 2, $p \leq 0.001$.
[b]Diagnosis of PSVT (Table 3).
[c]Diagnosis of "other symptomatic rhythm disorders" (Table 25) without the presence of PSVT.

Overall Association of Symptoms and Diagnosis of PSVT Attacks Based on Transtelephonic Monitoring Calls

PAF Patients

Diagnosis[a]	Calls With Symptoms N	Calls With Symptoms %	Calls Without Symptoms N	Calls Without Symptoms %	All Calls N	All Calls %
Normal Rhythm	165	12.6%	748	70.5%	913	38.4%
PSVT Attack[b]	909	69.2%	112	10.6%	1021	43.0%
Other[c] Symptomatic Rhythm Disorders	240	18.3%	201	18.9%	441	18.6%
Total	1314		1061		2375	
% of Total	55.3%		44.7%		100.0%	

[a]Statistically significant association between calls with and without symptoms and the presence or absence of symptomatic ECG diagnoses; Chi square = 369.5, df = 2, $p \leq 0.001$.
[b]Diagnosis of PSVT (Table 3).
[c]Diagnosis of "other symptomatic rhythm disorders" (Table 25) without the presence of PSVT.

Table 27 (R-818-065/066) TTM

Frequency of Specific Symptoms and Their Association With Various ECG Diagnoses

PAT Patients

WHO Preferred[a] Term	Frequency[b] of Reports	Symptomatic Rhythm Disorder[c] None N	None %	PSVT N	PSVT %	Other * N	Other * %
Tachycardia	230	17	7.4%	168	73.0%	45	19.6%
Palpitations	143	21	14.7%	90	62.9%	32	22.4%
Dyspnea	86	3	3.5%	65	75.6%	18	20.9%
Chest Pain	75	17	22.7%	45	60.0%	13	17.3%
Dizziness	65	6	9.2%	45	69.2%	14	21.5%
Asthenia	47	3	6.4%	28	59.7%	16	34.0%
Fatigue	24	3	12.5%	16	66.7%	5	20.8%
Nausea	13	2	15.4%	10	76.9%	1	7.7%
Nervousness	7	1	14.3%	1	14.3%	5	71.4%
Increased Sweating	18	4	22.2%	13	72.2%	1	5.6%
Syncope	3	1	33.3%	1	33.3%	1	33.3%
Combined Arrhythmia[d]	11	0	0.0%	10	90.9%	1	9.1%

[a]World Health Organization - Preferred term symptoms which were selected *a priori* by the 3M Riker medical monitor to be most likely to be reported with an attack of PSVT (see Table 7).
[b]Number of TTM calls where the patient reported this symptom.
[c]Number of times this symptom was recorded and the ECG diagnosis was consistent with no arrhythmia, an attack of PSVT, or possible other symptomatic arrhythmias.
[d]Combined arrhythmia were those calls in which the patient reported as his/her symptom one or more of the following: paroxysmal atrial tachycardia, supraventricular arrhythmia, supraventricular tachycardia, atrial arrhythmia, arrhythmia, or atrial flutter.

* Other - see the listing of ECG Dx. Table 25.

Frequency of Specific Symptoms and Their Association With Various ECG Diagnoses

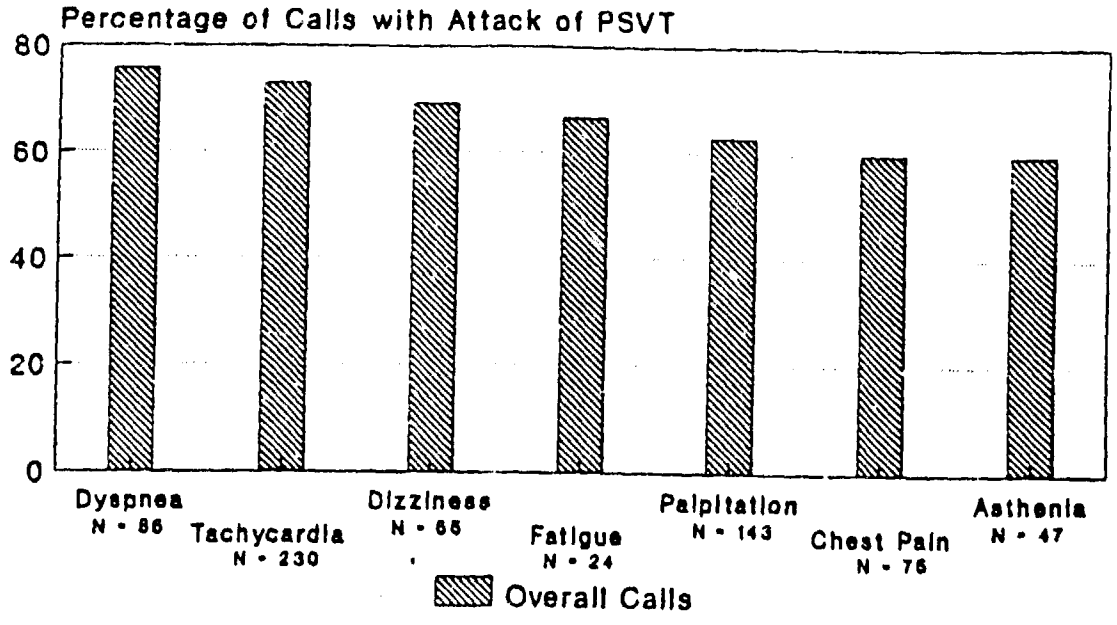
PAF Patients

WHO Preferred[a] Term	Frequency[b] of Reports	Symptomatic Rhythm Disorder[c] None N	None %	PSVT N	PSVT %	Other * N	Other * %
Tachycardia	232	28	12.1%	170	73.3%	34	14.7%
Palpitations	578	37	6.4%	453	78.4%	88	15.2%
Dyspnea	178	10	5.6%	136	76.4%	32	18.0%
Chest Pain	131	17	13.0%	86	65.6%	28	21.4%
Dizziness	112	10	8.9%	86	76.8%	16	14.3%
Asthenia	89	9	10.1%	62	69.7%	18	20.2%
Fatigue	87	36	41.4%	45	51.7%	6	6.9%
Nausea	14	7	50.0%	6	42.9%	1	7.1%
Nervousnes	43	4	9.3%	22	51.2%	17	39.5%
Increased Sweating	24	3	12.5%	19	79.2%	2	8.3%
Syncope	3	1	33.3%	1	33.3%	1	33.3%
Combined Arrhythmia[d]	155	7	4.5%	127	81.9%	1	13.6%

[a]World Health Organization - Preferred term symptoms which were selected *a priori* by the 3M Riker medical monitor to be most likely to be reported with an attack of PSVT (see Table 7).
[b]Number of TTM calls where the patient reported this symptom.
[c]Number of times this symptom was recorded and the ECG diagnosis was consistent with no arrhythmia, an attack of PSVT, or possible other symptomatic arrhythmias.
[d]Combined arrhythmia were those calls in which the patient reported as his/her symptom one or more of the following: paroxysmal atrial tachycardia, supra ventricular arrhythmia, supraventricular tachycardia, atrial arrhythmia, arrhythmia, or atrial flutter.

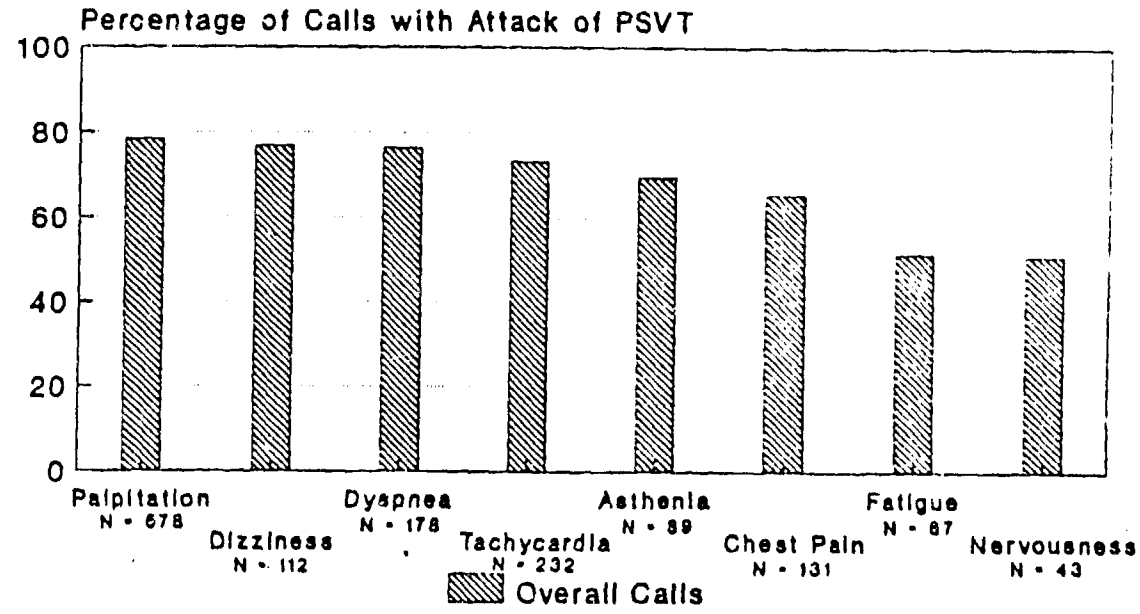
Figure 7 (R-818-065/066) TTM

Percent of Calls with Attacks of PSVT By Symptom: PAT Patients



N = Number of calls where this symptom was reported.

Percent of Calls with Attack of PSVT By Symptom: PAF Patients



N = Number of calls where this symptom was reported.

Table 28 (R818-065/066) TTM

Comparison of Frequency of Reported PSVT Symptoms While on Flecainide and Placebo Therapy During Double-Blind Crossover Phase

PAT Patients (N = 34)

Symptom[a]	Number of Patients Reporting One or More Occurrences While on Flecainide N	Flecainide %	Placebo N	Placebo %	Number of Calls Where This Symptom Was Reported Flecainide[b]	Placebo[b]	Paired Estimate[c] of Median Interval Between Occurrences Flecainide	Placebo	N[d]	P-Value[e]
Tachycardia	7[f]	20.6%	26[f]	76.5%	12	79	>55[g]	10.0	27	<0.001
Palpitations	5[f]	14.7%	12[f]	35.3%	10	23	>54[g]	22.0	15	0.024
Dyspnea	3[f]	8.8%	12[f]	35.3%	6	24	67.0	19.0	13	0.002
Chest Pain	3	8.8%	11	32.4%	8	23	>55[g]	14.8	12	0.012
Dizziness	3	8.8%	9	26.5%	3	15	67.0	27.0	11	0.028
Asthenia	1	2.9%	5	14.7%	1	11	[h]	[h]	6	[h]
Fatigue	2	5.9%	5	14.7%	3	5	[h]	[h]	7	[h]
Syncope	1	2.9%	0	0.0%	1	0	[h]	[h]	1	[h]
Nausea	2	5.9%	3	8.8%	3	7	[h]	[h]	4	[h]
Nervousness	0	0.0%	1	2.9%	0	1	[h]	[h]	1	[h]
Increased Sweating	1	2.9%	1	2.9%	1	2	[h]	[h]	2	[h]

[a] WHO Preferred Terminology
[b] There was a total of 1,860 days of monitoring on flecainide therapy and 1,215 days of monitoring on placebo therapy.
[c] Product limit estimate of the median days between occurrences of the symptom in those patients reporting the symptom on one or both treatments.
[d] Number of patients reporting the symptom on one or both treatments.
[e] P-value associated with the Paired Prentice-Wilcoxon test statistic.
[f] Statistically significant difference, $p \leq .05$, based on McNemar's test.
[g] Product limit estimate of median could not be determined directly due to so few patients having symptom. Sample median interval between occurrences was used to approximate the true median. This estimate is an underestimate of the true median.
[h] Insufficient data available to perform analysis.

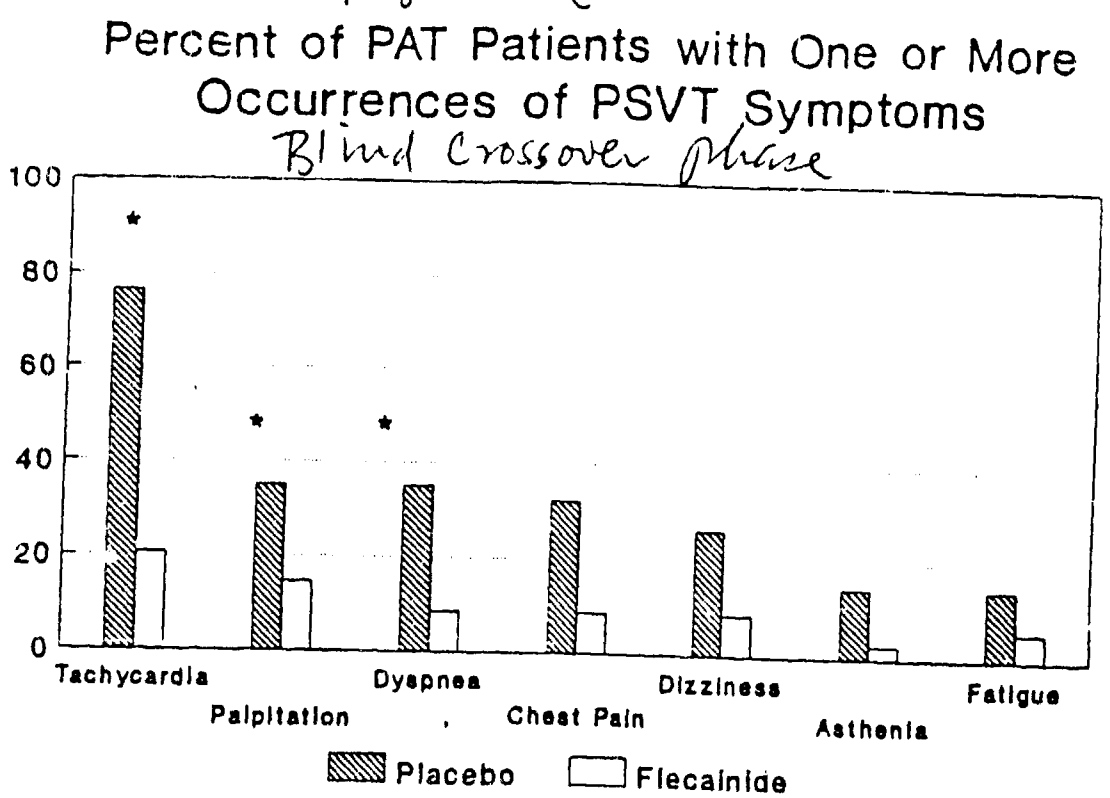
Comparison of Frequency of Reported PSVT Symptoms While on Flecainide and Placebo Therapy During Double-Blind Crossover Phase

PAF Patients (N = 48)

Symptom[a]	Number of Patients Reporting One or More Occurrences While on: Flecainide N	Flecainide %	Placebo N	Placebo %	Number of Calls Where This Symptom Was Reported Flecainide[b]	Placebo[b]	Paired Estimate[c] of Median Interval Between Occurrences Flecainide	Placebo	N[d]	P-Value[e]
Tachycardia	16	33.3%	20	41.7%	27	42	56.0	26.0	30	0.027
Palpitations	21[f]	43.8%	35[f]	72.9%	76	112	54.0	9.0	39	<0.001
Dyspnea	12[f]	25.0%	23[f]	4	25	54	54.0	13.0	25	0.003
Chest Pain	7	14.6%	14	2	22	30	59.0	20.0	17	0.023
Dizziness	7	14.6%	8	1...6	11	14	53.0	19.0	12	0.374
Asthenia	3	6.3%	9	18.8%	4	14	57.0	22.5	10	0.059
Fatigue	3	6.3%	6	12.5%	3	5	[g]	[g]	7	[g]
Syncope	1	2.1%	1	2.1%	1	1	[g]	[g]	2	[g]
Nausea	3	6.3%	1	2.1%	3	1	[g]	[g]	4	[g]
Nervousness	1	2.1%	6	12.5%	12	8	[g]	[g]	6	[g]
Increased Sweating	0	0.0%	3	6.3%	0	6	[g]	[g]	3	[g]

[a] WHO Preferred Terminology
[b] There was a total of 2,204 days of monitoring on flecainide therapy and 1,369 days of monitoring on placebo therapy.
[c] Product limit estimate of the median days between occurrences of the symptom in those patients reporting the symptom on one or both treatments.
[d] Number of patients reporting the symptom on one or both treatments.
[e] P-value associated with the Paired Prentice-Wilcoxon test statistic.
[f] Statistically significant difference, $p \leq .05$, based on McNemar's test.
[g] Insufficient data to perform analysis.

Figure 8 (R-818-065/066) TTM



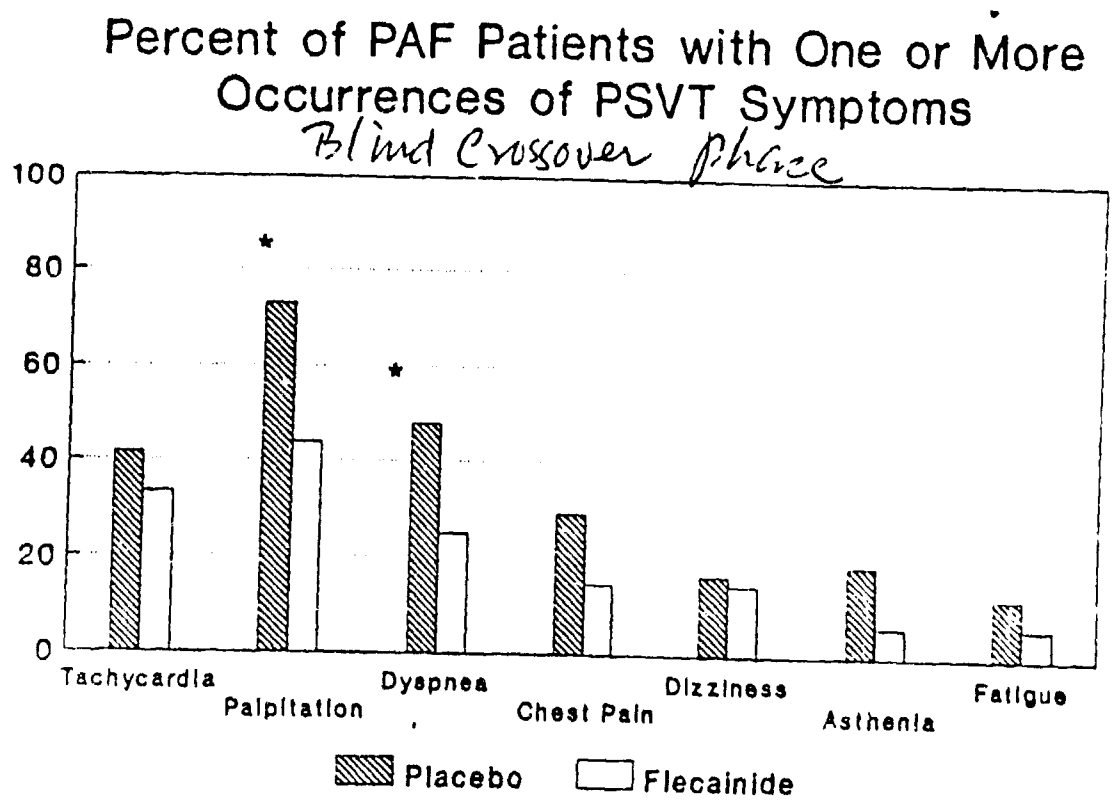


Table 29 Long-Term Rx (R-818-065/066)

NUMBER OF PATIENT MONTHS AND NUMBER OF PATIENTS
ON EACH TOTAL DAILY DOSE OF FLECAINIDE: PAT PATIENTS

Flecainide Total Daily Dose (mg)	Patient Months on Dose N=376	No. of Patients on Dose[a] N=25
50	2 (0.5%)	1 (4%)
100	14 (3.7%)	3 (12%)
150	13 (3.5%)	1 (4%)
200	131 (34.8%)	11 (44%)
250	8 (2.1%)	1 (4%)
300	128 (34.0%)	12 (48%)
400	80 (21.3%)	6 (24%)

[a] A patient may have taken more than one total daily dose of flecainide while receiving long-term therapy.

NUMBER OF PATIENT MONTHS AND NUMBER OF PATIENTS
ON EACH TOTAL DAILY DOSE OF FLECAINIDE: PAF PATIENTS

Flecainide Total Daily Dose (mg)	Patient Months on Dose N=556	No. of Patients on Dose[a] N=41
0[b]	7 (1.3%)	2 (5%)
100	1 (0.2%)	3 (7%)
150	1 (0.2%)	2 (5%)
200	181 (32.5%)	17 (41%)
250	28 (5.0%)	3 (7%)
300	181 (32.5%)	26 (63%)
350	0 (0.0%)	1 (2%)
400	116 (20.9%)	12 (29%)
450	10 (1.8%)	1 (2%)
500	26 (4.7%)	1 (2%)
600	5 (0.9%)	2 (5%)

[a] ...ave taken more than one total daily dose of flecainide
...long-term therapy.
[b] ...untreated (flor a total of 7 months
...rapy due toboth dosage regimens

Table 30 Long-Term Rx (R-818-065 + 066)

FLECAINIDE DOSAGE CHANGES DURING LONG-TERM THERAPY: PAT PATIENTS

Reason for Dosage Change	No. of Changes N=16	No. of Patients With Changes N=25[a]
Lack of Therapeutic Effect	7 (44%)	6 (24%)
Adverse Experience	5 (31%)	5 (20%)
Lack of Therapeutic Effect and Adverse Experience	4 (25%)	4 (16%)

[a] A patient may have had more than one reason for a dosage change; more than one dosage change; or no dosage change.

FLECAINIDE DOSAGE CHANGES DURING LONG-TERM THERAPY: PAF PATIENTS

Reason for Dosage Change	No. of Changes N=64	No. of Patients With Changes N=41[a]
Lack of Therapeutic Effect	20 (31%)	14 (34%)
Adverse Experience	29 (45%)	17 (41%)
Lack of Therapeutic Effect and Adverse Experience	14 (22%)	9 (22%)
Patient Lowered Dose on Own	1 (2%)	1 (2%)

Table 31 Long-Term Rx (R-615-CC-FAC)

REASONS FOR DISCONTINUATION: PAT PATIENTS

Study and Patient No.	No. of Days on Flecainide	Reason for Discontinuation	Comment
065-01-005	412	Personal	Patient did not want to participate any longer
065-05-002	377	Lost to Follow-up	----
065-08-006	353	Adverse Experience	Forgetfulness and memory loss
065-10-003	879	Personal	Patient decided to change physicians
066-04-001	59	Therapy no longer needed	Bypass tract surgically excised; arrnythmia no longer present
066-05-003	25	Lost to Follow-up	----
066-05-005	88	Therapy no longer needed	PSVT did not recur after patient discontinued therapy

REASONS FOR DISCONTINUATION: PAF PATIENTS

Study and Patient No.	No. of Days on Flecainide	Reason for Discontinuation	Comment
065-01-102	672	Inadequate response	Short bursts of A fib and frequent PACs
065-01-104	608	Adverse Experience	Constipation
065-01-106	475	Personal	Patient travels and is unable to make frequent visits
065-01-107	375	Personal	Patient can't travel to site anymore
065-01-109	264	Personal	Patient can't travel to study site
065-01-110	307	Personal	Patient discontinued drug himself due to hip and elbow pain. Investigator did not feel pain was related to flecainide.
065-10-102	63[illegible]	Noncompliance	----
065-10-104	343	Noncompliance	----
065-10-105	134	Inadequate response	Increased duration of attack
066-01-103	72	Inadequate response Arrnythmia worse[a]	Patient's perception and electrocardiogram More sustained (but slower) atrial flutter/ fib episodes have decreased in frequency but increased in duration.
[illegible]	314	Inadequate response	Increase in frequency and duration of attacks
[illegible]	[illegible]33	Other	Concomitant use of beta blocker
[illegible]	[illegible]	Lost to Follow-up	----
[illegible]	[illegible]	[illegible]adequate response	Incessant atrial fibrillation
[illegible]	[illegible]	[illegible]w-up	----
[illegible]	[illegible]	[illegible]ence	Impotence

[illegible]hythmic event probably related

[illegible]y after 133 days, at the request [illegible] to the concomitant use of flecainide and ventricular rate. The patient [illegible] beta blocker after leaving the

Table 32 Long-Term Rx (R-818-065 + -066)

NUMBER OF PSVT ATTACKS BY MONTH OVER ONE YEAR OF FLECAINIDE THERAPY: PAT PATIENTS (N=25)

Month	N[b]	X[c]	No. of Patients (%) Reporting X Attacks/Month[a] 0	1	2	3	>4
1	22		18 (82%)	1 (5%)	0 (0%)	1 (5%)	2 (9%)
2	17		13 (76%)	1 (6%)	1 (6%)	1 (6%)	1 (6%)
3	16		12 (75%)	1 (6%)	3 (19%)	0 (0%)	0 (0%)
4	14		10 (71%)	1 (7%)	0 (0%)	2 (14%)	1 (7%)
5	17		11 (65%)	3 (18%)	2 (12%)	1 (6%)	0 (0%)
6	16		14 (88%)	0 (0%)	2 (12%)	0 (0%)	0 (0%)
7	15		11 (73%)	1 (7%)	1 (7%)	0 (0%)	2 (13%)
8	18		13 (72%)	2 (11%)	0 (0%)	3 (17%)	0 (0%)
9	13		7 (54%)	2 (15%)	2 (15%)	2 (15%)	0 (0%)
10	16		11 (69%)	0 (0%)	2 (12%)	2 (12%)	1 (6%)
11	13		10 (77%)	0 (0%)	1 (8%)	2 (15%)	0 (0%)
12	19		12 (63%)	2 (11%)	1 (5%)	1 (5%)	3 (16%)

[a] If a reporting period covered more than 1 month, the number of PSVT attacks reported at that visit was divided by the number of months since the previous visit. If the result was a fraction, the number was rounded up to the nearest integer.
[b] Number of patients who were evaluated at the monthly time point after initiation of long-term flecainide therapy.
[c] Number of PSVT attacks per month.

NUMBER OF PSVT ATTACKS BY MONTH OVER ONE YEAR OF FLECAINIDE THERAPY: PAF PATIENTS (N=41)

Month	N[b]	X[c]	No. of Patients (%) Reporting X Attacks/Month[a] 0	1	2	3	>4
1	34		19 (56%)	5 (15%)	6 (18%)	1 (3%)	3 (9%)
2	31		16 (52%)	9 (29%)	1 (3%)	2 (6%)	3 (10%)
3	33		22 (67%)	3 (9%)	3 (9%)	1 (3%)	4 (12%)
4	28		16 (57%)	6 (21%)	2 (7%)	0 (0%)	4 (14%)
5	30		19 (63%)	5 (17%)	1 (3%)	3 (10%)	2 (7%)
6	28		18 (64%)	1 (4%)	3 (11%)	1 (4%)	5
7	29		17 (59%)	2 (7%)	6 (21%)	2 (7%)	
8	26		16 (62%)	5 (19%)	3 (12%)	2 (8%)	
9	26		17 (65%)	3 (12%)	1 (4%)	4 (15%)	
10	25		16 (64%)	3 (12%)	1 (4%)	5	
11	24		17 (71%)	4 (17%)	0 (0%)		
12	19		14 (74%)	1 (5%)	2 (11%)		

[a] If a reporting period covered more than ... attacks reported at that visit was ... since the previous visit. If the ... was rounded up to the nearest integer.
[b] Number of patients who were evaluated ... initiation of long-term flecainide therapy.
[c] Number of PSVT attacks per month.

Table 33 Long-Term Rx (R-818-065 + -066)

NUMBER OF PATIENT MONTHS (%) WITH A GIVEN NUMBER OF PSVT ATTACKS: PAT PATIENTS (N=25)

No. of Reported PSVT Attacks Per Month[a]	No. of Patient Months With This No. of PSVT Attacks
0	276 (75%)
1	33 (9%)
2	18 (5%)
3	18 (5%)
≥4	22 (6%)
Total No. of Patient Months With Efficacy Data	367

[a]If a reporting period covered more than 1 month, the number of PSVT attacks reported at that visit was divided by the number of months since the previous visit. If the result was a fraction, the number was rounded up to the nearest integer.

NUMBER OF PATIENT MONTHS (%) WITH A GIVEN NUMBER OF PSVT ATTACKS: PAF PATIENTS (N=41)

No. of Reported PSVT Attacks Per Month[a]	No. of Patient Months With This No. of PSVT Attacks
0	322 (64%)
1	65 (13%)
2	48 (9%)
3	24 (5%)
≥4	47 (9%)
Total No. of Patient Months With Efficacy Data	506

[a]If a reporting period covered more than 1 month, the number of PSVT attacks reported at that visit was divided by the number of months since the previous visit. If the result was a fraction, the number was rounded up to the nearest integer.

Table 34 Long-Term Rx (R-818-065/066)

INCIDENCES (%) OF REPORTED PSVT SYMPTOMS FOR LONG-TERM PAF PATIENTS

MONTHS N:	0-3 25	>3-6 21	>6-9 20	>9-12 19	>12-15 14	>15 9	OVERALL 25
PALPITATION	20	19	35	37	29	22	52
TACHYCARDIA	20	19	15	16	7		36
CHEST PAIN	4	5	5	5		22	20
DIZZINESS	4		10	11	7	11	20
ARRHYTHMIA				5	7	11	12
ASTHENIA	8		5				12
DYSPNEA	4	5	15	11	7		12
FATIGUE			5	5		11	12
AGITATION						11	4
NAUSEA			5				4
NERVOUSNESS		5					4
PULSUS MAGNUS	4						4
SWEATING INCREASED	4						4
TREMOR		5					4
VISION ABNORMAL	4						4
PERCENT OF PATIENTS REPORTING AT LEAST ONE SYMPTOM	40	33	55	53	36	33	76

INCIDENCES (%) OF REPORTED PSVT SYMPTOMS FOR LONG-TERM PAF PATIENTS

MONTHS N.	0-3 40 A	>3-6 37	>6-9 36	>9-12 31	>12-15 17	>15 13	OVERALL 41
PALPITATION	50	41	53	42	41	23	80
DYSPNEA	10	14	8	10			22
TACHYCARDIA	5	8	3	3	12	8	17
ARRHYTHMIA	10	3		3	6	15	15
ASTHENIA	8	11	8	6	6		15
CHEST PAIN	5	8	3	3			15
DIZZINESS	13	8		3			15
FATIGUE	8		6	6			10
NERVOUSNESS		5	3				7
NAUSEA	3	3					5
SWEATING INCREASED			3	3			5
ANXIETY	3						2
DYSPEPSIA	3						2
DYSPHORIA		3					2
FIBRILLATION ATRIAL					6		2
FIBRILLATION CARDIAC	3						2
FLUSHING	3						2
INSOMNIA			3	3			2
LARYNGISMUS	3		3				2
THINKING ABNORMAL	3						2
TREMOR	3						2
VISION ABNORMAL		3					2
PERCENT OF PATIENTS REPORTING AT LEAST ONE SYMPTOM	65	57	81	48	53	38	85

A: PATIENT NUMBER 085-10-104 DID NOT REPORT THE PRESENCE OR ABSENCE OF PSVT SYMPTOMS UNTIL MONTH

Table 35 (R-818-074)

PATIENT ACCOUNTABILITY: PAT PATIENTS

		No. of Patients
PERIOD 1	Entered	28
	Reasons for Discontinuation	
	Cardiac AE	1
	Noncardiac AE	3
	Personal	1
	Total Discontinued	5
PERIOD 2	Entered	23
	Reasons for Discontinuation	
	Other	2
	Total Discontinued	2
PERIOD 3	Entered	21
	Total Discontinued	0
PERIOD 4	Entered	21
	Reason Discontinuation	
	Cardiac AE	1
	Noncardiac AE	1
	Total Discontinued	2
PERIOD 5	Entered	19
	Reason Discontinuation	
	Noncardiac AE	2
	Total Discontinued	2
Completed study		17
Included in primary efficacy analyses		14

PATIENT ACCOUNTABILITY: PAF PATIENTS

		No. of Patients
PERIOD 1	Entered	45
	Reasons for Discontinuation	
	Noncardiac AE	1
	Other	2
	Lost to Follow-up	1
	Total Discontinued	4
PERIOD 2	Entered	41
	Reasons for Discontinuation	
	Inadequate Response	1
	Total Discontinued	1
PERIOD 3	Entered	40
	Reasons for Discontinuation	
	Cardiac AE	1
	Personal	1
	Total Discontinued	2
PERIOD 4	Entered	38
	Reason Discontinuation	
	Cardiac AE	1
	Noncardiac AE	2
	Personal	2
	Total Discontinued	5
PERIOD 5	Entered	33
	Reason Discontinuation	
	Noncardiac AE	4
	Personal	1
	Total Discontinued	5
Completed study		28
Included in primary efficacy analyses		28

Table 36. (R-818-074)

REASONS FOR PATIENT EXCLUSION FROM THE PRIMARY EFFICACY ANALYSES FOR PATIENTS ENTERING AND/OR COMPLETING PERIOD 5[a]

PAT Patients

Study No./Patient No.	Reason for Exclusion
R-818-074-05-001	Pt discontinued after day 1 in period 5
R-818-074-05-002	Study-drug noncompliant
R-818-074-05-003	Pt discontinued after day 2 in period 5
R-818-074-06-004	Study-drug noncompliant
R-818-074-21-002	Study-drug noncompliant

PAF Patients

Study No./Patient No.	Reason for Exclusion
R-818-074-02-104	Changes in digoxin dose
R-818-074-04-101	Unanalyzable arrhythmia data
R-818-074-05-102	Changes in propranolol dose
R-818-074-14-102	Unanalyzable arrhythmia data
R-818-074-20-101	Pt discontinued on day 3 in period 5

[a]Part of the arrhythmia data from patient R-818-074-02-[illegible] was excluded from the primary efficacy analysis. From 12/25/87 - 1/15/88 the patient ran out of period 4 drug. The patient also remained on study drug for 6 days after the end of period 5 on 2/13/88. The arrhythmia data collected between 12/25/87 - 1/15/88 and 2/13/88 - 2/19/88 was excluded from the primary efficacy analysis.

Table 37 (R-818-074)

QUALIFICATION SUMMARY: PAT PATIENTS

DAYS TO SECOND ATTACK IN SCREENING	ALL PATIENTS (N=28)		PATIENTS INCLUDED (N=14)		PATIENTS EXCLUDED (N=14)	
	N	(%)	N	(%)	N	(%)
1[a]	2	(7.1%)	1	(7.1%)	1	(7.1%)
2 - 7	11	(39.3%)	5	(35.7%)	6	(42.9%)
8 - 14	7	(25.0%)	5	(35.7%)	2	(14.3%)
15 - 21	6	(21.4%)	3	(21.4%)	3	(21.4%)
22 - 28	0	(0.0%)	0	(0.0%)	0	(0.0%)
>28	2[b]	(7.1%)	0	(0.0%)	2[b]	(14.3%)
TOTAL	28	(100.0%)	14	(100.0%)	14	(100.0%)
MEAN ± SD[c]			9.1 ± 4.9		12.7 ± 10.7	

[a]PATIENTS HAD TWO ATTACKS ON SAME DAY.
[b]ONE PATIENT HAD TWO ATTACKS IN 30 DAYS, AND ONE IN 36 DAYS.
[c]P-VALUE OF T-TEST COMPARING INCLUDED AND EXCLUDED PATIENTS, P < 0.285.

QUALIFICATION SUMMARY: PAF PATIENTS

DAYS TO SECOND ATTACK IN SCREENING	ALL PATIENTS (N=45)		PATIENTS INCLUDED (N=28)		PATIENTS EXCLUDED (N=17)	
	N	(%)	N	(%)	N	(%)
0	2[a]	(4.4%)	0	(0.0%)	2[a]	(11.8%)
2 - 7	16	(35.6%)	9	(32.1%)	7	(41.2%)
8 - 14	12	(26.7%)	9	(32.1%)	3	(17.6%)
15 - 21	6	(13.3%)	3	(10.7%)	3	(17.6%)
22 - 28	4	(8.9%)	3	(10.7%)	1	(5.9%)
>28	5[b,c]	(11.1%)	4[b]	(14.3%)	1[c]	(5.9%)
TOTAL	45	(100.0%)	28	(100.0%)	17	(100.0%)
MEAN ± SD[d]			14.1 ± 10.6		11.5 ± 9.4	

[a]TWO PATIENTS HAD ONLY ONE ATTACK IN SCREENING.
[b]ONE PATIENT HAD TWO ATTACKS IN 31 DAYS, ONE IN 32 DAYS, ONE IN 33 DAYS AND ONE IN 37 DAYS.
[c]ONE PATIENT HAD TWO ATTACKS IN 34 DAYS.
[d]P-VALUE OF TWO-TAILED T-TEST COMPARING INCLUDED AND EXCLUDED PATIENTS, P < 0.428.

Table 38 (R-818-0174)

NUMBER OF ATTACKS EXCLUDED FROM EFFICACY ANALYSIS

PAT PATIENTS

REASON FOR EXCLUDING ATTACK	DOSE (MG BID) 0	25	50	100	150	TOTAL
PATIENTS INCLUDED IN PRIMARY ANALYSES						
OCCURRED IN FIRST THREE DAYS	6	0	1	0	0	7
PATIENT ALREADY REPORTED FOUR ATTACKS	9	7	18	1	0	35
OCCURRED AFTER DAY 31	2	0	0	0	0	2
OCCURRED AFTER STUDY STOPPED	0	0	0	0	1	1
PATIENTS EXCLUDED FROM PRIMARY ANALYSES						
OCCURRED IN FIRST THREE DAYS	0	3	0	0	0	3
PATIENT ALREADY REPORTED FOUR ATTACKS	2	5	10	0	0	17
OCCURRED AFTER DAY 31	0	2	1	0	1	4

NUMBER OF ATTACKS EXCLUDED FROM EFFICACY ANALYSIS

PAF PATIENTS

REASON FOR EXCLUDING ATTACK	DOSE (MG BID) 0	25	50	100	150	TOTAL
PATIENTS INCLUDED IN PRIMARY ANALYSES						
OCCURRED IN FIRST THREE DAYS	2	1	1	0	0	4
BEFORE ADJUSTED START DATE	0	1	1	1	1	4
PATIENT ALREADY REPORTED FOUR ATTACKS	15	7	10	4	7	43
OCCURRED AFTER DAY 31	0	2	0	5	1	8
PATIENTS EXCLUDED FROM PRIMARY ANALYSES						
OCCURRED IN FIRST THREE DAYS	0	0	1	1	1	3
PERIOD DELETED	1	2	2	0	1	6
PATIENT ALREADY REPORTED FOUR ATTACKS	2	12	0	2	6	22

Table 39 (R-818-074)

NUMBER OF ATTACKS AND DAYS IN TREATMENT
(ALL ATTACKS BEGINNING AFTER STUDY DAY 3)

PAT PATIENTS INCLUDED IN PRIMARY EFFICACY ANALYSES

NUMBER OF ATTACKS	NUMBER OF PATIENTS REPORTING ATTACKS DOSE (MG BID) 0 N = 14	25 N = 14	50 N = 14	100 N = 14	150 N = 14
0	4	5	8	9	12
1	2	4	2	3	0
2	4	0	0	0	1
3	0	2	0	0	0
4	2	1	0	1	1
5	1	0	0	1	0
6	0	0	2	0	0
7	0	1	0	0	0
8	0	1	1	0	0
>8	1[a]	0	1[b]	0	0
DAYS ON DRUG: MEAN ± SD (AFTER DAY 3) (RANGE) TOTAL	26.0 ± 8.9 (7-40) 364	25.0 ± 3.8 (18-31) 350	23.5 ± 7.9 (4-33) 329	27.0 ± 5.1 (17-33) 378	26.4 ± 7.9 (2-33) 370

[a]PATIENT HAD 12 ATTACKS.
[b]PATIENT HAD 14 ATTACKS.

NUMBER OF ATTACKS AND DAYS IN TREATMENT
(ALL ATTACKS BEGINNING AFTER STUDY DAY 3)

PAT PATIENTS EXCLUDED FROM PRIMARY ANALYSES

NUMBER OF ATTACKS	NUMBER OF PATIENTS REPORTING ATTACKS DOSE (MG BID) 0 N = 10	25 N = 11	50 N = 7	100 N = 7	150 N = 3
0	4	2	3	5	1
1	0	2	2	0	0
2	1	1	0	2	0
3	2	1	1	0	1
4	2	2	0	0	1
5	0	1	0	0	0
6	1	1	0	0	0
7	0	0	0	0	0
8	0	1	0	0	0
>8	0	0	1[a]	0	0
DAYS ON DRUG: MEAN ± SD (AFTER DAY 3) (RANGE) TOTAL	15.9 ± 11.8 (1-32) 159	20.3 ± 11.2 (3-33) 223	27.0 ± 6.2 (16-36) 189	27.0 ± 10.4 (5-36) 189	31.0 ± 4.4 (28-36) 93

[a]PATIENT HAD 14 ATTACKS.

Table 40 (R-818-014)

NUMBER OF ATTACKS AND DAYS IN TREATMENT
(ALL ATTACKS BEGINNING AFTER STUDY DAY 3)

PAF PATIENTS INCLUDED IN THE PRIMARY EFFICACY ANALYSES

NUMBER OF ATTACKS	NUMBER OF PATIENTS REPORTING ATTACKS DOSE (MG BID) 0 N = 28	25 N = 28	50 N = 28	100 N = 28	150 N = 28
0	2	5	6	14	17
1	9	3	3	3	3
2	2	4	2	2	2
3	3	2	6	5	3
4	7	8	5	0	2
5	2	3	4	2	0
6	2	3	0	1	0
7	0	0	2	1	0
8	0	0	0	0	0
>8	1[a]	0	0	0	1[b]
DAYS ON DRUG: MEAN ± SD (AFTER DAY 3) (RANGE)	19.5 ± 8.3 (3-33)	21.2 ± 7.8 (6-33)	21.3 ± 7.8 (3-32)	23.9 ± 8.2 (3-33)	22.9 ± 8.8 (2-33)
TOTAL	546	593	596	669	641

[a]PATIENT HAD 13 ATTACKS.
[b]PATIENT HAD 11 ATTACKS.

NUMBER OF ATTACKS AND DAYS IN TREATMENT
(ALL ATTACKS BEGINNING AFTER STUDY DAY 3)

PAF PATIENTS EXCLUDED FROM PRIMARY ANALYSIS

NUMBER OF ATTACKS	NUMBER OF PATIENTS REPORTING ATTACKS DOSE (MG BID) 0 N = 14	25 N = 13	50 N = 10	100 N = 10	150 N = 4
0	5	0	2	3	1
1	1	5	1	2	1
2	3	0	4	3	0
3	2	1	0	0	0
4	1	0	3	1	0
5	2	4	0	0	0
6	0	2	0	1	0
7	0	0	0	0	2
8	0	1	0	0	0
>8	0	0	0	0	0
DAYS ON DRUG: MEAN ± SD (AFTER DAY 3) (RANGE)	20.1 ± 9.3 (5-32)	18.7 ± 7.0 (8-28)	19.1 ± 9.1 (5-28)	21.1 ± 9.8 (4-32)	27.3 ± 6.3 (21-36)
TOTAL	281	243	191	211	109

Table 41 (R-818-074)

NUMBER OF ATTACKS AND DAYS IN TREATMENT
(ALL ATTACKS BEGINNING AFTER STUDY DAY 3)

ALL PAT PATIENTS

NUMBER OF ATTACKS	NUMBER OF PATIENTS REPORTING ATTACKS DOSE (MG BID) 0 N = 24	25 N = 25	50 N = 21	100 N = 21	150 N = 17
0	8	7	11	14	13
1	2	6	4	3	0
2	5	1	0	2	1
3	2	3	1	0	1
4	4	3	0	1	2
5	1	1	0	1	0
6	1	1	2	0	0
7	0	1	0	0	0
8	0	2	1	0	0
>8	1[a]	0	2[b]	0	0
DAYS ON DRUG: MEAN ± SD (AFTER DAY 3) (RANGE) TOTAL	21.8 ± 11.2 (1-40) 523	22.9 ± 8.1 (3-33) 573	24.7 ± 7.4 (4-36) 518	27.0 ± 7.0 (5-36) 567	27.2 ± 7.5 (2-36) 463

[a]PATIENT HAD 12 ATTACKS.
[b]PATIENTS HAD 14 ATTACKS.

NUMBER OF ATTACKS AND DAYS IN TREATMENT
(ALL ATTACKS BEGINNING AFTER STUDY DAY 3)

ALL PAF PATIENTS

NUMBER OF ATTACKS	NUMBER OF PATIENTS REPORTING ATTACKS DOSE (MG BID) 0 N = 42	25 N = 41	50 N = 38	100 N = 38	150 N = 32
0	7	5	8	17	18
1	10	8	4	5	4
2	5	4	6	5	2
3	5	3	6	5	3
4	8	8	8	1	2
5	4	7	4	2	0
6	2	5	0	2	0
7	0	0	2	1	2
8	0	1	0	0	0
>8	1[a]	0	0	0	1[b]
DAYS ON DRUG: MEAN ± SD (AFTER DAY 3) (RANGE) TOTAL	19.7 ± 8.5 (3-33) 827	20.4 ± 7.5 (6-33) 836	20.7 ± 8.1 (3-32) 787	23.2 ± 8.6 (3-33) 880	23.4 ± 8.6 (2-36) 730

[a]PATIENT HAD 13 ATTACKS.
[b]PATIENT HAD 11 ATTACKS.

Table 42 (R-818-074)

RECORD OF EARLY CROSS-OVER-
STUDY NUMBER = R-818-074

PSVT GROUP =PAT STATUS =INCLUDED

CENTER	PTNO	VISIT	DOSE	START	STOP	TOTAL DAYS	ATTACKS	REASON
12	3	PER5	150	112787	120187	5	2	SEVERITY OF ATTACKS

PSVT GROUP =PAT STATUS =EXCLUDED

CENTER	PTNO	VISIT	DOSE	START	STOP	TOTAL DAYS	ATTACKS	REASON
05	1	PER5	150	101987	101987	1	0	NONCARDIAC ADVERSE EXPERIENCE
05	3	PER3	0	021787	030587	17	3	INTOLERABLE PSVT EVENTS DURING PERIOD 3
05	3	PER5	150	040387	040487	2	0	NONCARDIAC ADVERSE EXPERIENCE
06	4	PER1	25	110287	111387	12	3	FIRST 2 OF 5 ATTACKS OCCURRED BEFORE STEADY STATE
06	4	PER2	50	111387	120187	19	3	UNKNOWN
07	1	PER1	25	041587	041687	2		NONCARDIAC ADVERSE EXPERIENCE
07	103	PER4	100	061187	061887	8	0	NONCARDIAC ADVERSE EXPERIENCE
11	4	PER1	0	113087	120387	4	0	NONCARDIAC ADVERSE EXPERIENCE
12	4	PER1	0	111387	111987	7	3	PERSONAL
21	1	PER2	0	081387	081487	2	0	PRESTUDY LAB ABNORMALITIES

RECORD OF EARLY CROSS-OVERS
STUDY NUMBER = R-818-074

PSVT GROUP =PAF STATUS =INCLUDED

CENTER	PTNO	VISIT	DOSE	START	STOP	TOTAL DAYS	ATTACKS	REASON
04	102	PER5	150	112787	120187	5	0	NONCARDIAC ADVERSE EXPERIENCE
06	101	PER4	0	021987	022887	10	1	UNKNOWN
06	101	PER5	150	030187	031287	12	0	NONCARDIAC ADVERSE EXPERIENCE
06	104	PER5	150	122'87	010788	18	0	NONCARDIAC ADVERSE EXPERIENCE
08	101	PER1	25	041487	042687	13	3	FIRST ATTACK OF 4 OCCURRED BEFORE STEADY STATE
08	102	PER2	0	052887	060287	6	2	FIRST 2 OF 4 ATTACKS OCCURRED BEFORE STEADY STATE
08	102	PER3	50	060487	061187	8	3	FIRST ATTACK OF 4 OCCURRED BEFORE STEADY STATE
10	101	PER1	25	122786	010987	14	3	FIRST ATTACK OF 4 OCCURRED BEFORE STEADY STATE
10	101	PER5	150	022387	030487	10	2	INADEQUATE RESPONSE
14	104	PER4	0	031288	032388	12	1	NOT TOLERATING ARRHYTHMIA
21	112	PER5	150	021888	022388	8	0	NONCARDIAC ADVERSE EXPERIENCE
26	105	PER4	100	101987	110287	15	3	FIRST ATTACK OF 4 OCCURRED BEFORE STEADY STATE

PSVT GROUP =PAF STATUS =EXCLUDED

CENTER	PTNO	VISIT	DOSE	START	STOP	TOTAL DAYS	ATTACKS	REASON
02	101	PER3	50	072287	080387	13	2	PERSONAL
05	101	PER2	0	020387	021087	8	2	MOVED TO NEXT PERIOD DUE TO INCREASING FREQUENCY OF EPISODES
05	101	PER3	50	021187	021887	8	1	PROARRHYTHMIC EVENT
11	102	PER1	25	040887	042187	14	1	NONCARDIAC ADVERSE EXPERIENCE
20	101	PER5	150	072287	072487	3		PERSONAL
20	102	PER4	0	072787	080387	8	0	NONCARDIAC ADVERSE EXPERIENCE
21	101	PER4	100	102187	110587	16	1	PERSONAL
21	111	PER2	25	120987	122887	20	1	ELECTRICAL CARDIOVERSION ON STOP DATE
26	104	PER4	0	101287	101987	8	0	PERSONAL

Table 43 (R818-074)

EFFICACY RESULTS

PAT PATIENTS
N=14

	TREATMENT (MG BID FLECAINIDE)				
	PLACEBO	25	50	100	150
NUMBER OF PATIENTS WITH NO ATTACKS	4 (29%)	5 (36%)	8 (57%)	9 (64%)	12 (86%)
TIME TO FIRST ATTACK (DAYS): MEDIAN[a]	11.0	7.0	>24.0	>26.0	>28.0
RANGE	(1.0->29)	(1.0->29)	(1.0->29)	(4.0->29)	(1.0->29)
INTERVAL BETWEEN ATTACKS (DAYS): MEDIAN[a]	19.8	26.0	>26.0	28.0	>28.0
RANGE	(0.8->29)	(4.0->29)	(0.5->29)	(3.8->29)	(1.0->29)
RATE OF ATTACKS (ATTACKS/DAY): MEDIAN	0.06	0.04	0.04	0.04	0.04
RANGE	(0.03-1.33)	(0.03-0.25)	(0.03-2.00)	(0.03-0.27)	(0.03-1.00)
VENTRICULAR RATE DURING ATTACK (BPM) MEAN ± STD	190 ± 29	185 ± 35	188 ± 46	170 ± 10	141 ± 5
N	10	9	6	5	2

[a]PRODUCT-LIMIT ESTIMATES. A > SYMBOL INDICATES PRODUCT LIMIT MEDIAN WAS UNDEFINED AND SAMPLE MEDIAN IS REPORTED.

PAF PATIENTS
N=28

	TREATMENT (MG BID FLECAINIDE)				
	PLACEBO	25	50	100	150
NUMBER OF PATIENTS WITH NO ATTACKS	2 (7%)	5 (18%)	6 (21%)	15[a] (54%)	17[a] (61%)
TIME TO FIRST ATTACK (DAYS): MEDIAN[b]	3.0	4.0	5.0	>25.5[c]	>14.5[c]
RANGE	(1.0->27)	(1.0->29)	(1.0->29)	(1.0->29)	(1.0->29)
INTERVAL BETWEEN ATTACKS (DAYS): MEDIAN[b]	7.2	6.5	8.2	28.0[c]	>25.5[c]
RANGE	(1.0-28)	(1.0->29)	(0.5->29)	(1.0->29)	(1.8->29)
RATE OF ATTACKS (ATTACKS/DAY): MEDIAN	0.14	0.15	0.12	0.04[d]	0.04[d]
RANGE	(0.04-1.00)	(0.03-1.00)	(0.03-2.00)	(0.03-1.00)	(0.03-0.57)
VENTRICULAR RATE DURING ATTACK (BPM) MEAN ± STD	132 ± 21	129 ± 18	128 ± 16	119 ± 18[e]	122 ± 24
N	26	23	22	13	11

[a]SIGNIFICANTLY DIFFERENT FROM PLACEBO, P < 0.05 MCNEMAR'S TEST WITH BONFERRONI'S ADJUSTMENT.
[b]PRODUCT-LIMIT ESTIMATES. A > SYMBOL INDICATES PRODUCT LIMIT MEDIAN WAS UNDEFINED AND SAMPLE MEDIAN IS REPORTED.
[c]SIGNIFICANTLY DIFFERENT FROM PLACEBO, P < 0.05 PAIRED PRENTICE-WILCOXON TEST WITH BONFERRONIS ADJUSTMENT.
[d]SIGNIFICANTLY DIFFERENT FROM PLACEBO, P < 0.05 FRIEDMAN'S TEST FOR MULTIPLE COMPARISONS.
[e]SIGNIFICANTLY DIFFERENT FROM PLACEBO, P < 0.05 TWO-TAILED PAIRED T-TEST WITH BONFERRONI'S ADJUSTMENT.

Table 44 (R-818-074)

NUMBER OF PATIENTS REPORTING SYMPTOMS DURING DOCUMENTED PSVT ATTACKS OCCURRING DURING THE DOSE-RESPONSE PHASE

PAT PATIENTS
N=14

SYMPTOM[a]	PLACEBO N=10	FLECAINIDE MG BID 25 N=9	50 N=6	100 N=5	150 N=2
	N (%)	N (%)	N (%)	N (%)	N (%)
TACHYCARDIA	5 (50.0%)	8 (88.9%)	6 (100.0%)	4 (80.0%)	2 (100.0%)
PALPITATIONS	5 (50.0%)	4 (44.4%)	0 (0.0%)	2 (40.0%)	1 (50.0%)
CHEST PAIN	2 (20.0%)	4 (44.4%)	2 (33.3%)	0 (0.0%)	1 (50.0%)
DIZZINESS	4 (40.0%)	2 (22.2%)	0 (0.0%)	1 (20.0%)	1 (50.0%)
DYSPNEA	2 (20.0%)	3 (33.3%)	1 (16.7%)	1 (20.0%)	1 (50.0%)
SWEATING INCREASED	1 (10.0%)	1 (11.1%)	0 (0.0%)	1 (20.0%)	0 (0.0%)

[a]OTHER SYMPTOMS REPORTED ONLY ONCE INCLUDE PARESTHESIA, LARYNGISMUS, MALAISE, DYSPHORIA, ASTHENIA, FATIGUE, ARRHYTHMIA AND PHARYNGITIS.
[b]N = NUMBER OF PATIENTS REPORTING ATTACKS DURING TREATMENT. THE PERCENTAGES SHOWN ARE BASED ON THIS NUMBER.

PAF PATIENTS
N=28

SYMPTOM[a]	PLACEBO N=26	FLECAINIDE MG BID 25 N=23	50 N=22	100 N=13	150 N=11
	N (%)	N (%)	N (%)	N (%)	N (%)
PALPITATION	20 (76.9%)	22 (95.7%)	19 (86.4%)	10 (76.9%)	7 (63.6%)
TACHYCARDIA	14 (53.8%)	10 (43.5%)	9 (40.9%)	3 (23.1%)	5 (45.5%)
DYSPNEA	7 (26.9%)	3 (13.0%)	5 (22.7%)	3 (23.1%)	1 (9.1%)
FIBRILLATION	5 (19.2%)	3 (13.0%)	4 (18.2%)	3 (23.1%)	2 (18.2%)
ASTHENIA	4 (15.4%)	5 (21.7%)	3 (13.6%)	2 (15.4%)	1 (9.1%)
CHEST PAIN	4 (15.4%)	6 (26.1%)	3 (13.6%)	1 (7.7%)	1 (9.1%)
SWEATING INCREASED	3 (11.5%)	3 (13.0%)	3 (13.6%)	2 (15.4%)	0 (0.0%)
ARRHYTHMIA	3 (11.5%)	3 (13.0%)	1 (4.5%)	1 (7.7%)	2 (18.2%)
DIZZINESS	2 (7.7%)	3 (13.0%)	2 (9.1%)	2 (15.4%)	0 (0.0%)
FATIGUE	5 (19.2%)	1 (4.3%)	2 (9.1%)	1 (7.7%)	0 (0.0%)
NAUSEA	2 (7.7%)	0 (0.0%)	2 (9.1%)	2 (15.4%)	1 (9.1%)
HEADACHE	0 (0.0%)	4 (17.4%)	0 (0.0%)	2 (15.4%)	0 (0.0%)

[a]OTHER SYMPTOMS REPORTED ONLY ONCE INCLUDE MYALGIA, HYPOESTHESIA, AGITATION, DIARRHEA, BRADYCARDIA, DYSPEPSIA, LARYNGISMUS, PAIN, AND SKIN COLD AND CLAMMY.
[b]N = NUMBER OF PATIENTS REPORTING ATTACKS DURING EACH TREATMENT. THE PERCENTAGES SHOWN ARE BASED ON THIS NUMBER.

Table 45 (R-818-074)

DOSAGE RECOMMENDATION ANALYSIS

PAT PATIENTS
N=28

TREATMENT	NUMBER OF PATIENTS NOT EVALUATED	NUMBER OF PATIENTS EVALUATED	NUMBER (PERCENT) OF PATIENTS D/C CAE[a] N (%)	D/C NCAE[b] N (%)	INADEQUATE RESPONSE N (%)	NO ATTACKS N (%)	P-VALUE[c]
Placebo	4	24	1 (4.2%)	1 (4.2%)	16 (66.7%)	6 (25.0%)	
25	2	26	1 (3.8%)	2 (7.7%)	16 (61.5%)	7 (26.9%)	1.000
50	5	23	0 (0.0%)	2 (8.7%)	9 (39.1%)	12 (52.2%)	0.070
100	5	23	0 (0.0%)	3 (13.0%)	7 (30.4%)	13 (56.5%)	0.039
150	6	22	0 (0.0%)	5 (22.7%)	4 (18.2%)	13 (59.1%)	0.092

[a]DISCONTINUED DUE TO CARDIAC ADVERSE EXPERIENCE.
[b]DISCONTINUED DUE TO NONCARDIAC ADVERSE EXPERIENCE.
[c]P-VALUES FOR MCNEMAR'S TEST OF SIGNIFICANT CHANGE COMPARING THE PERCENT OF PATIENTS WITH NO ATTACKS AND PERCENT OF ALL OTHER CATEGORIES (CAE, NCAE AND INADEQUATE RESPONSE) FOR EACH TREATMENT TO PLACEBO. WITH BONFERRONI'S ADJUSTMENT, A $P = 0.0125$ IS REQUIRED FOR STATISTICAL SIGNIFICANCE.

PAF PATIENTS
N=45

TREATMENT	NUMBER OF PATIENTS NOT EVALUATED	NUMBER OF PATIENTS EVALUATED	NUMBER (PERCENT) OF PATIENTS D/C CAE[a] N (%)	D/C NCAE[b] N (%)	INADEQUATE RESPONSE N (%)	NO ATTACKS N (%)	P-VALUE[c]
Placebo	4	41	0 (0.0%)	1 (2.4%)	35 (85.4%)	5 (12.2%)	
25	3	42	0 (0.0%)	1 (2.4%)	36 (85.7%)	5 (11.9%)	1.000
50	6	39	1 (2.6%)	1 (2.6%)	29 (74.4%)	8 (20.5%)	0.344
100	6	39	1 (2.6%)	2 (5.1%)	19 (48.7%)	17 (43.6%)	0.004[d]
150	11	34	0 (0.0%)	6 (17.6%)	14 (41.2%)	14 (41.2%)	0.003[d]

[a]DISCONTINUED DUE TO CARDIAC ADVERSE EXPERIENCE.
[b]DISCONTINUED DUE TO NONCARDIAC ADVERSE EXPERIENCE.
[c]P-VALUES FOR MCNEMAR'S TEST OF SIGNIFICANT CHANGE COMPARING THE PERCENT OF PATIENTS WITH NO ATTACKS AND PERCENT OF ALL OTHER CATEGORIES (CAE, NCAE, AND INADEQUATE RESPONSE) FOR EACH TREATMENT TO PLACEBO. WITH BONFERRONI'S ADJUSTMENT, A $P \leq 0.0125$ IS REQUIRED FOR STATISTICAL SIGNIFICANCE.
[d]SIGNIFICANTLY DIFFERENT FROM PLACEBO; $P < 0.05$ MCNEMAR'S TEST WITH BONFERRONI'S ADJUSTMENT.

Table 45a. (R-818-074)

EFFICACY RESULTS IN PATIENTS COMPLETING FOUR OF FIVE TREATMENT PERIODS

PAT PATIENTS
N = 18

		TREATMENT			
			(MG BID FLECAINIDE)		
		PLACEBO	25	50	100
NUMBER OF PATIENTS WITH NO ATTACKS		6	6	11	12
INTERVAL BETWEEN ATTACKS (DAYS):	MEDIAN[a]	19.8	26.0	>26.0	>27.0[b]
	RANGE	(0.5 - >29)	(0.8 - >29)	(0.5 - >29)	(3.8 - >29)

[a]PRODUCT-LIMIT ESTIMATES. A > SYMBOL INDICATES PRODUCT-LIMIT MEDIAN WAS UNDEFINED AND SAMPLE MEDIAN IS REPORTED.

[b]SIGNIFICANTLY DIFFERENT FROM PLACEBO, P < 0.05 PAIRED PRENTICE-WILCOXON TEST WITH BONFERRONI'S ADJUSTMENT FOR THREE COMPARISONS.

EFFICACY RESULTS IN PATIENTS COMPLETING FOUR OF FIVE TREATMENT PERIODS

PAF PATIENTS
N = 34

		TREATMENT			
			(MG BID FLECAINIDE)		
		PLACEBO	25	50	100
NUMBER OF PATIENTS WITH NO ATTACKS		6	5	8	10[a]
INTERVAL BETWEEN ATTACKS (DAYS):	MEDIAN[b]	8.0	6.8	8.5	23.0[c]
	RANGE	(1.0 - 28)	(1.0 - >29)	(0.5 - >29)	(1.0 - >23)

[a]SIGNIFICANTLY DIFFERENT FROM PLACEBO, P < 0.05 MC NEMAR'S TEST WITH BONFERRONI'S ADJUSTMENT.

[b]PRODUCT-LIMIT ESTIMATES. A > SYMBOL INDICATES PRODUCT-LIMIT MEDIAN WAS UNDEFINED AND SAMPLE MEDIAN IS REPORTED.

[c]SIGNIFICANTLY DIFFERENT FROM PLACEBO, P < 0.05 PAIRED PRENTICE-WILCOXON TEST WITH BONFERRONI'S ADJUSTMENT FOR THREE COMPARISONS.

Table 46 (R-818-074)

MEAN TROUGH[a] PLASMA FLECAINIDE LEVELS (mcg/mL) BY DOSE REGIMEN

PAT PATIENTS

FLECAINIDE DOSE REGIMEN		PATIENTS INCLUDED IN EFFICACY ANALYSES (N=14)	ALL PATIENTS (N=28)
25 MG BID	MEANS ± SD RANGE N	0.083 ± 0.041 0 - 0.10 6	0.090 ± 0.037 0.0 - 0.12 8
50 MG BID	MEANS ± SD RANGE N	0.160 ± 0.050 <0.10 - 0.22 7	0.161 ± 0.044 <0.10 - 0.22 9
100 MG BID	MEANS ± SD RANGE N	0.267 ± 0.164 0.0 - 0.46 6	0.271 ± 0.150 0.0 - 0.46 7
150 MG BID	MEANS ± SD RANGE N	0.555 ± 0.094 0.46 - 0.67 4	0.487 ± 0.136 0.28 - 0.67 6

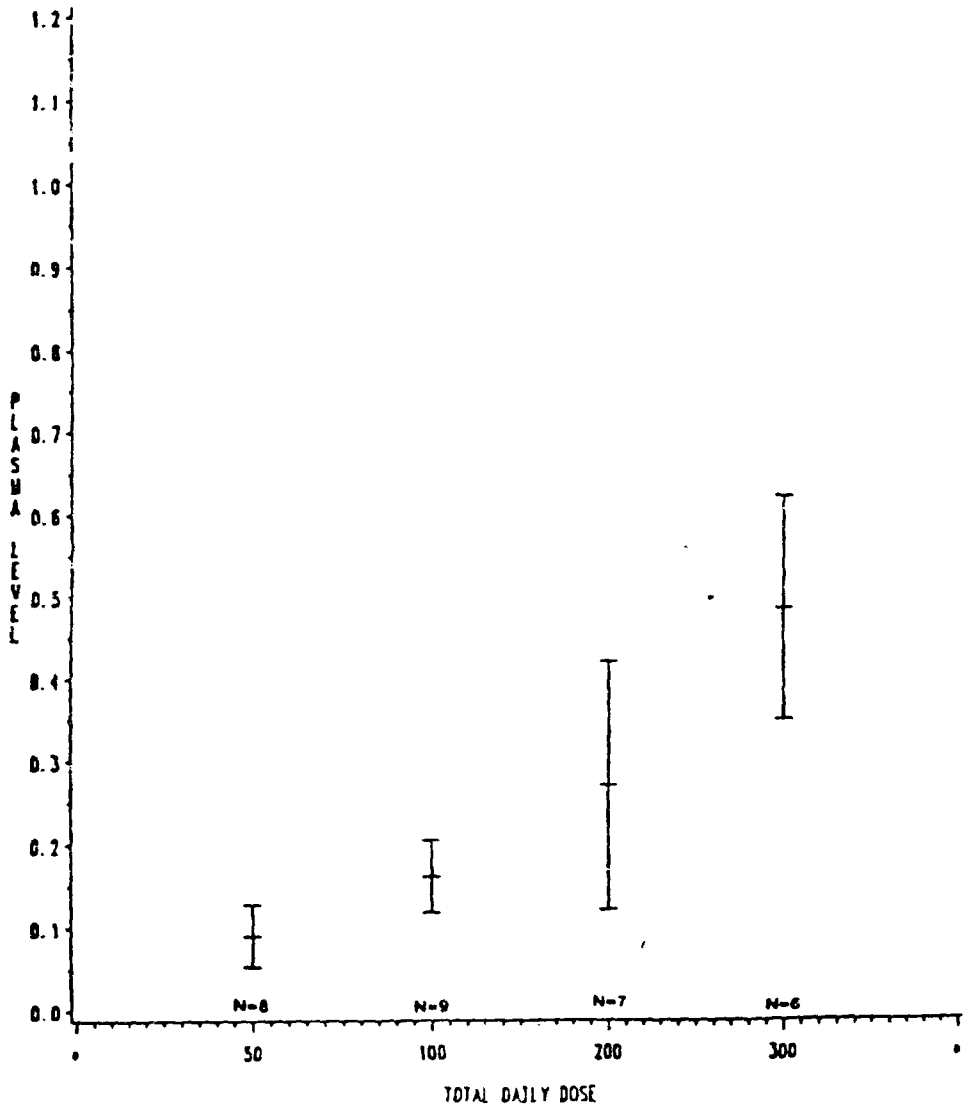
PAF PATIENTS

FLECAINIDE DOSE REGIMEN		PATIENTS INCLUDED IN EFFICACY ANALYSES (N=28)	ALL PATIENTS (N=45)
25 MG BID	MEAN ± SD RANGE N	0.094 ± 0.054 0 - 0.22 20	0.095 ± 0.047 0.0 - 0.22 27
50 MG BID	MEAN ± SD RANGE N	0.152 ± 0.089 0.037 - 0.42 16	0.164 ± 0.087 0.037 - 0.42 22
100 MG BID	MEAN ± SD RANGE N	0.299 ± 0.194 <0.10 - 0.91 15	0.326 ± 0 189 <0.10 - 0.91 21
150 MG BID	MEAN ± SD RANGE N	0.564 ± 0.374 0.14 - 1.78 16	0.584 ± 0.354 0.14 - 1.78 19

[a]TROUGH WAS DEFINED AS THOSE FLECAINIDE SAMPLES WHICH WERE COLLECTED 8 TO 16 HOURS AFTER THE LAST DOSE OF FLECAINIDE.

Figure 9 (R-818-074)

Mean (+SD) Trough Plasma Flecainide Levels (mcg/ml)
By Total Daily Dose (mg/day) of Flecainide
R-818-074 - PAT Patients



Mean (+SD) Trough Plasma Flecainide Levels (mcg/ml)
By Total Daily Dose (mg/day) of Flecainide
R-818-074 - PAF Patients

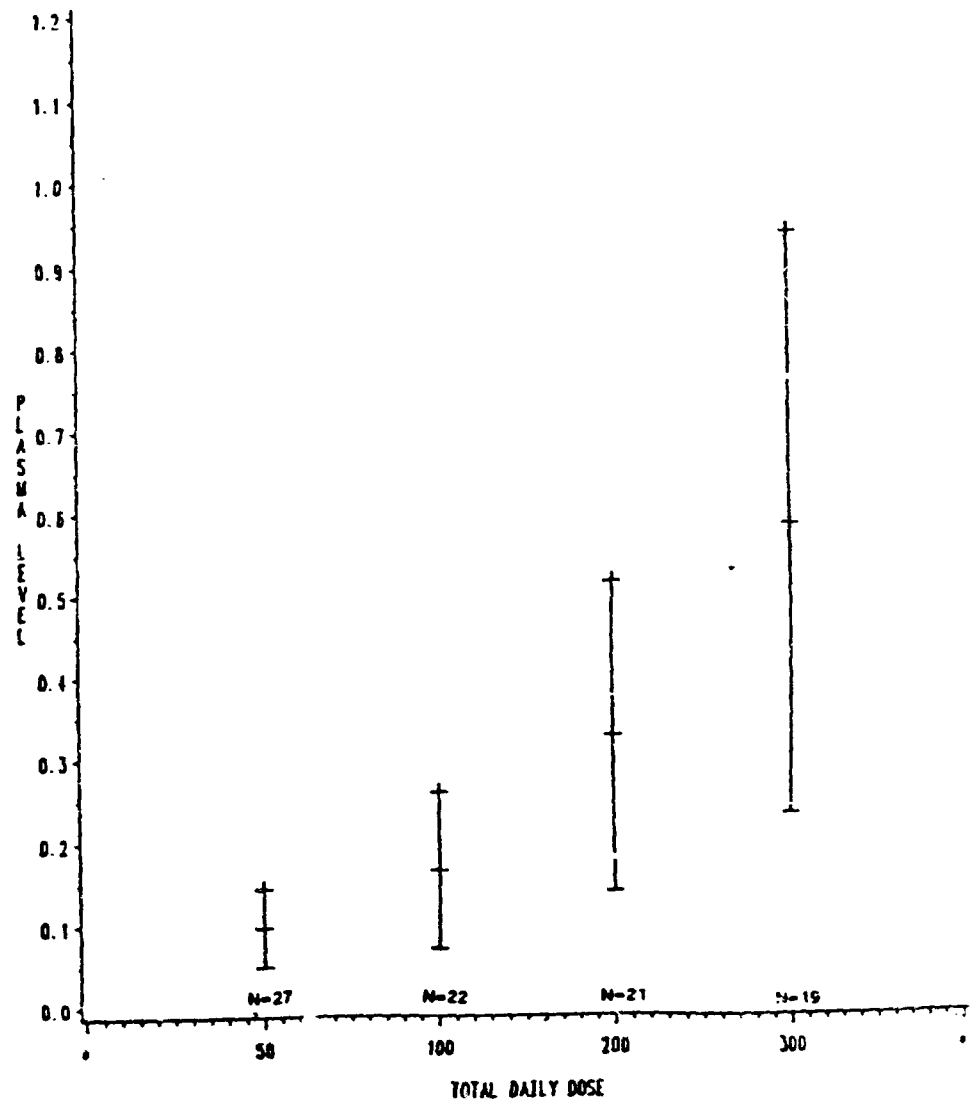


Table 47 (R-818-074)

REASONS FOR DISCONTINUATION - PAT PATIENTS (N=28)

FLECAINIDE DOSE (MG BID)/PLACEBO:	NO. OF PATIENTS PLACEBO	25	50	100	150	TOTAL
REASON						
CARDIAC ADVERSE EXPERIENCE	1	1	0	0	0	2
NONCARDIAC ADVERSE EXPERIENCE	1	2	0	1	2	6
PERSONAL	1	0	0	0	0	1
OTHER[a]	2	0	0	0	0	2
TOTAL	5	3	0	1	2	11
TOTAL NUMBER OF PATIENTS RECEIVING EACH DOSE	25	26	21	21	19	

[a]ONE PATIENT DISCONTINUED DUE TO A PRESTUDY LABORATORY ABNORMALITY, AND ONE PATIENT WAS DISCONTINUED BECAUSE HE FAILED TO MAKE FOLLOW-UP CALLS TO SURVIVAL TECHNOLOGY.

REASONS FOR DISCONTINUATION - PAF PATIENTS (N=45)

FLECAINIDE DOSE (MG BID)/PLACEBO:	NO. OF PATIENTS PLACEBO	25	50	100	150	TOTAL
REASON						
CARDIAC ADVERSE EXPERIENCE	0	0	1	1	0	2
NONCARDIAC ADVERSE EXPERIENCE	1	1	0	1	4	7
PERSONAL	1	0	1	1	1	4
INADEQUATE RESPONSE	0	1	0	0	0	1
LOST TO FOLLOW-UP	1	0	0	0	0	1
OTHER[a]	1	1	0	0	0	2
TOTAL	4	3	2	3	5	17
TOTAL NUMBER OF PATIENTS RECEIVING EACH DOSE	43	43	40	38	33	

[a]ONE PATIENT WAS DISCONTINUED FOR RECEIVING EXCLUDED CONCOMITANT MEDICATIONS. ONE PATIENT WAS DISCONTINUED FOR A PROTOCOL VIOLATION. THE PATIENT HAD A HISTORY OF SYNCOPE ASSOCIATED WITH PSVT EVENTS. THE PROTOCOL VIOLATION WAS DISCOVERED DURING PERIOD 1 WHEN THE PATIENT HAD A SYNCOPAL EPISODE ASSOCIATED WITH A PSVT EVENT.

Table 48 (R-818-074)

OVERALL FREQUENCY OF REPORTED CARDIAC ADVERSE EXPERIENCES WHILE ON ORAL FLECAINIDE

EXPERIENCE	NO. OF PATIENTS PAT N=28 N	(%)	PAF N=45 N	(%)
PROARRHYTHMIC EVENTS	1	(3.6%)	2	(4.4%)
CONDUCTION DISTURBANCE	0	(0%)	0	(0%)
MI	0	(0%)	0	(0%)
DEATH	0	(0%)	0	(0%)
CHF	1	(3.6%)	0	(0%)

Table 49 (R-818-074)

PATIENT LISTING OF REPORTED CARDIAC ADVERSE EXPERIENCES WHILE RECEIVING ORAL FLECAINIDE THERAPY

CAE	PATIENT GROUP	SITE/PATIENT NO.	PERIOD NO.	FLECAINIDE DOSE (MG BID)	EVENT
PROARRHYTHMIC EVENT	PAT	R-818-074-06-003	1	25	INCESSANT PAT
	PAF	R-818-074-05-101	3	50	SUSTAINED ATRIAL FLUTTER WITH AN INCREASED VENTRICULAR RESPONSE RATE
	PAF	R-818-074-11-101	4	100	SUSTAINED VENTRICULAR TACHYCARDIA
CHF	PAT	R-818-074-11-001	3	50	DEVELOPED CHF SYMPTOMS: PEDAL EDEMA, SOB, AND ABDOMINAL DISTENSION

Table 50 (R-818-074)

Most Frequent Noncardiac Adverse Experiences

PAT Patients

NCAE	Treatment: Placebo (N=24) N (%)	Flecainide mg bid: 25 (N=26) N (%)	50 (N=21) N (%)	100 (N=21) N (%)	150 (N=19) N (%)
Headache	1 (4%)	1 (4%)	2 (10%)	3 (14%)	3 (16%)
Dizziness	1 (4%)	4 (15%)	1 (5%)	0 (0%)	3 (16%)
Nausea	1 (4%)	0 (0%)	0 (0%)	0 (0%)	3 (16%)
Dyspnea	0 (0%)	0 (0%)	3 (14%)	0 (0%)	1 (5%)
Flushing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (11%)
Fatigue	2 (8%)	0 (0%)	1 (5%)	1 (5%)	0 (0%)
No. of Pts reporting at least one NCAE	7 (29%)	6 (23%)	7 (33%)	6 (29%)	10 (53%)

PAF Patients

NCAE	Treatment: Placebo (N=42) N (%)	Flecainide mg bid: 25 (N=43) N (%)	50 (N=40) N (%)	100 (N=38) N (%)	150 (N=33) N (%)
Dizziness	1 (2%)	2 (5%)	3 (8%)	5 (13%)	9 (27%)
Fatigue	2 (5%)	2 (5%)	3 (8%)	3 (8%)	4 (12%)
Vision Abnormal	2 (5%)	1 (2%)	3 (8%)	4 (11%)	3 (9%)
Dyspnea	0 (0%)	1 (2%)	2 (5%)	2 (5%)	3 (9%)
Myalgia	3 (7%)	0 (0%)	0 (0%)	1 (3%)	3 (9%)
Headache	2 (5%)	2 (5%)	3 (8%)	1 (3%)	0 (0%)
Nausea	2 (5%)	2 (5%)	2 (5%)	2 (5%)	2 (6%)
Tinnitus	1 (2%)	2 (5%)	1 (3%)	1 (3%)	2 (6%)
Edema	1 (2%)	1 (2%)	1 (3%)	1 (3%)	2 (6%)
Tremor	0 (0%)	0 (0%)	0 (0%)	1 (3%)	2 (6%)
Chest Pain	1 (2%)	1 (2%)	1 (3%)	2 (5%)	1 (3%)
No. of Pts reporting at least one NCAE	13 (31%)	10 (23%)	12 (30%)	14 (37%)	18 (55%)

Table 51 (R-818-074)

ECG DOSE-RESPONSE: MEAN CHANGE (AND STANDARD DEVIATION) FROM BASELINE FOR THE 16 PAT PATIENTS WHO RECEIVED ALL FIVE DOSES AND WHO HAD ANALYZABLE ECGS FROM ALL FIVE PERIODS

PAT Pts

INTERVAL	DOSE (MG BID) 0	25	50	100	150
PR	0.002 (0.018)	0.003 (0.020)	0.012 (0.018)	0.010 (0.021)	0.023 (0.027)
QRS	-0.007 (0.016)	0.001 (0.013)	-0.002 (0.016)	0.001 (0.020)	0.003 (0.019)
QT	-0.001 (0.037)	0.000 (0.042)	0.003 (0.051)	0.004 (0.042)	0.008 (0.034)
QTC	-0.006 (0.033)	-0.007 (0.030)	0.005 (0.034)	0.001 (0.042)	0.011 (0.030)
JT	0.007 (0.034)	-0.001 (0.039)	0.006 (0.047)	0.003 (0.036)	0.005 (0.029)

PAT Pts.

INTERVAL	DOSE (MG BID) 0	25	50	100	150
PR	0.000 (0.021)	0.003 (0.018)	0.007 (0.020)	0.010 (0.021)	0.029 (0.032)
QRS	0.004 (0.014)	0.002 (0.010)	0.006 (0.013)	0.008 (0.019)	0.019 (0.019)
QT	-0.001 (0.031)	-0.003 (0.028)	0.002 (0.035)	0.002 (0.034)	0.023 (0.034)
QTC	-0.006 (0.025)	-0.002 (0.031)	0.003 (0.022)	0.005 (0.024)	0.024 (0.015)
JT	-0.006 (0.033)	-0.006 (0.028)	-0.005 (0.028)	-0.006 (0.038)	0.004 (0.039)

Table 52. Chronic Rx (-065/66 + -074)

Baseline Arrhythmia Diagnosis:[a] PAT Patients

Diagnosis	No. of Patients (N=14) N	%
PSVT	3	21%
Atrial Arrhythmias		
- Ectopic	1	7%
- Reentry	1[b]	7%
Atrioventricular Reentry (AVR)		
- Wolff-Parkinson-White Syndrome	3	21%
- Concealed Bypass Tract	1	7%
- Atrioventricular Nodal Reentry	5	36%
- AVR (Not Otherwise Specified)	2[b]	14%

Baseline Arrhythmia Diagnosis:[a] PAF Patients

Diagnosis	No. of Patients (N=18) N	%
Atrial Fibrillation Only	14	78%
Atrial Fibrillation and Flutter	4	22%
Atrial Flutter Only	0	0%

[a] At initiation of the parent study.
[b] One patient in this group is also listed under WPW.

Table 53 Chronic Rx (R818-065/066 + -074)

Reasons for Excluding Patients From All Efficacy Analyses

Study Number-Patient No.	Patient Group	Reason for Exclusion
R-818-066-01-001	PAT	Received concomitant digoxin therapy during Chronic Efficacy; digoxin was not taken during the double-blind study.
R-818-066-03-002	PAT	Received concomitant digoxin therapy during Chronic Efficacy; digoxin was not taken during the double-blind study.
R-818-074-06-004	PAT	Noncompliant during the double-blind study, and the flecainide dosage was changed during Chronic Efficacy, in addition to taking digoxin during Chronic Efficacy that was not prescribed during the double-blind study.
R-818-074-11-002	PAT	Received daily concomitant verapamil therapy during Chronic Efficacy; verapamil was not taken daily during the double-blind study.
R-818-066-03-101	PAF	Received concomitant propranolol therapy during Chronic Efficacy; propranolol was not taken during the double-blind study.
R-818-074-02-103	PAF	Patient was discontinued on day 3 of Chronic Efficacy due to a decreased WBC.

Table 54 Chronic Rx (R818-065/066+-074)

Summary of Efficacy Results
Placebo vs Chronic Efficacy

Parameter		PAT Patients (N=10) Double-Blind[a] Placebo	Chronic Efficacy Flecainide	P-Value
Patients with No Attacks		2	9	0.004
Time to First Attack (Days)	Mean ± SE[b]	19.1 ± 6.9	>29.0[c]	0.016
	Median	7.0	>29.0[c]	
Interval Between Attacks (Days)	Mean ± SE[b]	21.6 ± 6.8	>29.0[c]	0.026
	Median	12.9	>29.0[c]	
Rate of Attacks (Attacks/Days)	Mean ± SE[d]	0.14 ± 0.05	0.04 ± 0.01	0.147
	Range	0.02 - 0.57	0.02 - 0.11	
Ventricular Rate for Patients with Attacks in Both Periods (N=0)	Mean ± SE[d]	[e]	[e]	[e]
	Range	[e]	[e]	

[a]Data from the double-blind studies during which the same patients were on placebo therapy.
[b]Product limit estimates for mean, standard error of mean (SE), and median were analyzed using Paired Prentice-Wilcoxon test for censored paired data.
[c]Actual product limit estimate could not be determined. Estimate based on median treatment duration.
[d]SE = Standard error of mean.
[e]No analysis was performed.

Parameter		PAF Patients (N=16) Double-Blind[a] Placebo	Chronic Efficacy Flecainide	P-Value
Patients with No Attacks		2	9	<0.001
Time to First Attack (Days)	Mean ± SE[b]	>7.8 ± 2.2	>34.6 ± 5.0	0.002
	Median	3.0	48.0[c]	
Interval Between Attacks (Days)	Mean ± SE[b]	>17.9 ± 5.6	>44.9 ± 5.2	0.002
	Median	6.9	58.0[c]	
Rate of Attacks (Attacks/Days)	Mean ± SE[c]	0.25 ± 0.07	0.04 ± 0.01	0.010
	Range	0.02 - 1.00	0.02 - 0.15	
Ventricular Rate for Patients with Attacks in Both Periods (N=7)	Mean ± SE[c]	119.1 ± 12.6	113.1 ± 5.4	0.781
	Range	75 - 166	95.5 - 134	

[a]Data from the double-blind studies during which the same patients were on placebo therapy.
[b]Product limit estimates for mean, standard error of mean (SE), and median were analyzed using Paired Prentice-Wilcoxon test for censored paired data.
[c]SE = Standard error of mean.

Table 55 Chronic Rx (R-81P-065/066+054)

Symptoms Reported During TTM
Documented Attacks

PAT Patients
N=4[a]

WHO[b] Preferred Term	N	%
Asthenia	1	25.0%
Dizziness	1	25.0%
Dyspnea	1	25.0%
Fatigue	1	25.0%
Fibrillation - cardiac	1	25.0%
Palpitation	1	25.0%
Tachycardia	1	25.0%

[a]Four of 14 PAT patients documented attacks by transtelephonic monitor (TTM) during the Chronic Efficacy follow-up period.

[b]WHO = World Health Organization.

Symptoms Reported During TTM
Documented Attacks

PAF Patients
N=7[a]

WHO[b] Preferred Term	N	%
Palpitation	5	71.4%
Fibrillation - cardiac	2	28.6%
Anxiety	1	14.3%
Asthenia	1	14.3%
Chest Pain	1	14.3%
Fatigue	1	14.3%
Pharyngitis	1	14.3%
Tachycardia	1	14.3%

[a]Seven of 18 PAF patients documented attacks by transtelephonic monitoring (TTM) during the Chronic Efficacy follow-up period.

[b]WHO = World Health Organization.

Table 56 Chronic Rx (R518-065/066 + -074)

INCIDENCES OF ADVERSE EXPERIENCES IN PAT PATIENTS

BODY SYSTEM PREFERRED TERM	INCIDENCE (%) (N = 14)
AUTONOMIC NERVOUS SYSTEM DISORDERS	
SWEATING INCREASED	1 (7%)
BODY AS A WHOLE - GENERAL DISORDERS	
CHEST PAIN	1 (7%)
GASTRO-INTESTINAL SYSTEM DISORDERS	
ABDOMINAL PAIN	1 (7%)
HEART RATE AND RHYTHM DISORDERS	
TACHYCARDIA	1 (7%)
METABOLIC AND NUTRITIONAL DISORDERS	
WEIGHT DECREASE	1 (7%)
RESPIRATORY SYSTEM DISORDERS	
DYSPNEA	1 (7%)
VISION DISORDERS	
VISION ABNORMAL	2 (14%)
NUMBER OF PATIENTS REPORTING AT LEAST ONE ADVERSE EXPERIENCE	4 (29%)

INCIDENCES OF ADVERSE EXPERIENCES IN PAF PATIENTS

BODY SYSTEM PREFERRED TERM	INCIDENCE (%) (N = 18)
AUTONOMIC NERVOUS SYSTEM DISORDERS	1 (6%)
FLUSHING	1 (6%)
BODY AS A WHOLE - GENERAL DISORDERS	4 (22%)
FATIGUE	3 (17%)
CHEST PAIN	2 (11%)
EDEMA	1 (6%)
HEADACHE	1 (6%)
PAIN	1 (6%)
CENTR & PERIPH NERV SYST DISORDERS	5 (28%)
DIZZINESS	2 (11%)
TREMOR	2 (11%)
HYPOESTHESIA	1 (6%)
PARESTHESIA	1 (6%)
GASTRO-INTESTINAL SYSTEM DISORDERS	3 (17%)
CONSTIPATION	2 (11%)
GI DISORDERS (UNSPECIFIED)	1 (6%)
NAUSEA	1 (6%)
HEART RATE AND RHYTHM DISORDERS	3 (17%)
PALPITATION	2 (11%)
ARRHYTHMIA VENTRICULAR	1 (6%)
MUSCULO-SKELETAL SYSTEM DISORDERS	1 (6%)
MYALGIA	1 (6%)
PSYCHIATRIC DISORDERS	3 (17%)
ANXIETY	1 (6%)
DEPRESSION	1 (6%)
INSOMNIA	1 (6%)
LIBIDO DECREASED	1 (6%)
NERVOUSNESS	1 (6%)
RESPIRATORY SYSTEM DISORDERS	3 (17%)
DYSPNEA	3 (17%)
COUGHING	1 (6%)
VISION DISORDERS	6 (33%)
VISION ABNORMAL	5 (28%)
PHOTOPHOBIA	1 (6%)
WHITE CELL AND RES DISORDERS	1 (6%)
LEUKOPENIA	1 (6%)
NUMBER OF PATIENTS REPORTING AT LEAST ONE ADVERSE EXPERIENCE	9 (50%)

Table 57 CIND

Demographics and Secondary Arrhythmia Diagnoses for Patients With AV Reentrant Tachycardia

Patient No.	Age	Sex	Height (cm)	Weight (kg)	Race	Secondary Arrhythmia Diagnoses
901	22	M	183	92.5	White	WPW
902	35	M	170	74.5	White	WPW
903	36	F	168	53.5	White	WPW
904	40	F	157	60.2	White	Atrial tachyarrhythmia associated with ventricular preexcitation
905	40	M	165	60.6	White	WPW
910	30	F	135	65.1	White	WPW
911	40	M	177	92.2	White	WPW
914	31	M	188	88.9	White	WPW
918	23	M	168	97.0	White	Concealed bypass
919	46	M	175	84.8	White	Concealed bypass
921	47	F	157	44.1	Other	WPW
927	26	F	168	47.6	White	Concealed bypass
933	66	M	-[a]	84.7	White	Atrial tachyarrhythmias associated with ventricular preexcitation
936	25	M	-[a]	83.5	White	WPW
937	61	M	173	72.6	White	WPW
942	56	M	185	96.8	White	WPW
945	55	F	152	64.4	Black	Concealed bypass
946	24	M	-[a]	98.0	White	WPW
949	38	M	173	87.9	Black	WPW
952	71	M	170	76.9	White	WPW
956	17	F	168	60.3	White	Paroxysmal junctional reentrant tachycardia
958	66	M	165	88.1	White	Concealed bypass
960	16	M	183	74.0	White	WPW
961	35	M	178	80.1	White	WPW
Mean	39.4		169.4	76.2		
SD	16.1		12.2	16.0		
Range	16-71		135-188	44.1-98.0		

[a]No height was recorded.

AV Nodal Reentrant Tachycardia

Patient No.	Age	Sex	Height (cm)	Weight (kg)	Race
905	40	F	160	57.7	White
907	44	M	180	89.2	White
912	54	F	168	67.1	White
935	37	F	168	83.4	White
940	25	F	170	48.5	White
962	45	M	185	72.6	White
Mean	42.3		171.8	69.[illegible]	
SD	10.2		9.9	15.[illegible]	
Range	25-5		160-185	48.5-89.2	

Table 58 C/ND

EFFECTS OF INTRAVENOUS AND ORAL FLECAINIDE ON CHARACTERISTICS OF ATRIOVENTRICULAR REENTRANT TACHYCARDIA

PATIENT NUMBER	TREATMENT	INDUCED	PSVT CYCLE LENGTH	PSVT A-H	PSVT H-V	PSVT V-A	ANTEROGRADE BLOCK CYCLE LENGTH ACCESSORY PATHWAY	ANTEROGRADE BLOCK CYCLE LENGTH ATRIOV. NODE	RETROGRADE BLOCK CYCLE LENGTH ACCESSORY PATHWAY	RETROGRADE BLOCK CYCLE LENGTH VENTRIC.ATRIAL CONDUCTION SYSTEM
901	CONTROL	+	270	140	40	90	<220	NM	<200	.
	IV-FLEC	+	350	150	70	130	290	300	270	.
	ORAL-FLEC	+	340	150	70	120	280	300	270	.
	ORAL FLEC&BB	+	360	190	65	ND	ND	ND	ND	.
902	CONTROL	+	290	190	30	70	<250	.	<250	.
	ORAL-FLEC	+	340	170	50	120	300	.	300	.
903	CONTROL	+	370	180	40	150	.	280	270	.
	IV-FLEC	+	460	160	50	250	.	ND	ND	.
904	CONTROL	-	NO SPONTANEOUS PSVT				<240	.	ND	ND
	IV-FLEC @	-	NOT INDUCIBLE				.	.	.	.
906	CONTROL	+	290	70	50	170	.	270	<240	.
	IV-FLEC	-	NOT INDUCIBLE				.	250	V	375
	ORAL-FLEC	-	NOT INDUCIBLE				.	300	.	500#
910	CONTROL	+	320	150	40	130	430	270	260	.
	IV-FLEC	-	NOT INDUCIBLE				.	290	V	V
	ORAL-FLEC	-	NOT INDUCIBLE				.	260	.	450#
911	CONTROL	+	340	140	40	160	.	290	340	.
	IV-FLEC	-	NOT INDUCIBLE				.	300	V	420
	ORAL-FLEC	-	NOT INDUCIBLE				.	340	.	490#
914	CONTROL	+	260	120	40	100	240	.	240	.
	IV-FLEC	+	320	120	50	150	300	.	270	.
918	CONTROL	+	360	180	50	130 ◆	.	360	320	.
	CONTROL	+	500	320	50	130 ◆◆	.	.	.	.
	IV-FLEC	-	NOT INDUCIBLE				.	420	V	.
	ORAL-FLEC	-	NOT INDUCIBLE				.	3[illegible]	V	.
919	CONTROL	+	340	150	50	140	.	340	270	.
	IV-FLEC	-	NOT INDUCIBLE				.	320	V	V
921	CONTROL	+	340	210	40	90	.	260	230	.
	IV-FLEC	+	360	210	50	100	.	280	300	.
	ORAL-FLEC	+	430	260	50	120	.	340	430	.
927	CONTROL	+	330	110	40	180	.	320	230	.
	IV-FLEC	-	NOT INDUCIBLE				.	360 *	490	.
933	CONTROL	-	NOT INDUCIBLE				<300	ND	993	NM
	IV-FLEC	-	NOT INDUCIBLE				.	.	.	.
936	CONTROL	+	240	70	170	50	280	<240	210	.
	IV-FLEC	-	NOT INDUCIBLE				##	280	280	.
937	CONTROL	+	280	130	80	70	260	.	240	.
	IV-FLEC		NOT DONE ▲							
942	CONTROL	+	350	200	35	115	.	280	220	.
	IV-FLEC	+	420	200	35	170	.	300	360	.
945	CONTROL	+	380	250	50	90	.	280	290	380
	IV-FLEC	-	NOT INDUCIBLE				.	<300	V	V
946	CONTROL	+	310	110	70	60	240	.	220	
	IV-FLEC	+	310	.	.	50	210	.	210	
949	CONTROL	+	260	130 ▲▲	.	130	<230	.	<300	
	IV-FLEC	+	440	220 ▲▲	.	220	ND	ND	450	
952	CONTROL	+	370	235 ▲▲	.	135	<280	.	<270	
	IV-FLEC	-	NOT INDUCIBLE				.	410	360	
956	CONTROL	+	360	160	40	160	.	260	440	
	IV-FLEC	-	NOT INDUCIBLE				.	400	V	V
958	CONTROL	+	370	150	55	115	.	ND	<280	
	IV-FLEC	-	NOT INDUCIBLE				.	380	V	V
960	CONTROL	+	355	150	55	150	<220	.	<240	.
	IV-FLEC	-	NOT INDUCIBLE				340	.	520	.
961	CONTROL	+	340	140	45	155	250	.	250	.
	CONTROL	+	360	140	45	155	.	.	.	.
	IV-FLEC	+	430	.	.	.	##	.	<410	.

FOOTNOTES: ALL MEASURES ARE RECORDED IN MILLISECONDS
ND = NOT DONE
V = VA BLOCK
= NO DELTA WAVE
@ = ATRIAL FLUTTER WAS NOT TERMINATED FOLLOWING IV FLECAINIDE; NO MEASUREMENTS WERE TAKEN
# = CORONARY SINUS RECORDING NOT DONE
V = VA BLOCK
◆ = FAST PATHWAY - USED IN ANALYSIS
◆◆ = SLOW PATHWAY

▲ = PATIENT LOST CONSCIOUSNESSS;
▲▲ MEASUREMENT IS THE AV INTERVAL

Table 59 CIN

Effects of ... ous F... inide (Mean ± SD) on
Cycle Leng... AH, H... and AV Inter... in
Patient... with AV Reentrant Tachycar...

Parameter	Control Mean ± SD	N	Pre and Post IV Flecainide: Control Mean ± SD	Post Mean ± SD	Difference Mean ± SD	N	Paired t-test	P-value
PSVT Cycle Length	322 ± 41	22	313 ± 44	386 ± 58	74 ± 54	8	3.87	p=.006[b]
AH Interval	150 ± 44	20	170 ± 39	168 ± 37	-2 ± 11	5	0.41	p=.704
HV Interval	53 ± 30	20	39 ± 2	51 ± 12	12 ± 11	5	2.45	p=.071
VA Interval	122 ± 38	22	105 ± 30	153 ± 69	48 ± 40	7	3.20	p=.019[b]
AV Interval	201 ± 41	22	196 ± 47	219 ± 30	23 ± 37	6	1.56	p=.180

Effects of Intravenous Flecainide (Mean ± SD) on
Antegrade Block Cycle Length in Patients
With AV Reentrant Tachycardia[a]

Antegrade BCL	Control Mean ± SD	N	Pre and Post IV Flecainide: Control Mean ± SD	Post Mean ± SD	Difference Mean ± SD	N	Paired t-test	P-value
Accessory Pathway	269 ± 55	13	230 ± 12	285 ± 55	55 ± 62	4	1.76	p=.176
Atrioventricular Node	288 ± 35	12	288 ± 37	318 ± 53	30 ± 44	11	2.28	p=.046[b]

Effects of Intravenous Flecainide (Mean ± SD) on
Retrograde Block Cycle Length in Patients
With AV Reentrant Tachycardia[a]

Retrograde Block Cycle Length	Control Mean ± SD	N	Pre and Post IV Flecainide: Control Mean ± SD	Post Mean ± SD	Difference Mean ± SD	N	Paired t-test	P-value
Accessory Pathway	264 ± 53	22	237 ± 28	356 ± 101	119 ± 90	11	4.38	p=.001[b]
Ventriculoatrial Conduction System	38.0	1	ND[c]	ND	ND			

[a] All measurements are in milliseconds.
[b] Significant change ($p \leq 0.05$).
[c] Not done.

Table 60 (IND)

EFFECTS OF INTRAVENOUS AND ORAL FLECAINIDE ON CHARACTERISTICS OF ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA

PATIENT NUMBER	TREATMENT	INDUCED	PSVT CYCLE LENGTH	PSVT H-A	PSVT A-H	BLOCK CYCLE LENGTH ANTEROGRADE	BLOCK CYCLE LENGTH RETROGRADE
905	CONTROL	+	280	200	80	250	230
	IV-FLEC	-	NOT INDUCIBLE			320	V
	ORAL-FLEC	-	NOT INDUCIBLE			360	ND
907	CONTROL	+	380	350	30	<300	<330
	IV-FLEC	-	NOT INDUCIBLE			300	V
	ORAL-FLEC	-	NOT INDUCIBLE			340	V
912	CONTROL	+	320	280	40	280	260
	IV-FLEC	-	NOT INDUCIBLE			380	V
	ORAL-FLEC	-	NOT INDUCIBLE			450	V
935	CONTROL	+	350	20	330	320	260
	IV-FLEC	-	NOT INDUCIBLE			310	380
940	CONTROL	+	260	110	150	290	260
	IV-FLEC	+	260	125	135	260	300
962	CONTROL @	+	370	70	300	360	ND
	CONTROL @	+	320	200	120	.	.
	IV-FLEC @	+	465	70	395	ND	ND
	IV-FLEC @	+	370	205	165	.	.

FOOTNOTES: ALL MEASUREMENTS ARE RECORDED IN MILLISECONDS
V = VA BLOCK
ND = NOT DONE
@ = DUAL PATHWAYS - AVERAGE USED IN ANALYSIS FOR THIS PATIENT

Effects of Intravenous Flecainide (Mean ± SD) on Cycle Length, HA and AH Intervals in Patients With AV Nodal Reentrant Tachycardia[a]

Parameter	Control Mean ± SD	N	Pre and Post IV Flecainide: Control Mean ± SD	Post Mean ± SD	Difference Mean ± SD	N	Paired t-test	P-value
PSVT Cycle Length	323 ± 45	6	303 ± 60	339 ± 111	36 ± 51	2	0.71	p=0.607
HA Interval	183 ± 120	6	130 ± 28	130 ± 7	0 ± 21	2	0.00	p=1.000
AH Interval	140 ± 116	6	173 ± 53	209 ± 101	36 ± 48	2	0.76	p=0.586

[a]All measurements in milliseconds.

Effects of Intravenous Flecainide (Mean ± SD) on Block Cycle Lengths in Patients With AV Nodal Reentrant Tachycardia[a]

Parameter	Control Mean ± SD	N	Pre and Post IV Flecainide: Control Mean ± SD	Post Mean ± SD	Difference Mean ± SD	N	Paired t-test	P-value
Anterograde	288 ± 26	5	288 ± 26	314 ± 43	26 ± 56	5	0.46	p=0.669
Retrograde	268 ± 37	5	260 ± 0	340 ± 57	80 ± 57	2	1.41	p=0.393

[a]All measurements in milliseconds.

Table 61 (IND oral)

Evidence of Supraventricular Tachycardia Following the Initiation Visit

Pt No.	No Evidence of SVT Following the Initiation Visit	Visit(s) During Which SVT was Evident	Days on Flecainide[a] at D/C or Last Visit
AV Reentrant Tachycardia			
901		wk1, mo3	855 (mo24)
902		wk1	1361 (mo45)
903		D/C	6 (wk1)
904		mo1	163 (mo3)
905		mo33	1062 (mo36)
910		mo3	437 (mo14)
911		mo33	995 (mo33)
914	N/A		1 (initiation)
918	X		372 (mo12)
919		mo12	628 (mo21)
921		mo3, mo6, mo9, mo15, mo18	674 (mo18)
927	N/A		1 (initiation)
933		wk1, mo1	261 (mo9)
936	X		76 (mo1)
937	N/A		1 (initiation)
942		wk1, final	183 (mo7)
945		mo6	257 (mo9)
946	N/A		1 (initiation)
949		wk1, mo6	178 (mo6)
952		mo6	184 (mo6)
956		wk1	24 (wk1)
958		wk1	215 (mo6)
960	X		132 (mo1)
961	X		168 (mo6)
AV Nodal Reentrant Tachycardia			
905	X		1110 (mo36)
907	X		1056 (mo33)
912	X		385 (mo13)
935		mo3, mo12	401 (mo12)
940		wk1	9 (wk1)
962	N/A		1 (initiation)

N/A = Patients who had no post-initiation visits

[a]Patient Nos. 903, 904, 910, 912, 914, 918, 927, 936, 937, 940, 942, 946, 956, 960, and 962 were discontinued from the study. The remaining patients were ongoing at the time the database was closed.

Table 62 (R-818-065 Amend A)

Baseline Arrhythmia Diagnoses

	PAT PATIENTS (N=16)		PAF PATIENTS (N=5)	
	N	%	N	%
ECTOPIC ATRIAL TACHYCARDIA	2	12.5%	*	0.0%
ATRIAL-VENTRICULAR REENTRY	4	25.0%	*	0.0%
WPW	4	25.0%	*	0.0%
CONCEALED BYPASS TRACT	6	37.5%	*	0.0%
AVNR	0	0.0%	5	100.0%
PA FIBRILLATION#	0	0.0%	1	20.0%
PA FLUTTER#				

*NOT APPLICABLE.
#ONE PATIENT HAD BOTH ATRIAL FIBRILLATION AND FLUTTER AT BASELINE.

Table 63 (R-818-065 Amendment A)

Associated Cardiac Disorders

	ALL PATIENTS# (N=20)		PAT PATIENTS# (N=15)		PAF PATIENTS (N=5)	
	N	%	N	%	N	%
HYPERTENSION	5	25.0%	2	13.3%	3	60.0%
ATHEROSCLEROSIS	4	20.0%	1	6.7%	3	60.0%
MITRAL VALVE PROLAPSE	2	10.0%	2	13.3%	0	0.0%
RHEUMATIC HEART DISEASE	2	10.0%	1	6.7%	1	20.0%
CONDUCTION DISTURBANCE	2	10.0%	2	13.3%	0	0.0%
CARDIOMEGALY	1	5.0%	1	6.7%	0	0.0%
ASYSTOLE	1	5.0%	1	6.7%	0	0.0%
CHF (CLASS I OR II)	1	5.0%	0	0.0%	1	20.0%
NONE	9	45.0%	9	60.0%	0	0.0%

*A PATIENT MAY HAVE MORE THAN ONE REPORTED CARDIAC DISORDER.
#DATA WAS MISSING FOR ONE PATIENT.

Table 64 (R-818-065 Amendment A)

Average Conduction Intervals in Sinus Rhythm

	PAT Patients Without WPW Syndrome (N=12)			PAT Patients With WPW Syndrome (N = 4)			PAF Patients (N = 5)		
	Mean ± SD	Range	N	Mean ± SD	Range	N	Mean ± SD	Range	N
Sinus Cycle Length (msec)									
Baseline	829.2 ± 87.6	720-980	12	675.0 ± 106.3	560-800	4	778.0 ± 64.2	680-840	5
Post Flecainide	748.3 ± 101.0	610-920	12	640.0 ± 78.3	560-740	4	822.0 ± 102.3	700-940	5
Paired Difference	-80.8 ± 80.3*	-230-20	12	-35.0 ± 71.9	-140-20	4	44.0 ± 81.1	-50-140	5
P-A Interval (msec)									
Baseline	31.0 ± 19.6	10-65	10	41.3 ± 17.5	20-60	4	40.0 ± 7.1	30-45	4
Post Flecainide	34.5 ± 23.7	10-80	11	30.0 ± 14.1	20-50	4	36.0 ± 9.6	20-45	5
Paired Difference	6.0 ± 7.4	-10-15	10	-11.3 ± 19.3	-40-0	4	-3.8 ± 14.9	-25-10	4
A-H Interval (msec)									
Baseline	90.4 ± 28.7	45-140	12	71.3 ± 23.2	40-95	4	92.0 ± 16.4	70-110	5
Post Flecainide	94.6 ± 32.0	50-170	12	92.5 ± 61.3	50-180	4	101.0 ± 24.6	80 140	5
Paired Difference	4.2 ± 18.1	-35-30	12	21.3 ± 44.8	-20-85	4	9.0 ± 20.1	-20-30	5
H-V Interval (msec)									
Baseline	49.2 ± 6.3	40-60	12	30.0 ± 14.1	10-40	4	46.0 ± 6.5	35-50	5
Post Flecainide	59.2 ± 9.5	40-80	12	46.3 ± 11.1	35-60	4	52.0 ± 6.7	40-55	5
Paired Difference	10.0 ± 8.3*	-10-25	12	16.3 ± 23.6	-5-50	4	6.0 ± 10.8	-10-20	5

*Significantly different from zero ($p \leq .01$), Wilcoxon Signed Rank test.

Table 65 (R-818-065 Amendment 7)

Summary of IV Flecainide Results and Comparison to Oral Efficacy: PAT Patients

SITE	PATIENT NUMBER	BASELINE ARRHYTHMIA INDUCTION	POST FLECAINIDE ARRHYTHMIA INDUCTION	IV FLECAINIDE RESULTS	ORAL RESULTS# NO. OF ATTACKS/DAYS PLACEBO	FLECAINIDE
01	001	SUSTAINED	SUSTAINED*	EFFECTIVE**	##	##
01	002	SUSTAINED	SUSTAINED	NONEFFECTIVE	1/10	1/21
01	003	NONSUSTAINED	NONSUSTAINED	NONEFFECTIVE	5/54	0/58
01	004	SUSTAINED	NONSUSTAINED	NONEFFECTIVE	***	***
01	006	SUSTAINED	SUSTAINED	NONEFFECTIVE	***	***
01	007	SUSTAINED	NONINDUCIBLE	EFFECTIVE	***	***
01	008	SUSTAINED	NONSUSTAINED	NONEFFECTIVE	***	***
01	009	SUSTAINED	SUSTAINED	NONEFFECTIVE	###	###
04	003	SUSTAINED	NONINDUCIBLE	EFFECTIVE	1/11	1/55
04	004	SUSTAINED	NONINDUCIBLE	EFFECTIVE	4/17	0/54
04	005	SUSTAINED	NONINDUCIBLE	EFFECTIVE	1/54	0/54
04	006	SUSTAINED	NONINDUCIBLE	EFFECTIVE	##	##
08	002	SUSTAINED	NONINDUCIBLE	EFFECTIVE	5/4	0/61
08	003	SUSTAINED	SUSTAINED	NONEFFECTIVE	##	##
08	005	NONINDUCIBLE	NONINDUCIBLE	NA****	4/8	0/54
10	004	SUSTAINED	NONINDUCIBLE	EFFECTIVE	5/126	***

*THE INVESTIGATOR CHECKED "EFFECTIVE" OR "NONEFFECTIVE" IN THE PATIENT'S CASE REPORT FORM.
#COMPLETE SUMMATION OF ORAL RESULTS WITH SUPPORTING DATA IS FOUND IN THE SPONSOR'S CLINICAL REPORT FOR STUDY R-818-065.
**FLECAINIDE SUPPRESSED SVT, BUT INDUCED VENTRICULAR FIBRILLATION.
##DID NOT GO ON TO ORAL THERAPY.
***DISCONTINUED DURING DOSE RANGING.
###PATIENT DISCONTINUED DURING CROSSOVER PHASE, AND NO EFFICACY DATA WERE COLLECTED FOR THIS TREATMENT.
****NOT EVALUATED DUE TO NONINDUCIBLE ARRHYTHMIA AT BASELINE.

Summary of IV Flecainide Results and Comparison to Oral Efficacy: PAF Patients

SITE	PATIENT NUMBER	BASELINE ARRHYTHMIA INDUCTION	POST FLECAINIDE ARRHYTHMIA INDUCTION	IV FLECAINIDE RESULTS	ORAL RESULTS# NO. OF ATTACKS/DAYS PLACEBO	FLECAINIDE
01	106	SUSTAINED	NONINDUCED	EFFECTIVE	3/19	0/47
01	107	SUSTAINED	SUSTAINED	NONEFFECTIVE	5/12	2/39
01	108	NONINDUCED	NONINDUCED	EFFECTIVE	**	1/13
08	102	NONINDUCED	SUSTAINED##	NA***	5/12	4/19
08	103	SUSTAINED	NONINDUCED	EFFECTIVE	1/24	0/54

*THE INVESTIGATOR CHECKED "EFFECTIVE" OR "NONEFFECTIVE" IN THE PATIENT'S CASE REPORT FORM.
#COMPLETE SUMMATION OF ORAL RESULTS WITH SUPPORTING DATA IS FOUND IN THE SPONSOR'S CLINICAL REPORT FOR STUDY R-818-065.
**PATIENT DISCONTINUED IN PERIOD A ON FLECAINIDE, NO PLACEBO DATA.
##ARRHYTHMIA INDUCED AFTER RECEIVING A MORE VIGOROUS STIMULUS THAN RECEIVED AT BASELINE.
***NOT EVALUATED DUE TO NONINDUCIBLE ARRHYTHMIA AT BASELINE.

Table 66 (R-818-EG-11)

Initial and Final Flecainide Total Daily Doses, Duration of Flecainide Treatment, and Duration of Drug-Free Interval by Patient and Diagnosis

Patient No.	Flecainide Treatment: Total Daily Dose (mg) Initial	Flecainide Treatment: Total Daily Dose (mg) Final*	Flecainide Treatment: Duration (Weeks)	Drug-Free Interval: Duration (Weeks)
Wolff-Parkinson-White Patients				
002	200	200	113	28
005	300	300	5	-#
006	300	300	133	1
007	400	300	31	2
011	300	200	44**	-#
017	300	200	76	6
021	300	200	60	3
023	200	200	52	7
024	400	200	59	7
030	300	200	29	14
033	300	200	71##	2
034	300	200	12	5
035	400	300	35**	-#
		Mean ± SD	55.4 ± 36.9	7.5 ± 8.1
		Range	5 - 133	1-28
AV Nodal Reentry Tachycardia Patients				
003	300	400	131	2
008	200	200	89	10
020	200	200	60	21
029	200	200	6	-#
032	200	200	54	4
036	200	200	59	-#
		Mean ± SD	66.5 ± 41.4	9.3 ± 8.5
		Range	6 - 131	2-21

*Flecainide total daily dose at end of flecainide treatment period.
#No drug-free interval.
**Noncompliance suspected during flecainide treatment.
##Total duration of 71 weeks includes 33 on flecainide and 38 on combination of flecainide and amiodarone.

Table 67 (R-818 - EG-11)

Patient Status at the Last Study Visit by Patient and Arrhythmia Diagnosis

Patient No.	Status at Last Study Visit
Wolff-Parkinson-White Patients	
002	Continuing flecainide prn to terminate SVT attacks.
005	Discontinued due to adverse experiences.
006	Continuing daily flecainide therapy.
007	Lost to follow-up.
011	Discontinued due to suspected noncompliance.
021	Continuing daily flecainide therapy.
023	Continuing daily flecainide therapy.
024	Continuing daily flecainide therapy.
030	Continuing flecainide prn to terminate SVT attacks.
033	Continuing daily flecainide therapy.
034	Discontinued due to inadequate effect.
035	Discontinued due to suspected noncompliance.
AV Nodal Reentry Tachycardia Patients	
003	Continuing daily flecainide therapy.
008	Continuing daily flecainide therapy.
020	Continuing flecainide prn to terminate SVT attacks.
029	Discontinued due to adverse experiences.
032	Continuing daily flecainide therapy.
036	Continuing daily flecainide therapy.

Table 68 (R-818 - EG-11)

Estimates of SVT Attacks Per Week for All Patients by Diagnosis Included in the Efficacy Analysis

Patient No.	SVT Attacks Per Week: Predrug	Flecainide Treatment	Drug-Free Interval
Wolff-Parkinson-White Patients			
002	*	0.21	1.14
005	5.00	0.00	#
006	*	0.00	*
007	5.00	0.10	4.00
017	1.50	0.00	2.83
021	0.75	0.10	1.00
023	2.50	0.23	0.57
024	*	0.00	1.00
030	0.38	0.07	0.64
033	6.00	2.54	6.00
034	*	6.92	7.20
AV Nodal Reentry Tachycardia Patients			
003	5.00	0.54	2.50
008	1.50	0.07	1.40
020	1.50	0.07	0.62
029	2.50	0.00	#
032	2.50	0.02	1.50
036		0.00	#

*Unable to calculate estimated SVT attacks per week.
#No drug-free interval.

Table 69 (R-818-075-01)

Cardiac Diagnoses

Diagnosis	No. of Patients (%) (N = 14)
Valvular Disorders and Cardiomegaly	5 (36%)
Valvular Disorders	3 (21%)
Valvular Disorders and Hypertension	2 (14%)
Hypertension and Cardiomegaly	2 (14%)
Hypertension and Cardiomyopathy	1 (7%)
Cardiomegaly	1 (7%)

Table 70 (R818-075-01)

Reasons for Discontinuing From the Study

Pt No.	Period	Treatment	Reason for Discontinuation
2	1	Flecainide 100 mg bid	Uncontrolled ventricular rate and heart failure with fatigue, dyspnea and rales 3 days following discontinuation of the patient's usual digoxin therapy.
8	1	Digoxin 0.375 mg qd	Dizziness and headache.
13	2	Flecainide 100 mg bid	Post-exercise ventricular flutter-ventricular fibrillation requiring electrocardioversion.
15	2	Flecainide 100 mg bid + Digoxin 0.25 mg qd	Study stopped by investigator.

Table 71 (R818-075-01)

Mean ± Standard Deviation of Heart Rates (bpm) From Holter Tapes for Study Drugs in Periods 1, 2, and 3

Parameter	No. Pts	Flecainide	Digoxin	Flecainide-Digoxin	P-Value[a]
Minimum Heart Rate in Each 15-Minute Interval	6[b]	81.0 ± 23.1	70.5 ± 11.1	62.8 ± 13.0	P = 0.01[c]
Mean Heart Rate in Each 15-Minute Interval	6[b]	97.4 ± 26.3	85.7 ± 13.3	76.8 ± 14.0	P = 0.01[c]
Maximum Heart Rate in Each 15-Minute Interval	6[b]	133.9 ± 34.7	125.3 ± 26.4	108.0 ± 19.8	P = 0.04[c]

[a] = P-value compares heart rates between the three treatment groups by analysis of variance for crossover designs.

[b] = Two patients did not have Holter data for one or more periods.

[c] = Flecainide-digoxin heart rate significantly lower than flecainide heart rate.

Table 72 (R818-075-01)

Mean ± Standard Deviation of Exercise Heart Rate (bpm) at Each Minute During the ETT for Study Drugs in Periods 1, 2, and 3

Minutes of Exercise	No. Pts	Flecainide	Digoxin	Flecainide-Digoxin	P-Value[a]
Control Period	8	89.6 ± 25.3	81.5 ± 17.6	71.5 ± 12.1	P = 0.07
1	8	111.0 ± 31.5	106.8 ± 27.3	101.1 ± 17.1	P > 0.10
2	8	120.3 ± 34.0	113.1 ± 24.1	103.1 ± 18.5	P > 0.10
3	8	117.8 ± 31.5	118.5 ± 26.9	105.0 ± 18.3	P > 0.10
4	8	126.6 ± 31.8	127.2 ± 33.6	116.6 ± 21.5	P > 0.10
5	7[b]	130.9 ± 29.2	127.8 ± 36.5	110.9 ± 26.3	P > 0.10
6	7[b]	135.9 ± 28.8	134.3 ± 29.2	112.4 ± 28.9	P > 0.10
7	7[b]	146.0 ± 29.7	141.1 ± 29.6	118.5 ± 29.1	P = 0.06
8	7[b]	136.4 ± 37.3	138.2 ± 34.5	126.7 ± 23.0	P > 0.10
9	7[b]	147.3 ± 31.8	150.8 ± 27.9	128.3 ± 21.1	P = 0.037[c]
10	6[d]	151.7 ± 27.7	163.2 ± 22.8	141.4 ± 31.2	P = 0.052
11	6[d]	165.3 ± 34.7	169.6 ± 19.5	143.9 ± 27.7	P = 0.023[e]

[a] = P-value compares mean heart rate between the three treatment groups by analysis of variance for crossover designs.

[b] = One patient did not have exercise heart rate data for one or more periods.

[c] = Flecainide-digoxin heart rate significantly lower than digoxin.

[d] = Two patients did not have exercise heart rate data for one or more periods.

[e] = Flecainide-digoxin heart rate significantly lower than flecainide or digoxin.

Table 73 (R818-075-01)

Mean ± Standard Deviation of Exercise Test Parameters
for Study Drugs in Periods 1, 2, and 3

Parameter	No.Pts	Flecainide	Digoxin	Flecainide-Digoxin	P-Value[a]
Duration of Exercise (min)	8	12.4 ± 3.3	12.2 ± 3.8	13.5 ± 2.8	P > 0.10
Resting Heart Rate (bpm)	8	87.6 ± 27.2	77.1 ± 18.4	72.4 ± 11.6	P = 0.09
Maximum Heart Rate (bpm)	8	187.6 ± 24.6	181.3 ± 22.4	179.2 ± 20.6	P > 0.10
Systolic Blood Pressure at Maximal Exercise (mmHg)	8	168.2 ± 22.5	167.4 ± 26.3	183.7 ± 33.7	P = 0.026[b]
Diastolic Blood Pressure at Maximal Exercise (mmHg)	5[c]	81.6 ± 3.7	85.2 ± 4.2	78.8 ± 16.1	P > 0.10
Maximum Pressure-Rate Product	8	31478 ± 5670	30411 ± 6330	32631 ± 5686	P > 0.10

[a] = P-value compares parameters between the three treatment groups by analysis of variance for crossover designs.

[b] = Flecainide-digoxin systolic blood pressure significantly higher than flecainide or digoxin.

[c] = Three patients did not have diastolic blood pressure at maximal exercise recorded for one or more periods.

Table 74 (R818-075-01)

Mean ± Standard Deviation of Recovery Heart Rate (bpm) at
Each Minute Post-ETT for Study Drugs in Periods 1, 2, and 3

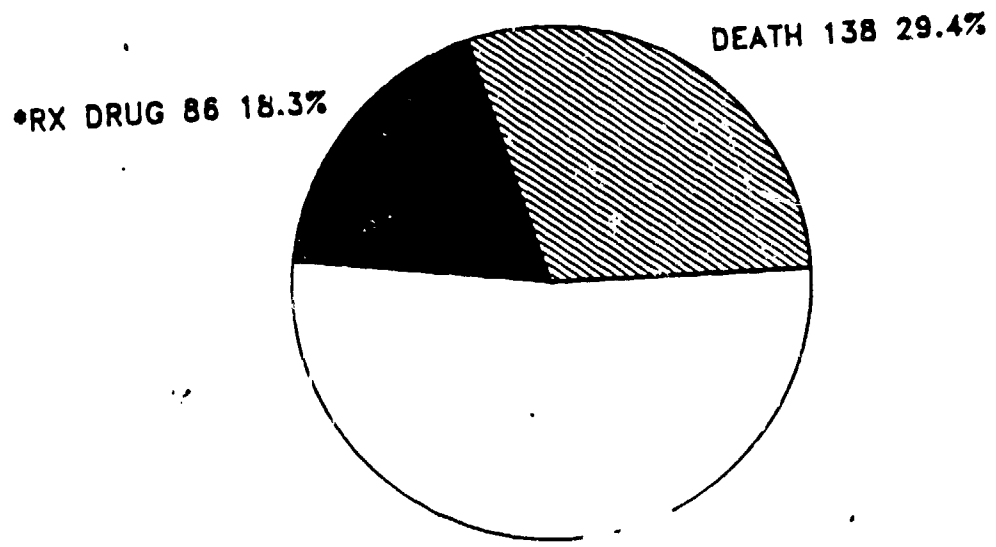
Minutes Post-ETT	No.Pts	Flecainide	Digoxin	Flecainide-Digoxin	P-Value[a]
0	8	183.4 ± 18.1	182.5 ± 20.0	168.0 ± 20.4	P < 0.01[b]
1	8	137.1 ± 32.4	133.5 ± 22.2	127.0 ± 15.4	P > 0.10
2	8	117.0 ± 27.3	104.9 ± 19.9	99.9 ± 23.1	P > 0.10
3	8	112.5 ± 27.4	104.6 ± 25.4	93.5 ± 24.9	P > 0.10
4	8	105.0 ± 32.7	105.5 ± 38.2	89.4 ± 18.7	P > 0.10
5	8	105.7 ± 31.7	98.7 ± 24.9	91.8 ± 26.6	P > 0.10

[a] = P-value compares mean heart rate between the three treatment groups by analysis of variance for crossover designs.

[b] = Flecainide-digoxin recovery heart rate significantly lower than flecainide or digoxin.

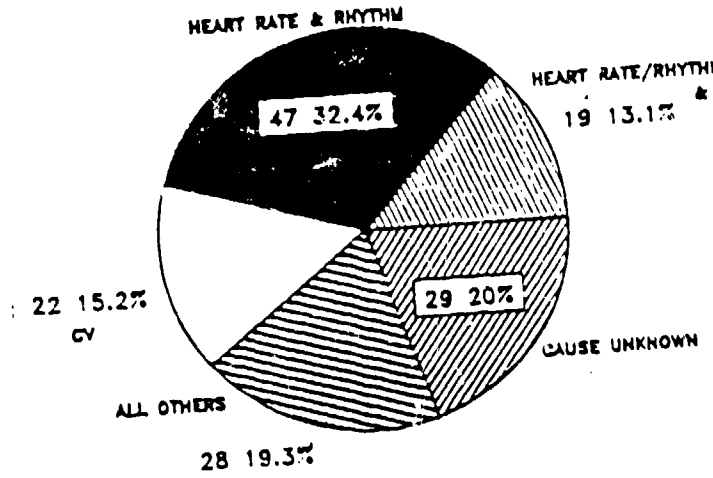
Figure 10

NDA REPORTABLE FLECAINIDE TABLET CASES
WORLDWIDE DRUG EXPERIENCE REPORTS
CRITERIA FOR "SERIOUS" CLASSIFICATION
469 CASES

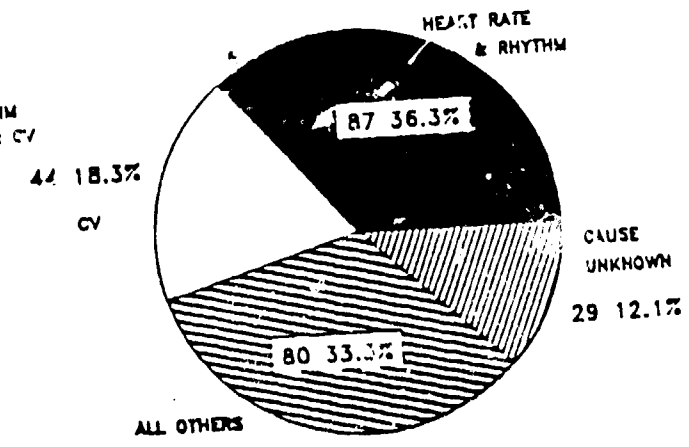


•SOLE CRITERION OF SERIOUS

NDA REPORTABLE FLECAINIDE TABLET CASES
WORLDWIDE DRUG EXPERIENCE REPORTS
ALL DEATHS REPORTED TO FDA 138 CASES 240 REACTION TERMS
DISTRIBUTION BY BODY SYSTEM



138 CASES



240 REACTION TERMS

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Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
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ORIGINAL

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3M

November 30, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experience which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Enclosure: 15 Day Report
-[redacted]

Certified Mail P 504 523 767

12/3/87

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1985

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	53	M	10	29	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

LEUKOPENIA, SEPTICEMIA, DISSEMINATED INTRAVASCULAR COAGULATION, THROMBOCYTOPENIA, FEVER, RASH, HEPATIC FAILURE, RENAL FAILURE, GASTRO-INTESTINAL HEMORRHAGE Death

Man 53 years old with long history of severe coronary artery disease had an episode of cardiac arrest on 10/4/87, was rescusitated, admitted to hospital & 4-artery coronary artery bypass performed on 10/13/87. Post-operatively, he developed episodes of wide QRS ventricular ectopy, & was started on flecainide 100mg bid on 10/5/87. Discharged 10/17/87, he was taking flecainide, dipyridamole, & aspirin, & oxycodone-acetamenophen prn. He fared well until 10/28/87, when he developed mild fever, for which he was given indomethacin, but found that drug intolerable after

13. RELEVANT TESTS LABORATORY DATA

see #7 above. Details to be added.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
200MG	ORAL

17. INDICATION(S) FOR USE

VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*	19. THERAPY DURATION
10/15/87 - 11/04/87	2 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?

[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DILTIAZEM HCL		DIPYRIDAMOLE	
ASPIRIN		TEMAZEPAM	5 DAYS
RANITIDINE HCL	1 DOSE	OXYCODONE HCL, ACETAMINOPHEN	3 DOSES

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

History of subendocardial myocardial infarction. See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
[redacted] /18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
11/ 9/87	[ ] FOREIGN [ ] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
[X] YES [ ] NO	[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/ INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

2 doses. Aspirin dose, which had been 325mg/day, was then increased, & fever was controlled. A diffuse rash then began, followed by nausea, vomiting, diarrhea, marked weakness, & sore throat. He was seen by his surgeon 11/4/87, all drugs were stopped, & he was admitted to hospital late that night. Temperature on admission was 38.4C, spiked to 39.6C 24 hours later, & thereafter generally followed a diurnal spiking pattern, ranging from 37.0/37.6 AM to 38.8/39.4 PM, until terminal 2 days, when it was often <normal. Initial hemogram showed profound leukopenia: 100 WBC, all lymphocytes. Hematocrit, 31.8mm on 11/17/87, was 30.4mm. Blood culture grew E. coli. Shortly after admission he became severely hypotensive, had a brief episode of ventricular tachycardia (treated

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 31 .80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO	DA.	YR.
[redacted] (PAGE 3)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

with IV lidocaine), & transferred to corona_/ care unit. Vigorous antibiotic therapy included imipenem-cilistatin, tobramycin, & metronidazole Evidences of renal & hepatic failure appeared early & progressed inexorably. Leukopenia did not respond to steroid therapy. Platelet count was normal in AM 11/5/87, but dropped to 76,000 that evening, & declined to 12,000 within the next 24 hours. Rectal & upper gastrointestinal bleeding supervened, to be stemmed from time to time by platelet infusions. Repeated white blood cell transfusions were ineffectual. Renal dialysis was performed on 11/8/87, but rapid deteriorization of the patient's condition prevented repitition, & acidosis was uncontrollable. Weight increased 10Kg. On 11/11/87 ventricular tachycardia started, was

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
[redacted]

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
	☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
☐ YES ☐ NO	☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

25.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 4)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

converted with lidocaine, recurred promptly, superceded by ventricular fibrillation, then unresuscitable cardiac arrest at 11:50PM.
Fibrin Split Products were <10ug/ml (normal) on 11/5/87, but rose to the >10 <40ug/ml range by early 11/6/87, & remained in that range thereafter
The patient had been given tonocard 400mg q8h (1200mg/day) from 10/9/87 to 10/14/87, immediately prior to initiation of flecainide. He also received diltiazem & temazepam during that period.
Autopsy report to follow, with details of laboratory data.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
	☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
☐ YES ☐ NO	☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

15.1

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

Pkt. 4 - NDA 18-830

November 14, 1988

3M

Food and Drug Administration
Center for Drugs and Biologics
Division of Cardio-Renal Drug Products HFN-110
5600 Fishers Lane
Rockville, MD 20857

Attention: Dr. S.K. Chun

Subject: NDA 18-830, Tambocor®, ADE Periodic Report

Dear Dr. Chun:

Reference is made to our telephone conversation of October 24, 1988 concerning the most recent Tambocor Periodic ADE Report, during which you asked if we would consider further the possibility of a flecainide-theophylline drug interaction, and review the incidence of congenital anomalies.

A narrative response to these queries has been prepared and is included herein along with several 1639s and references.

We hope this information adequately addresses your concerns.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Affairs Coordinator

:an
Attachment

FLECAINIDE-THEOPHYLLINE INTERACTION: Our Tambocor Adverse Drug Experience data base contains 35 reports in which theophylline is listed as a concomitant medication, involving 50 different Adverse Experience terms. Only one report states Drug Interaction as one of the Adverse Experiences: [redacted], an 80 year old man who developed theophylline intoxication when flecainide was added to a regimen that already included theophylline, and who was found to have mild renal insufficiency induced by ibuprofen.

[redacted] the cased that raised this question, is the 2nd report stating Pulmonary Fibrosis as an Adverse Experience term. The prior case, [redacted], was a 63 year old man with history of myocardial infarction, pulmonary embolism and congestive heart failure, who was given flecainide 100 mg/day for 2 weeks as prophylactic treatment of ventricular tachycardia; flecainide was discontinued when he was hospitalized because of hemoptysis, dyspnea and fever. Four weeks later he died; death was attributed to sepsis and respiratory failure, and autopsy showed pulmonary interstitial fibrosis. He has been treated with amiodarone for 34 days prior to hospitalization. He had not been treated with theophylline.

It seems quite unlikely that an interaction between flecainide and theophylline was etiologically pathogenic in [redacted], in the perspective of 34 other cases in which the two drugs were adminstered concomitantly with no suggestion of pulmonary fibrosis. There must be many patients unknown to us who have taken these two drugs concomitantly, with no apparent ill effect. Copies of [redacted], [redacted], and [redacted] are included.

CONGENITAL ANOMALIES: The frequency of major congenital malformations is taken to be at about 3%, according to "consensus" (Kalter & Warkany, 1983). This figure is largely derived from birth certificate information. A recently reported prospective study of the incidence of congenital malformations in infants born to asthmatic women included 259 women who used inhaled beta-agonist drugs during their pregnancy, an asthmatic control population of 101 women who did not use inhaled beta-agonist drugs during their pregnancy, and a non-asthmatic control group of 295 women (Schatz et al, 1988). The rate of occurrence of major congenital anomalies in the total study population of 655 pregnancies was 5.34%; no significant differences occurred between the three study groups. It is generally accepted that prospective clinical studies discover a higher incidence of malformations than surveys of birth certificates or hospital records. The incidence of minor congenital defects is much higher and figures cited vary with the definitions applied. "Normal variations" occur even more often. A major congenital malformation is one that has serious medical, surgical, or cosmetic consequences or implications (Holmes LB, in Nelson Textbook of Pediatrics, 11th Ed., 1975).

The intracranial arteriovenous fistula reported in [redacted] is clearly a major congenital anomaly. The mother of this infant had mitral valve prolapse and developed polyhydramnios during the later part of her pregnancy; the latter condition is frequently associated with the presence of a major congenital anomaly, but is usually a consequence and not a cause of infants malformation.

Of the other three cases, one is a minor defect ([redacted]) - pes varus and metatarsus varus - susceptible easily to non-surgical correction, and most improbably causally related to flecainide (flecainide was used by the mother only during the 3rd trimester of pregnancy, long after limb organogenesis occurs); one is a normal variation or at most a minor defect ([redacted]) - a small, asymptomatic interventricular defect which was expected to close spontaneously (follow-up information is being sought); the third case is a major congenital abnormality ([redacted]) -- intracranial calcification with severe neurological deficit, occurring in an infant whose mother had taken flecainide only during the last two weeks of a 37 week gestation. Suspicion of a causal relationship to flecainide is considerably vitiated by the very late, brief exposure to the drug. The pathogenesis of this infants intracranial lesion remains obscure, but the most probable causes are parasitic infestation or intracranial hemorrhage.

In summary, without regard to judgment of possible causality, we have two major and two minor congenital abnormalities, and 19 reports of pregnancies completed with normal infants resulting. Using 23 as a denominator (which is only that part of the universe of flecainide-associated pregnancies of which we have been informed), we could be said to have an 8.7% incidence of each of these classes of congenital malformations. Considering the small total number of cases, the strong probability that the real denominator is considerably greater than 23 (and that the unreported cases have all produced normal infants), and the lack of a pattern of abnormalities, it is our judgment that the available evidence does not support a conclusion that flecainide is teratogenic in the human when administered in the recommended doses during all or a part of pregnancy. Copies of these four Adverse Drug Experience Reports are attached.

REFERENCES CITED:

Kalter H, Warkany J. Congenital Malformations. N Engl J Med 1983:308:424-31.

Schatz M, Zeiger RS, Harden KM, et al. The Safety of Inhaled B-agonist Bronchodilators During Pregnancy. J Allergy Clin Immunol 1988:82:686-95.

Holmes LB. Congenital Malformations. In: Vaughan VC, McKay RJ, Behrman RE, eds. Nelson Textbook of Pediatrics, 11th ed. Philadelphia: WB Saunders Co. 1979:370-71.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO	DA.	YR.
[redacted]	63	M	01	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

HEMOPTYSIS, NAUSEA, ANOREXIA, FEVER, DYSPNEA, INTERSTITIAL FIBROSIS
This 63 year old white male has a medical history of Myocardial Infarction, Pulmonary Embolism, Thrombophlebitis, Class I Congestive Heart Failure, and Malignant Arrhythmias. He was hospitalized on 01-16-87 for hemoptysis, accompanied by nausea, anorexia, fevers and increasing dyspnea. He was placed on a respirator and all oral medication was stopped. His condition progressively worsened and he expired on 02-10-86. The immediate cause of death was listed on the death certificate as shock due to sepsis and respiratory insufficiency associated with amiodarone. He had been on Flecainide 50mg bid for 17 days. It is the opinion of the investigator that the event was not

8-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- [X] LIFE THREATENING

13. RELEVANT TESTS LABORATORY DATA
TEMPERATURE: 101.4
CHEST X-RAY: DIFFUSE BILATERAL INTERSTITAL INFILTRATES.
LABS: WBC-16,900, WITH 79% PMN, 6%-BANDS , PLATELETS-343,000, HGB-12.2.
BLOOD GASES: PH-7.47, PCO2-33, PO2-45, BICARB-24.
AUTOPSY: INTERSTITIAL FIBROSIS (PULMONARY)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

DAILY DOSE
100MG

16. ROUTE OF ADMINISTRATION
ORAL

INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*
12/31/85 - 01/16/86

19. THERAPY DURATION
17 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ATENOLOL	7 DAYS	ACETAMINOPHEN	36 DAYS
ASPIRIN	18 DAYS	AMIODARONE	34 DAYS
PROPRANOLOL	14 DAYS	SODIUM WARFARIN	15 DAYS
DIOCYTL SODIUM SULFOSUCCINATE	21 DAYS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
[redacted] /16-830

24b. MFR CONTROL NO.
[redacted]

DATE RECEIVED MANUFACTURER
11/ 3/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

due to Flecainide therapy.
11/3/87: Indication for flecainide treatment was - sustained & non-sustained ventricular tachycardia, & history of ventricular fibrillation

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

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MEDICAL PROGRESS

CONGENITAL MALFORMATIONS

Etiologic Factors and Their Role in Prevention

(First of Two Parts)

HAROLD KALTER, PH.D., AND JOSEF WARKANY, M.D.

IT is just over 20 years since an earlier review of ours of the causes and nature of congenital malformations appeared in these pages.[1] When we wrote that report, teratology was a little-known branch of medicine, and the study of teratogenesis was the province of a limited number of scientists. Attempts were under way to discover general and specific causes of birth defects by critical evaluation of family and pregnancy histories, population data, and animal experiments. But it was already clear that the causative factors were heterogeneous and complex and that for the majority of birth defects the knowledge of causation that then existed was fragmentary and tentative.

To show how far teratogenesis has come in the past two decades we merely need to recall that our review of 1961 did not even mention the word "thalidomide." Our article appeared in the November 16 and November 23, 1961, issues of the *Journal*, and at almost the same time — on November 19, 1961 — Lenz[2] first announced to his pediatric colleagues his suspicion of the association between the then-popular soporific drug and a rash of bizarre defects of the limbs and other parts that had been occurring in Germany. Soon after, we saw McBride's[3] letter in the December 16 issue of *Lancet* and Lenz's[4] in that of January 6, 1962, which put the matter on record and teratology on the map.

The situation has changed considerably since then; many facts have been discovered, and many new concerns have been expressed. Progress has been made in understanding and dealing with some of the problems posed by the occurrence of birth defects, as they have often come to be called. Their frequency and distribution in time and space have been better defined; the role of spontaneous abortion in moderating their occurrence at birth is now well appreciated; their manifold causes have taken on clearer outlines; innovative postnatal and in utero diagnostic and reparative pro-

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cedures have been devised; and the potential of all ... of chemicals for causing prenatal harm has been ...ized and is better guarded against. By and large, however, such refinements have not fundamentally modified the scientific concepts of teratogenesis or the incidence of the conditions.

What has happened, ironically, is an evolution in the notions of the public about the causes of congenital malformations. After the thalidomide tragedy, popular writers and television producers found that birth defects were a subject of compelling interest to their readers and viewers. Given simplified presentations, the general public was convinced that the causes of congenital malformations were well understood and the defects preventable, that they could be predicted before birth, and that parents could be informed with certainty of the risks they would run in future pregnancies. Because of such distorted beliefs, physicians, employers, and drug companies have often been accused of neglect when a child has been born with malformations, and such accusations have led in some instances to trials in which verdicts have often been decided on an emotional basis. Regulations and legislation are demanded for situations that are not sufficiently understood, expert advice is sought about teratogenic dangers that cannot be predicted with certainty, and the public demands authoritative and simple an... ...rs ...estions of great complexity.

...the following pages some of the frequently contradictory literature is discussed. We do not claim to be authorities on the many aspects of this subject, and we direct the reader to the original articles dealing with the etiologic factors of interest.

Classification of Causes

The principles of teratogenesis are few, but the details are complicated.[5] At the crux is causation, and though this numerous and diverse catalogue of phenomena[6] is clearly heterogeneous in its causes, some order and a classification have emerged. Roughly, malformations are divided into those of simple genic origin (caused by single major mutant genes); those held to be due to interactions between hereditary tendencies and nongenetic, usually undefined, factors; those associated with chromosomal aberrations; those attributed to discrete environmental factors as the major cause; and all others — i.e., those with no identified cause. The last group cannot be discussed, except to note that it is numerically the largest (one writer[7] estimates that about 60 per cent of congenital malformations are in this category) and presents the greatest challenges. The second group will also not be discussed, but its salient aspects have been well summarized.[8] Its contribution to the total number of malformations has been conjectured to be about 20 per cent.[7]

These categories will be considered one by one, and ...re possible the proportion of the total number of ...genital malformations for which each is responsible ...ll be estimated.

Definition and Overall Frequency

Clinicians and others generally accept congenital malformations as constituting structural abnormalities of prenatal origin that are present at birth and that seriously interfere with viability or physical well-being. Frequently termed "major" congenital malformations, these are the conditions that we are mainly dealing with here. From numerous surveys during the past 30 years has emerged the present consensus that approximately 3 per cent of newborn children are affected by such malformations. To this figure is added a similar proportion with types of an...nalies not usually detected in the neonatal period ...discovered in the months and years after birth. H... ...for purposes of discussion and for the calcula... ...made below, we shall use the 3 per cent figure that pertains to the newborn, since malformations in this population are the ones most commonly ascertained and the ones whose incidences are most often cited.

The ascertainment of minor structural blemishes and aberrations, which are usually of little or no medical importance, of reduced birth weight at term, of "spontaneous" abortion, and of ...ental retardation is often liable to biases; and only with circumspection can they be the subjects of epidemiologic and comparative studies.

Causes of Congenital Malformations

Monogenic Causes

Many mutant genes — recessive and dominant, autosomal and gonosomal — cause congenital malformations, and though they are individually rare, together they form a considerable sum.

Estimates made in the past 20 years of the frequency of congenital malformations caused by mutant genes have varied from about 0.5 to 8 per 1000 births. The extremes may be attributed, respectively, to incomplete ascertainment of monogenic conditions and overassignment of defects to this classification. On the basis of an intermediate figure — e.g., 2.25 per 1000 live births[9] — about 7.5 per cent of all congenital malformations have a monogenic basis, at least for the populations in northwest Europe and the northeastern United States.

This figure is only negligibly changed downward by the inclusion of stillbirths, since the vast majority of the defects of stillborn infants are of complex and not monogenic origin.[10]

Chromosomal Causes

When it comes to major chromosomal abnormalities, there exist relatively objective criteria for diagnosing and classifying karyotypic anomalies, and fairly uniform findings have emerged.

In recent years many surveys of unselected, consecutively born children have been conducted to determine the frequency and type of chromosomal abnormalities present at birth. The main limitation of such studies has been that in none was the entire group of

newborns simultaneously examined for malformations. The studies we considered informative[11-21] included 66,162 karyotyped infants of diverse ethnic and racial composition, 412 (0.62 per cent) of whom had major chromosomal abnormalities. Of this number, 121 (29.4 per cent) had serious congenital malformations (7.5 and 42.5 per cent, respectively, of those with gonosomal and autosomal abnormalities; of the latter, 71.6 per cent had Down syndrome). The rate of chromosomal abnormalities and malformations combined was therefore 0.18 per cent, and taking 3 per cent as the frequency of congenital malformation, about 6 per cent of all serious malformations in live-born children are associated with major chromosomal abnormalities. This figure is only negligibly higher when the findings for stillbirths are included.

Anatomic and Cytogenetic Abnormalities in Abortuses

It is important to consider the relation between chromosomal abnormalities and congenital malformations in embryos and the role of spontaneous abortion in reducing the prevalence of these defects at birth. The rate of chromosomal abnormalities in newborn infants, which as noted above is about 0.6 per cent, is one tenth of that found in abortuses of 5 to 12 weeks' gestational age.[22] Similarly, the frequency of malformations at term, about 3 per cent, is appreciably smaller than that in unselected abortuses.[23] These great reductions are due to the powerful effect of spontaneous abortion in differentially eliminating many embryos and fetuses with these forms of abnormality.[24,25]

Although the available data are imperfect,[24-26,27] it seems that a sizable fraction of abortions are not associated with chromosomal or morphologic defects.

Major Environmental Causes

A handful of discoveries in our century overturned the belief that the human embryo is shielded from external causes of maldevelopment — namely, the discoveries that ionizing irradiation, the rubella virus, and the chemicals aminopterin and thalidomide are teratogenic. These discoveries were made in 1920, 1941, 1952, and 1961, respectively. Concerning the first, irradiation, it has become clear since our earlier review appeared[1] that medical diagnostic radiation — or more generally, 5 rad of x-rays or less — poses no threat or only a negligible one to prenatal development.[28] About the other classes of teratogens — maternal disorders and chemicals — much still remains to be learned, and it is on these topics that we will concentrate.

Maternal Infections

Maternal illnesses have the advantage for our purposes that their prevalences, or approximations to them, are frequently known. Infectious agents will be considered in some detail, this being one etiologic class that usually leaves objective, that is, immunologic — evidence of its occurrence.

In the years since the discovery that maternal rubella infection can be teratogenic,[29] intensive searches have been conducted to learn whether other infectious organisms can also cause malformations in human conceptuses. Remarkably few have been found to do so.[30] The present evidence indicates that, besides the rubella virus, only cytomegalovirus and *Toxoplasma gondii* unquestionably cause congenital abnormalities. Prenatal transmission of several additional infectious agents (herpes simplex virus Type 2, Group B coxsackievirus, Venezuelan equine encephalitis virus, *Treponema pallidum*, varicella, and urinary-tract infectious agents) may occur and in some instances has been associated with congenital malformations, but these alleged associations are as yet poorly documented.[30]

How often during pregnancy does infection with the unquestionably teratogenic organisms occur, and how often do they cause maldevelopment? These are difficult questions to answer, because epidemicity waxes and wanes, silent maternal infections occur, and immunization practice is inconsistent.

Cytomegalovirus infection may be present in 0.5 to 1.5 per cent of newborn children in the United States, and perhaps as many as 5 to 10 per cent of them may later be found to be deaf and mentally retarded. But severe defects that are apparent at birth occur in only 0.1 to 0.05 per 1000 newborn infants.[30] Although the incidence of maternal toxoplasmosis during pregnancy is about 0.5 per cent in the United States, perhaps as few as 0.5 per 1000 live births are grossly damaged as a result of transplacental toxoplasma infection, since only acute infection causes prenatal maldevelopment.[30] The 1964 epidemic of rubella in the United States caused malformations in more than 20,000 children. Since 1969, the year the rubella vaccine was first licensed, the disease has greatly abated, and the yearly number of cases of the congenital rubella syndrome in the United States has ranged between 23 and 77,[31] for an average during 1970–1980 of 1.33 per 100,000 live births.

When the rates of congenital malformation due to these three diseases are totaled, the result is about 58 per 100,000 live births, or about 2 per cent of the total number of major congenital malformations. If the possible harm done by all the other infectious diseases suspected of being teratogenic (see above) were added to this estimate, the resulting increase would be far less than 1 per cent.

Other Maternal Illnesses

Several noninfectious maternal illnesses known to cause fetal maldevelopment and occurring rarely (phenylketonuria, virilizing tumors, and endemic cretinism and other dysthyroidisms) account for a trivial percentage of the total amount of congenital malformation. Another disease, however, diabetes mellitus, is relatively common.

Diabetes. In order to estimate the role of this disease in the overall problem, information is needed on the prevalence of the condition in women of childbearing

We are considering here only frank diabetes that before the beginning of pregnancy (that is, ... classes B to F), since prediabetes, gestational diabetes, and abnormal glucose tolerance do not appear to be associated with an increased risk of maldevelopment in the conceptus.[32,33]

Estimates of the prevalence of frank diabetes in women of reproductive age have ranged from 1 to 10.8 per 1000.[34,35] Several other surveys have discovered an intermediate rate, such as the 4.7 per 1000 found in the Collaborative Perinatal Project.[36] Using this figure and assuming that overt diabetes does not interfere with conception or increase the rate of spontaneous abortion[37] (and taking the figure 3,646,000 as the total number of births in the United States in 1981[38]), one finds that the number of frankly diabetic women giving birth in that year was 17,282.

The frequency with which malformed children were born to such women and recognized as being malformed in the neonatal period ranged in recent studies[39-46] from 6.6 to 13.0 per cent, with a mean rate of 9.1 per cent, or about three times the number of malformed newborn infants found in the general population. On the basis of this figure, these 17,282 births would have included 1573 congenitally malformed infants, or 1.44 per cent of the total number of such ...ts.

...ong the types of malformations found in infants ... diabetic mothers there are some that, relative to the general picture, are overrepresented, such as cardiovascular, neural-tube, sacral, and femoral malformations. But the spectrum of malformations in such children has not yet been satisfactorily defined.

Confirmation of recent findings indicating that good metabolic control of maternal diabetes before and during the early stages of pregnancy may be associated with decreased levels of congenital malformations[46-48] is to be hoped for.

Thyroid diseases. The prevalence of thyroid diseases in women of reproductive age is fairly high. In the Collaborative Perinatal Project the combined rate for hypothyroidism and hyperthyroidism in white and black women was 0.82 per cent.[49] But aside from possible fetal thyrotoxicosis and goiter with tracheal obstruction in instances of high maternal concentrations of thyroid-stimulating immunoglobulin and following maternal treatment for hyperthyroidism, no congenital defects have been associated with these states.[50]

Endemic cretinism is still common in some parts of the world. In Zaire, for example, the prevalence of this disorder is 7.6 per cent, and in villages in Papua, New Guinea, it has been reported to be as high as 15 per cent[51]; in Europe, Canada, and the United States, on the other hand, exogenous forms of the disease are at present nonexistent.[6]

...ylketonuria. Another maternal illness that can be ...nsible for congenital defects (microcephaly and congenital heart disease) and mental retardation is phenylketonuria (PKU). Although its contribution to the overall incidence of congenital defects is negligible, PKU is of interest because it is associated with a proud medical achievement.

Until the widespread practice of screening for PKU was introduced and early dietary treatment of infants with the disease was instituted about 30 years ago, reproduction by women with the condition was rare. The dietary therapy permits relatively normal physical and mental development and reproduction. But it may be that unless the regimen begins before pregnancy and is strictly continued throughout pregnancy, fetal abnormality can result, and even close compliance may not ensure normality.[52]

Instances of this phenomenon and cases of abnormality due to the persistence of PKU that had been undetected in infancy became conspicuous by 1970, when Hansen[53] identified 26 mothers with hyperphenylalaninemia who had 19 mentally retarded but biochemically normal children. By 1980 Lenke and Levy,[54] in an international survey, reported that in 524 pregnancies of 155 women with PKU, defective children were produced by 95 per cent of those with blood phenylalanine concentrations of 20 mg per deciliter or higher.

Fortunately, however, the impact of such pregnancies on the overall number of congenital malformations in the United States is minute.

Fetal-virilizing diseases. Other maternal disease states that are well recognized as being associated with the risk of prenatal maldevelopment are tumors, hyperplasias, and functional lesions of the ovary and adrenal gland that may cause various degrees of virilization of the female embryo. The frequency of these occurrences is so low that the total risk of such maldevelopment is negligible.[55]

Vaginal bleeding. Numerous other maternal disorders have sometimes been said to be associated with fetal maldevelopment, but most are either so rare (e.g., acrodermatitis enteropathica[56]) or so little credited (neurosis or mental illness) that they do not warrant discussion. But two — vaginal bleeding and maternal fever — will be considered.

An association between vaginal bleeding early in pregnancy and congenital malformations has been noted in some retrospective and prospective investigations[57-60] but not in others.[61-63] Whether there is such an association or not, it is unlikely that the relation is causal, as has been claimed.[60] Because early vaginal bleeding is frequently an indication of threatened abortion and because spontaneously aborted fetuses are frequently malformed (see above), the association may be due to failure of the uterus to follow through on the threat to expel a conceptus with a preexisting malformation. In studies of induced abortions, maternal vaginal bleeding was interpreted as a consequence of the conception of an abnormal embryo.[64]

Hyperthermia. In retrospective analyses it was found that febrile illness or sauna bathing during the early weeks or months of pregnancy was associated with prenatal maldevelopment.[65-69] Increased frequencies of anencephaly, spina bifida, microphthalmia, and unusual facies were reported. Prospective analyses failed

to reveal any association.[70,71] Two recent studies canceled each other out: a positive one from Japan[72] and a negative one from Finland.[73]

Summing up the estimates arrived at above, we find that about 2 per cent of all congenital malformations are due to infectious diseases, 1.4 per cent to diabetes, and probably far less than 1 per cent to other diseases. Thus, about 3.5 per cent of all congenital malformations are due to maternal illness.

Environmental Substances

The purpose of investigating exogenous teratogens is to eliminate them. Investigators have been moderately successful at doing this over the years, and every such triumph has changed the picture we are portraying. Thus, the discoveries that therapeutic pelvic irradiation may be teratogenic, that folic acid analogue abortifacients often cause malformations, that synthetic progestins may masculinize embryos, that thalidomide is devastating to the unborn — all led to the abandonment or modification of the indicted substances or procedures.

These teratogenic practices had been introduced by 20th-century medicine, and their withdrawal left accounts as they had been before. The discovery of the teratogenicity of rubella was different, since fetal damage from that cause had been occurring ever since humankind first had the disease. Measures to combat it therefore made a dent in the bedrock of congenital-malformation occurrence. It has not always been possible to deal with some of the more recently discovered teratogenic agents as effectively, because they involve therapeutic drugs that are used to treat serious diseases and cannot be withheld.

The only important (noninfectious) exogenous causes of congenital malformations today are chemicals of several categories: "environmental" substances, substances used because of personal habits and predilections, and medicinal drugs.

Environmental chemicals (such as additives, contaminants, and pollutants) have aroused much public concern because of their ubiquity and insidiousness, but especially because people seldom have any say about whether they will be exposed to them. By now, many such substances have been suspected of being teratogenic or of having other embryotoxic effects, including prenatal growth retardation and death. But, since practically all chemicals if administered in sufficiently high dosages will retard the growth of some embryos or kill them, without necessarily causing malformations, categorically to equate prenatal mortality or growth retardation with environmentally induced malformation is unjustifiable.

Table 1 lists some environmental substances that are suspected of being embryotoxic. However, most of these suspicions have not been confirmed. The following sections give a few examples.

Hexachlorophene, spray adhesives, chemical wastes. For these supposedly embryotoxic agents the initial allegations were followed by contradictory findings that

Table 1. Environmental Substances Suspected of Causing Congenital Malformations in Human Beings.*

A. Contaminants and additives	C. Personal habits
Cadmium	Alcohol
Cyclamates	Cigarettes
Dioxin	Coffee
Dichlorodiphenyl trichloroethane	Gasoline sniffing
Food colorings	Lysergic acid diethylamide
Hair dyes	Marijuana
Lead	Methadone
Love Canal pollutants	Phencyclidine
Mercury	Tea
Monosodium glutamate	Tobacco chewing
Nitrates	Toluene sniffing
Nitrites	D. Occupational exposure
Polyhalogenated biphenyls	Anesthetic gases
Saccharin	Pen solvents
Sodium fluoride	Hair-spray adhesives
2,4,5-T	Hexachlorophene
B. Natural substances	Hydrocarbons
Blighted potatoes	Organic solvents
Cyanide in cassava	Printing trades
Estrogens in brassicas	Smelter
	University laboratories

*Of these substances only mercury is today accepted to be a proven human teratogen.

weakened or fatally impaired their credibility. Reports[75,76] that the children of hospital nurses who repeatedly used hexachlorophene for hand washing had an unusually high rate of malformations could not be confirmed.[77,78] An alleged association[79] between the occurrence of malformations in children and the exposure of their parents to spray adhesives was later refuted,[80,81] but in the meantime it had widespread medical and economic repercussions.[82] It was feared that the chemical wastes dumped at the Love Canal site were responsible for pervasive chromosomal and reproductive damage.[83] A report from the New York State Department of Health[84] attempted to put this problem in perspective and noted that there was no increase in congenital malformations or low birth weight among the children in areas directly adjacent to the canal and only a slight increase or no increase at all in the level of spontaneous abortions.

Lead. We know of no evidence that lead contamination causes human congenital malformations. Mild brain damage in several infants has been attributed to lead in illegal whiskey that the mothers drank during pregnancy.[85] It is still unclear whether prenatal exposure to low-level lead pollution can interfere with mental development, and this question is presenting great difficulties.[86]

Trichlorophenoxyacetic acid. The environmental chemical most persistently charged with teratogenicity and other types of embryotoxicity has been the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and the product of which it was a component, Agent Orange. The first reports about Agent Orange appeared in Saigon newspapers in 1969,[87] claiming the chemical was responsible for congenital malformations and miscarriages in Vietnamese populations exposed as a result of its use as a defoliant by the U.S. military.

The tale soon became confused, because Agent Orange as it was formulated before about 1969 contained 2,4,5-T that had much larger average concentrations

of a toxic contaminant (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, called simply dioxin or TCDD) than the 2,4,5-T that was manufactured afterward. It was [illegible] re unclear whether the earliest accusations were [illegible] d against the herbicide itself or its contaminant. Experimental studies have shown that both substances are animal teratogens,[88] but only in rodents given far larger relative quantities than human beings have probably ever been exposed to.[89]

Similar charges were leveled against 2,4,5-T (and dioxin) over the next decade in several parts of the world,[90-93] but in every instance, attempts to verify the alleged episodes or to discover additional possible associations have been fruitless.[90,94-99]

Mercury. For only one environmental substance — organic mercury — is there clear evidence of an effect on human prenatal development. In several parts of the world, especially Japan and Iraq, ingestion by pregnant women of foods contaminated with various forms of organic mercury (usually methylmercury) led to nonspecific neurologic symptoms in children exposed to the chemical in utero. It was not always certain to what extent the problems were the outcome solely of exposure before birth, since the mercury was often received postnatally through maternal milk or other food, as well as transplacentally.

The poisonings in Japan went on for 12 to 15 years.[100] The disease was first recognized in an infant in 1953, and later in adults and children, in Minamata [illegible] seaside community in southwest Japan; it thus [illegible] to be known as Minamata disease. A second outbreak occurred in 1965 in Niigata City, another coastal town, in northwest Japan. In both instances the disease stemmed from consumption of fish and shellfish contaminated with methylmercury that had been discharged into nearby rivers from industrial plants producing acetaldehyde and using mercury as the catalyst. By 1972 at least 704 authenticated cases of organic mercury poisoning had occurred in the Minamata region and 121 in Niigata, and there were perhaps another 1200 awaiting validation. Among the children the cases were divided into fetal and infantile poisoning, apparently according to the time of initial exposure. The total of fetal (and presumably embryonic) cases was 26 — 25 in Minamata and one in Niigata[100] — though Harada[101] mentioned that there were 40 congenital cases.

In Iraq the epidemic was of much shorter duration than in Japan, but apparently far more devastating.[102] It originated with the consumption of bread made from imported grain that had been treated with a fungicide containing methylmercury. The grain arrived in September and October 1971 and was distributed until about January 1972, when the authorities issued warnings about it. By late March 1972 the final total, 6530 cases, had been reached,[102,103] but the number of prenatally damaged infants was only 32 (ref. 104). Thus, in both countries the total number of affected c[illegible] n whose initial exposure was in utero was possi[illegible] nany as 72.

The frequency of such cases in Iraq is unknown but was apparently quite low. Fragmentary data from Japan show that in severely affected areas in the Minamata district there were 19 congenital cases in 357 births (5.3 per cent) during the years of heavy affliction.[105] Only crude relations have been established between the amount of maternal mercury exposure and the severity of symptoms, and it has been difficult to ascertain maximum levels that are without overt developmental effects.[106]

It can be concluded that long-term prenatal exposure to organic mercury, caused by pollution of the environment, has caused neurologic damage that was probably due to disturbed brain development. Most if not all of the disturbances were sustained during the later months of gestation. Exposure during the first trimester apparently had no harmful consequences, since major congenital malformations, which would be expected to result from exposure during this period, did not occur. Another possible effect of such early exposure — an increased abortion rate, which was produced in experimental studies by the administration of relatively high levels of mercury[107] — was apparently not investigated. It is of interest that the extensive literature on adverse reactions to inorganic mercury does not mention congenital malformations.[108]

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MEDICAL INTELLIGENCE

CURRENT CONCEPTS

FUNCTIONAL GASTROINTESTINAL DISORDERS

J. E. Lennard-Jones, M.D.

IN most of us the the gastrointestinal tract is quiet, unobtrusive, and efficient, but it gives trouble to at least one person in three. Often symptoms are slight, and simple traditional remedies suffice. A few people experience recurrent or constant symptoms that are severe enough to be disabling and for which no explanation can be found. The symptoms of at least one fifth of the patients who consult a gastroenterologist remain unexplained.[1,2] The clinical problem of functional gastrointestinal symptoms cannot be ignored.

Definition

For the purpose of this review, a functional symptom is defined as one for which no structural, infective, or biochemical cause can be found. The symptom may apparently occur anywhere along the length of e gastrointestinal tract. Terms such as "esophageal spasm," "tender esophagus," "enterospasm," "irritable bowel," "spastic colon," or "proctalgia" describe particular features of a larger problem that are brought together under the general term "sensorimotor" symptoms, because increased visceral sensation or disturbed motor activity (or both) can often be demonstrated.

Certain structural changes in the gastrointestinal tract, as in colonic diverticular disease, or in the striated muscle sphincters may be secondary to disorders of function. For simplicity, these structural abnormalities will not be considered here.

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The Indistinct Boundary between a Nuisance and an Illness

In England one fifth of a sample from the general population had experienced abdominal pain more than six times in the previous year; this discomfort had the characteristics of colonic pain in 13 per cent of the sample. In addition, 6 per cent had painless constipation and 3.7 per cent painless diarrhea.[3] Similarly, in the United States about one quarter of a sample of apparently healthy subjects reported that they had experienced abdominal pain more than six times in the previous year, and 17 per cent had symptoms that fulfilled a rigorous definition of bowel dysfunction.[4] Why, then, do some people seek medical help and not others? Is it that their symptoms are more severe or that they are less able to cope with them? Similarly, why does a patient with longstanding symptoms seek help now? There is no dividing line between health and disease, only between those who shrug off their symptoms, seeking little or no medical help, and those whose lives are affected to a greater or lesser extent by a troublesome gastrointestinal tract.

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The safety of inhaled β-agonist bronchodilators during pregnancy

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To assess the safety of inhaled β-agonist bronchodilators during pregnancy, perinatal outcomes in 259 prospectively managed women with asthma using these medications during pregnancy were compared to perinatal outcomes in 101 concurrently followed pregnant subjects with asthma not using inhaled bronchodilators and to perinatal outcomes in 295 concurrently followed pregnant control subjects without asthma. No significant differences between women with asthma using inhaled bronchodilators and subjects not receiving inhaled bronchodilators were found in the following parameters: perinatal mortality, congenital malformations, preterm births, low birth weight infants, mean birth weight, small for gestational age or low ponderal index infants, Apgar scores, labor/delivery complications, or postpartum bleeding. Increased incidences of maternal chronic and pregnancy-induced hypertension and transient tachypnea of the neonate were observed in the pregnancies of subjects with asthma using regular inhaled bronchodilators compared to control subjects, but a logistic regression analysis within the sample of subjects with asthma did not significantly associate the use of inhaled bronchodilators with these outcomes. In the light of the known substantial perinatal risks of severe, uncontrolled asthma and the relatively sparse evidence of human gestational safety for alternative asthma medications, these data support the use of inhaled β-agonist bronchodilators as part of the management of asthma during pregnancy. (J ALLERGY CLIN IMMUNOL 1988;82:686-95.)

Asthma is a common and potentially serious medical problem that complicates approximately 1% of pregnancies.[1] Retrospective studies have associated severe maternal asthma with increased perinatal mortality and morbidity,[1, 2] possibly through the adverse effect on the infant of asthma-induced maternal hypoxia,[3, 4] hypocapnia,[3] and/or alkalosis.[5] Current recommendations suggest that asthma should be adequately controlled during pregnancy to prevent maternal blood gas abnormalities and their subsequent potential adverse effects on the fetus.[6, 7] Since adequate control of asthma usually requires the use of medication, optimal management of gestational asthma involves choosing medications that control maternal asthma without inducing harm to the fetus. Presently, however, no asthma medications can be considered safe during pregnancy based on "adequate and well-controlled studies in pregnant women" according to Food and Drug Administration stan-

Abbreviation used
TTN: Transient tachypnea of the neonate

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dards.[8, 9] Such necessary use of medication of unproved safety during pregnancy also places physicians managing asthma during pregnancy in potential medicolegal jeopardy in the current litigation-oriented society.[10] Against this background, some investigators have endorsed the use of inhaled β-agonist bronchodilators during pregnancy because of their minimal systemic effects.[11-14] Other investigators, however, have cautioned against the gestational use of these medications until human data supporting their safety during pregnancy are published.[6]

Since 1978, the Kaiser-Permanente Prospective Study of Asthma During Pregnancy has compared the outcome of pregnancy in prospectively managed women with asthma to concurrently prospectively followed, matched control subjects. This ongoing study provided the opportunity to analyze the safety of inhaled bronchodilator use during pregnancy because inhaled bronchodilators were an integral part of the asthma-management protocol. This study demonstrates the perinatal safety of inhaled β-agonist bronchodilators used in treating asthma during pregnancy in 259 women.

METHODS

Subjects

Subjects were members of the San Diego Kaiser-Permanente Medical Care Program, a large Health Maintenance Organization with approximately 4200 deliveries per year. All women presenting for prenatal care before the third trimester of pregnancy were asked to complete a questionnaire directed at identifying a history of asthma or asthma symptoms. Women with a positive history of asthma or asthma symptoms were then evaluated by one of the investigators (M. S.) in the allergy clinic by history, physical examination, and spirometry. After obtaining informed consent, pregnant women with a clinical diagnosis of asthma were enrolled in the "Asthma" group of the study. Women who denied asthma or asthma symptoms and who could be matched regarding age and smoking status to a previously entered asthma subject were entered into the "Control" group of the study after giving their informed consent. Age matching for women aged 35 years or younger was within 5 years of their exact age; women with asthma older than age 35 years were matched to control women older than age 35 years. Based on information that was available early in the study,[15-17] "smokers" were considered to be those subjects who smoked 10 or more cigarettes per day for more than 1 month of pregnancy. Seventy-one percent of the subjects with asthma entered the study during their first trimester and 29% in their second trimester. The research protocol was approved by the Kaiser Foundation Hospitals Institutional Review Board. Patients completing the study between June 1978 and December 1984 are described in the present article.

Management and assessment during pregnancy

All subjects received routine prenatal and obstetric care by the Kaiser-Permanente obstetrician of their choice. The course and complications of pregnancy, labor, and delivery were recorded on standardized forms. All subjects underwent complete pulmonary function testing (including spirometry, flow-volume loop, body plethysmographic volume, and resistance measurements) at 32 to 36 weeks gestation (without bronchodilator testing) and again at 6 to 12 weeks postpartum (before and after bronchodilators). After entering the study, all subjects kept a medication, x-ray, alcohol, and infection diary.

In addition to the above, subjects with asthma maintained an asthma-symptom diary card and were evaluated at least monthly by a study allergist (M. S.), at which time historical, physical examination, and spirometric data were obtained and management decisions were made. Inhaled bronchodilators were used (1) as needed in patients with intermittent symptoms, (2) regularly in patients requiring chronic asthma treatment, and (3) in mechanical nebulizers as part of the treatment of acute asthma in the clinic or emergency room. Metaproterenol, being the most selective β-agonist commercially available at the onset of the study, was chosen as the specific inhaled bronchodilator to be used in this phase of the study. However, use of other inhaled bronchodilators sometimes occurred either before entrance into the study or based on individual patient preferences. Subjects recorded their use of inhaled bronchodilators in terms of number of puffs per day. Other medications frequently used, when these were indicated, included theophylline (in 66%), cromolyn (in 12%), beclomethasone (in 10%), and prednisone (in 14%). The major goals of asthma therapy in the prospectively managed pregnant subjects included the prevention of (1) acute asthmatic episodes and (2) interference with sleep or normal activity.

Asthma/control group confirmation

Confirmation of the diagnosis of asthma required documentation of reversible obstructive airway disease on the basis of at least one of the following four criteria (the proportion of subjects documented by each criteria are indicated): (1) obstructive spirometry (abnormal age-related FEV_1/FVC ratio or maximum midexpiratory flow rate <65% predicted) with at least 20% reversibility after bronchodilator (48%), (2) obstructive spirometry (as above) on at least one occasion with normal spirometry on another occasion and a significant difference between the two values, based on serial population testing[18] (36%), (3) a positive postpartum methacholine challenge by standard methodology and criteria[19] (3%), or (4) auscultatory wheezing during tidal breathing on one occasion with clear lungs on another occasion (13%). The latter criterion was used in women with a history of asthma and documented wheezing in whom complete pulmonary function testing and serial spirometry did not document reversible airway obstruction and in whom postpartum methacholine challenges were not performed.

TABLE I. General characteristics of asthma and control subjects

Parameter	Asthma				Control subjects
	Any IB*	No IB	Intermittent IB†	Regular IB‡	
Sample size	259	101	179	78	295
Mean age (± SEM)	26.7 ± 0.3	26.6 ± 0.5	26.4 ± 0.3	27.6 ± 0.5	27.0 ± 0.2
Smokers	11.2%§	12.9%§	11.2%	11.7%	5.4%
Race: white	84.9%	90.1%	81.0%‖	93.5%	88.4%
Primiparas	39.8%¶	42.6%¶	36.9%¶	48.1%#	65.8%
Asthma requirement					
Emergency therapy	17.8%**	0.0%	11.2%	32.5%††	—
Corticosteroids	17.8%§§	2.0%	8.4%	39.0%††	—
Regular theophylline use‡‡	37.2%**	6.9%	20.1%	76.6%††	—

*IB is inhaled bronchodilator, dose uncertain in two subjects.
†Average of less than one puff daily throughout pregnancy.
‡Average of one or more puffs daily throughout pregnancy.
§$p < 0.05$ compared to control subjects.
‖$p < 0.05$ compared to intermittent inhaled bronchodilator users.
¶$p < 0.001$ compared to control subjects.
#$p < 0.01$ compared to control subjects.
**$p < 0.00001$ compared to subjects with asthma using no inhaled bronchodilators.
††$p < 0.001$ compared to intermittent inhaled bronchodilator users.
‡‡Average of ≥200 mg daily throughout pregnancy.
§§$p = 0.0001$ compared to subjects with asthma using no inhaled bronchodilators.

Only documented subjects with asthma who experienced symptoms of wheezing, cough, or chest tightness *during pregnancy* were included in the final data analysis. The control subjects were required to have normal pulmonary function tests during pregnancy and postpartum.

Data analysis

Perinatal outcome data were extracted from the standard prenatal, labor, delivery, postpartum, and nursery records by a research nurse who did not know at the time of data collection to which group (asthma versus control) the subject belonged. Only subjects delivering single births ≥20 weeks gestation whose asthma and control status could be confirmed were included in the data analysis. Thus, seven subjects with asthma and five control subjects were excluded because of twin pregnancies, 20 subjects with asthma and 15 control subjects were excluded because of spontaneous abortions (<20 weeks), and 25 subjects with asthma and 71 control subjects were excluded because of not fulfilling the above confirmation criteria.

Criteria for inclusion in the final data analysis were met by 360 subjects with asthma and 295 control subjects. Control subjects could not be identified for 65 subjects with asthma, largely caused by the inability to identify/recruit enough control subjects who smoked. Of the 360 subjects with asthma, 259 used inhaled β-agonist bronchodilators at some time during pregnancy, and 180 used these medications during the first trimester. First trimester-inhaled bronchodilator use was uncertain in seven additional subjects, and data from these subjects were not included in first trimester analyses.

For all the analyses to be described, the occurrence of 10 perinatal events in the population being evaluated was set as the minimum required for statistical analysis. Two-tail statistical significance was set at the 5% level for all the statistical analyses.

Comparisons of two populations. Chi-square analysis was used for dichotomous variables and Student's *t* test was used for continuous variables for all the population analyses to be described. A preliminary comparison of asthma versus control groups demonstrated that they were well matched with respect to age and race, but not parity (Table I). To account for differences in parity, all asthma versus control analyses were stratified by parity for perinatal outcomes known to be influenced by parity.

Linear trend analysis. Chi-square tests for linear trend[5] were used to test the association in the population with asthma of level of inhaled bronchodilator use with the incidence rate of perinatal outcomes. Level of use was defined by the known average daily dose of inhaled bronchodilators during the entire pregnancy: none ($N = 101$), less than one puff daily ($N = 179$), one to two puffs daily ($N = 29$), two to four puffs daily ($N = 25$), and more than four puffs daily ($N = 24$).

Regression analyses. Logistic regression analyses were conducted in the 360 total subjects with asthma for important perinatal outcomes that occurred in >10 subjects. Perinatal outcomes that were analyzed in this manner included chronic

TABLE II. Incidence of congenital malformations in relationship to maternal inhaled bronchodilator use

	Asthma*						
			Linear trend analysis				
	Any IB	No IB	<1 puff	1-2 puffs	2-4 puffs	>4 puffs	Control subjects
Anytime use							
N†	259	101	179	29	25	24	295
Major	3.9%	6.0%	4.0%	0.0%	4.0%	8.3%	6.4%
Minor	4.7%	5.0%	4.5%	6.9%	4.0%	4.2%	7.5%
1st trimester use							
N‡	180	172	109	18	22	30	295
Major	3.9%	5.3%	2.8%	5.6%	4.5%	6.7%	6.4%
Minor	2.2%	6.4%	1.8%	0.0%	0.0%	6.7%	2.5%

IB = inhaled bronchodilator.
*No significant differences ($p < 0.05$) were found between users of any inhaled bronchodilator (Any IB) and control groups, and no significant linear relationships ($p < 0.05$) were found in the linear trend analysis.
†Dose uncertain in two subjects.
‡First trimester use uncertain in seven subjects, and first trimester dosage uncertain in one additional subject.

hypertension, pregnancy-induced hypertension, preterm births (<37 weeks), low birth weight infants (<2500 gm), low ponderal index (<2.2), TTN, major congenital malformations, and minor congenital malformations. Independent (predictor) variables in the regression analyses included (1) age, (2) smoking status, (3) parity, (4) occurrence of acute asthma requiring emergency treatment, (5) asthma severity (based on a medication requirement scale), (6) use of inhaled bronchodilators at any time during pregnancy (presented in five categories, as in the linear trend analysis), (7) regular theophylline use (≥200 mg daily), (8) use of oral corticosteroids, and (9) mean gestational office FEV_1. To control for the effects of age, parity, and smoking, these variables were forced into the equation. An additional separate analysis was performed for major and minor congenital malformations in which only first trimester drug use in variables 6 to 8 above were considered. Cesarean section was included as an independent variable in the TTN analysis because of the known relationship between TTN and cesarean section.[21]

RESULTS

Of the 259 subjects using inhaled bronchodilators, 78 (30%) used them regularly (average of one or more puffs daily throughout pregnancy), 179 (69%) used them intermittently (average of less than one puff per day throughout pregnancy), and the dose in two subjects (1%) was uncertain. Subjects who used inhaled bronchodilators required significantly more emergency therapy, corticosteroids, and regular theophylline for asthma than women with asthma not using inhaled bronchodilators, and more women who used *regular* inhaled bronchodilators required emergency treatment, corticosteroids, and theophylline compared to *intermittent* users (Table I). As expected from the matching problem discussed above, subjects with asthma were significantly more likely to smoke than control subjects (Table I), but there was no significant difference in the proportion of smokers between subjects with asthma not using inhaled bronchodilators, subjects with asthma using intermittent inhaled bronchodilators, and subjects with asthma using regular inhaled bronchodilators (Table I).

The specific inhaled β-agonist bronchodilators used by study subjects were as follows: metaproterenol (83%), isoetharine (27%), epinephrine (13%), albuterol (8%), and isoproterenol (4%). More than one specific inhaled bronchodilator was used by 82 (32%) subjects.

The incidence of major and minor congenital malformations in relation to inhaled bronchodilator dose used during the first trimester and the entire pregnancy is presented in Table II. There was no significant increase in the incidence of congenital malformations in any category of inhaled bronchodilator use compared to control subjects, and no evidence of a dose-dependent increase in congenital malformations was observed in subjects with asthma.

Tables III and IV display other perinatal outcomes with n ≥ 10 in the total population in subjects with asthma using any or regular inhaled bronchodilators compared to subjects with asthma not using inhaled bronchodilators and to control subjects. Significantly

TABLE III. Incidence of pregnancy, delivery, and postpartum complications in relationship to inhaled bronchodilator use

Parameter	Incidence (%)*			
	Asthma IB		No IB	
	Any IB	Regular IB†	Asthma	Control subject
N	259	78	101	295
Chronic hypertension	3.9‡	7.8§	1.0	0.3
Primiparas	2.0	5.6‡	0.0	0.0
Multiparas	5.2	10.0‡	1.7	1.0
Pregnancy-induced hypertension	10.1	17.1‖	8.0	10.5
Primiparas	12.7	19.4	7.1	14.9
Multiparas	8.4¶	17.1‡	8.6	2.0
Premature labor	3.5	3.8	2.0	4.1
Primiparas	5.8	5.4	2.4	4.7
Multiparas	1.9	2.4	1.7	3.0
Primary cesarean section	12.0	18.2	10.9	14.9
Primiparas	22.3	32.4	18.6	21.1
Multiparas	5.2	5.0	5.2	2.0
Postpartum bleeding	3.9	5.1	2.0	4.8

IB = inhaled bronchodilator.
*Significant differences ($p < 0.05$) between subjects with asthma using inhaled broncholilators (Asthma IB) (any or regular) and subjects using no inhaled bronchodilators (No IB) (subjects with asthma or control subjects) are noted.
†Average of one or more puffs daily throughout pregnancy.
‡$p < 0.01$ compared to control subjects.
§$p < 0.001$ compared to control subjects, and $p < 0.05$ compared to subjects with asthma using no inhaled bronchodilators (Asthma No IB).
¶$p < 0.05$ compared to control subjects.
‖$p < 0.05$ compared to subjects with asthma using no inhaled bronchodilators (Asthma No IB).

more subjects with asthma using inhaled bronchodilators demonstrated chronic hypertension and pregnancy-induced hypertension (in multiparas) compared to control subjects, and these increases were most prominent in regular inhaled bronchodilator users (Table III). Regular inhaled bronchodilator users also exhibited both forms of hypertension significantly more commonly than subjects with asthma not using inhaled bronchodilators (Table III). In addition, infants of subjects with asthma using inhaled bronchodilators manifested TTN more frequently than infants of control subjects (Table IV). There were no significant increases in any of the other perinatal outcomes in Tables III and IV in subjects with asthma using inhaled bronchodilators (any or regular) compared to subjects with asthma not using inhaled bronchodilators or compared to control subjects. Perinatal outcomes in Tables II to IV were also evaluated in subjects with asthma using inhaled metaproterenol specifically compared to control subjects (data not presented); no significant differences were found that were not also observed in the analysis of total inhaled bronchodilator users versus control subjects.

There were no maternal deaths in this series. The incidence of infant respiratory distress syndrome, which occurred in five total subjects, was 0.8% in subjects with asthma using inhaled bronchodilators compared to 0.7% in control subjects.

Linear trend analysis revealed a significant dose-dependent relationship between increased inhaled bronchodilator use and an increased incidence of chronic hypertension ($p = 0.0005$) and pregnancy-induced hypertension ($p < 0.012$). No significant linear relationships were found between increasing inhaled bronchodilator use and increased premature labor, primary cesarean section, low birth weight infants, preterm births, congenital malformations, low ponderal index infants, TTN, or postpartum hemorrhage.

With a multivariate regression analysis to control for age, parity, and smoking, and to account for the effects of asthma severity and other medications, no

TABLE IV. Relationship of infant characteristics to maternal inhaled bronchodilator use

Parameter	Asthma IB*		No IB	
	Any IB	Regular IB†	Asthma	Control subjects
N	259	78	101	295
Perinatal deaths (%)	1.2	3.9	4.0	1.4
Mean birth weight (gm) (± SEM)	3416 ± 35	3416 ± 75	3361 ± 68	3477 ± 32
Primiparas	3340 ± 56	3384 ± 107	3345 ± 107	3440 ± 40
Multiparas	3466 ± 44	3373 ± 107	3373 ± 90	3549 ± 54
Preterm births (<37 wk) (%)	3.9	6.4	6.0	2.7
Primiparas	4.9	5.4	7.1	3.6
Multiparas	3.2	7.3	5.2	1.0
Low birth weight (<2500 gm) (%)	4.6	5.1	6.0	3.1
Primiparas	4.9	5.4	4.8	3.6
Multiparas	4.5	4.9	6.9	2.0
Small for gestational age (%)	1.6	1.3	3.1	1.0
Low ponderal index (<2.2) (%)	7.0	5.2	12.4	10.2
Mean Apgar 1 min ± SEM	7.82 ± 0.08	7.76 ± 0.13	7.85 ± 0.16	7.86 ± 0.06
Mean Apgar 5 min ± SEM	8.84 ± 0.04	8.89 ± 0.05	8.69 ± 0.11	8.84 ± 0.04
TTN	2.8‡	3.9‡	4.0	0.3
Primiparas	3.0‡	5.6‡	7.1	0.0
Multiparas	2.6	2.5	1.8	1.0

*Significant differences ($p < 0.05$) between subjects with asthma using inhaled bronchodilators (Asthma-IB) (any or regular) and subjects using no inhaled bronchodilators (No IB) (subjects with asthma or control subjects) are noted.
†Average of one or more puffs daily thoughout pregnancy.
‡$p < 0.05$ compared to control subjects.

TABLE V. Ninety-five percent confidence intervals of study results in comparison to general population figures

	Perinatal mortality			Major congenital malformations		
	N	Incidence	CI	N	Incidence	CI
Inhaled bronchodilator users*	259	1.4%	0.4 – 3.4%	259	3.5%	1.8 – 6.5%
General population†	1,999,254	1.2%	—	—	3.0%	—

CI = confidence intervals.
*Current study.
†State of California, 1978 to 1982,[36] perinatal mortality, and major congenital malformations.[34]

relationship was found between inhaled bronchodilator use and any of the perinatal parameters evaluated, including congenital malformations (related to inhaled bronchodilator use any time during pregnancy or specifically during the first trimester), chronic hypertension, pregnancy-induced hypertension, and TTN. Multivariate analysis did associate chronic hypertension with increased age ($p = 0.003$), increased asthma severity ($p = 0.008$), and increased need for emergency therapy ($p < 0.025$); pregnancy-induced hypertension was associated with increased age ($p = 0.004$) and with oral corticosteroid use ($p < 0.005$); TTN was associated with cesarean section ($p < 0.05$).

DISCUSSION

The study data were analyzed in four ways to clearly assess the safety of inhaled β-agonist bronchodilators in these pregnant, prospectively managed subjects with asthma: (1) perinatal outcomes in subjects with asthma using any inhaled bronchodilators were compared to perinatal outcomes in a concurrently fol-

TABLE VI. Published human studies of the safety of asthma medication during pregnancy*

Ref	Drug	Sample size	Concurrent control population	Prospective surveillance: Medication	Prospective surveillance: Obstetric	Complications assessed other than congenital malformations	Result: Major congenital malformations	Result: Other
28	Epinephrine	189	Yes	Yes	Yes	No	Increased† ($r < 0.05$)	Not described
28	Ephedrine	373	Yes	Yes	Yes	No	Not increased†	Not described
28	Theophylline/ Aminophylline	193	Yes	Yes	Yes	No	Not increased†	Not described.
29	Cromolyn	296	No	No	No	No	1.4%	Not described
30	Beclomethasone	45	No	Some patients	No	Yes	2.3%	Increased incidence of low birth weight infants
31	Prednisone	70	No	No	No	Yes	2.8%	Increased incidence of preterm births
Current study	Inhaled bronchodilators	259	Yes	Yes	Yes	Yes	3.5%	See text

*Includes only studies with more than 40 subjects.
†Incidence of [illegible] congenital malformations not specifically presented; incidence of total malformations compared in exposed versus nonexposed subjects.

lowed, control sample without asthma well matched for age and race, (2) perinatal outcomes in a smaller group of subjects with asthma using regular inhaled bronchodilators were compared to perinatal outcomes in the control group, (3) perinatal outcomes were compared in subjects with asthma using no inhaled bronchodilators to the outcomes in subjects with asthma using various doses of inhaled bronchodilators, and (4) multifactorial analyses of perinatal outcomes were performed that accounted for the potential effects of age, smoking, parity, other asthma medications, and asthma-severity factors. The results of these analyses in this prospective study suggest that the use of inhaled β-agonist bronchodilators for the management of asthma during pregnancy is not associated with an increased frequency of adverse maternal or infant perinatal outcomes.

The control group in this study was identified from the same population as the treated subjects and was concurrently prospectively followed at the same institution. This control group was thus comparable to the treated subjects with regard to contemporary and uniform obstetric management, perinatal assessment, and demographic variables. In addition, the control group was identified prenatally, allowing for documentation of the absence of pulmonary abnormalities in control subjects both during and after pregnancy. Indeed, nearly 20% of the pregnant women with no history of asthma or asthma symptoms who volunteered for the study were excluded from the final data analysis because of abnormal pulmonary function tests (almost always obstructive airway disease).

Adverse perinatal outcomes did not appear to occur more commonly in this carefully defined control group than in the general population[21-23] with the possible exception of major congenital malformations, which occurred in 6.4% of the 295 total control subjects compared to the "consensus" general population figure of 3.0%.[24] However, "the incidence of birth defects is a function of how one defines and ascertains a birth defect." [25] Assessment by means of nursery records, as performed in this study, will produce a higher incidence than assessment by means of birth certificates or delivery records.[25] The major point relative to this study is that, with the use of uniform definitions and assessment, the incidence of congenital malformations in subjects using inhaled bronchodilators at any time during pregnancy or specifically during the first trimester was not significantly different than the incidence in prospectively followed control subjects without asthma.

Increases in chronic and pregnancy-induced hyper-

tension were observed in women with asthma using inhaled bronchodilators compared to subjects with asthma and/or control women not using inhaled bronchodilators, and these increases were particularly prominent with higher dose inhaled bronchodilator use. However, (1) because inhaled bronchodilator users required significantly more emergency room therapy, corticosteroids, and theophylline compared to nonusers, and (2) because regular users experienced significantly more of these events than intermittent users, the dose-dependent relationships between inhaled bronchodilators and these increased adverse perinatal outcomes cannot automatically be attributed to the inhaled bronchodilators themselves. Indeed, after accounting for potential confounding factors such as asthma severity and other medication use in the multivariate analysis, the use of inhaled bronchodilators could not be demonstrated to significantly increase the risk of chronic hypertension or pregnancy-induced hypertension in pregnancies of subjects with asthma. The factors that were significantly associated with these adverse outcomes in the regression analyses will be discussed in a subsequent article.

A significant increase in TTN was also observed in the infants of subjects with asthma using inhaled bronchodilators compared to control infants. This increase was most prominent in the offspring of primiparas and did not appear to be dose dependent by linear trend analysis. As previously recognized,[21] there was an association between TTN and cesarean section in our population. Although the mechanism of this increase is uncertain, the multivariate analysis suggested that inhaled bronchodilator use did not significantly increase the risk of TTN in the offspring of subjects with asthma.

The statistical power resulting from the sample size in this study is of importance in the evaluation of the significance and practical application of the safety aspects of the findings. Evaluation of 95% confidence intervals of the results can reveal insight into the impact of sample size. The 95% confidence intervals of two important outcomes, perinatal mortality and major congenital malformations, are presented in Table V in comparison to results from larger samples in reference populations. As presented in Table V although the results obtained in this study are similar to general population figures, the present sample size does not allow exclusion of some increase in incidence of adverse outcomes in subjects with asthma using inhaled β-agonist bronchodilators during pregnancy. An ongoing second phase of this study, which will lead to an approximate doubling of the sample size, will permit narrowing of these confidence limits.

The decision whether to use inhaled bronchodilators in the management of asthma during pregnancy at this time must be made by evaluating the data in this study in relationship to (1) the risk of uncontrolled asthma during pregnancy and (2) the human gestational safety data available for alternative asthma medications. Two large retrospective studies have evaluated perinatal outcome in pregnancies of subjects with asthma compared to the general population. Bahna and Bjerkedal[2] compared 381 pregnancies in women with asthma to the pregnancies of 112,530 control women with no medical disease. They observed a statistically significant increase in preterm births, low birth weight infants, and neonatal mortality in women with asthma compared to pregnancies in control women. Gordon et al.[1] compared the outcome of pregnancy in 277 women with asthma to the outcome of pregnancy in 30,861 total pregnant women followed by them. These authors reported that the perinatal mortality rate was nearly doubled in women with asthma versus control women ($p < 0.05$). Two additional observations suggest that severe/uncontrolled asthma is particularly a risk factor. First, women with "severe" asthma (N = 16) in the study of Gordon et al.[1] exhibited a 28% perinatal death rate and an incidence of 35% of low birth weight infants. Second, in a more recent series of prospectively managed, steroid-dependent pregnant women with asthma, Fitzsimmons et al.[27] reported that the mean birth weight in eight infants born to seven mothers who required hospitalization for status asthmaticus during pregnancy was 2764 gm compared to a mean birth weight of 3184 gm in 41 infants from 40 gravidas with asthma who required no emergency therapy for asthma during pregnancy ($p = 0.03$). The perinatal risk of the use of inhaled bronchodilators during pregnancy appears to be clearly less than the risk of severe, uncontrolled gestational asthma.

Studies in humans describing the safety of asthma medications during pregnancy are summarized in Table VI. Included in this table are important aspects of study design that must be considered in evaluating the validity and applicability of the data. The present study is the sole investigation of the use of asthma medications during pregnancy to include all of the following features: concurrent control population, prospective surveillance of both medication usage and obstetric outcome, an assessment of adverse perinatal outcomes other than congenital malformations, and relatively large sample size. Considering these safety studies, inhaled bronchodilators appear to be at least as safe as alternative asthma medications available for use during pregnancy.

Since 69% of our subjects used inhaled bronchodilators intermittently (average of less than one puff

per day throughout pregnancy), the statistical power of our conclusions is greater for intermittent than for regular inhaled bronchodilator use during pregnancy. However, the following points regarding regular or higher dose use in our series can be made: (1) There was no apparent trend toward increasing congenital malformations with increasing inhaled bronchodilator usage within the inhaled bronchodilator dose range required by this general population of pregnant women with asthma (Table II). (2) A dose-dependent relationship between inhaled bronchodilator use and increased complications was also not observed for most other perinatal parameters that were evaluated. (3) The complications that were more prominent in higher dose users (discussed above) could not be attributed to the inhaled bronchodilators themselves once confounding factors, such as asthma severity and other medication use, were accounted for. (4) The subjects requiring regular inhaled bronchodilators experienced more severe asthma than subjects requiring intermittent inhaled bronchodilators (Table I) and thus would appear to be at greater risk of experiencing gestational complications caused by the asthma itself (as discussed above). We therefore believe that, until further information becomes available, the data from this study plus benefit-risk considerations tend to support the *regular* as well as intermittent use of inhaled bronchodilators, when it is indicated, in the management of asthma during pregnancy.

The present data do not allow the determination of whether the apparent safety of inhaled β-agonist bronchodilators is due to their minimal systemic absorption at the doses used or due to the safety of systemically absorbed medication. An analogous study of perinatal outcomes in women using regular *oral* β-agonist bronchodilators during pregnancy would be necessary to make this differentiation. However, regardless of the mechanism, the current data demonstrate that inhaled β-agonist bronchodilators, as used clinically in the general population of pregnant women with asthma, do not increase the risk of adverse perinatal outcomes.

A final consideration regards the *specific* inhaled bronchodilator to suggest at the current time when inhaled bronchodilators are indicated for the management of asthma during pregnancy. Inhaled bronchodilators were analyzed in this study as a group rather than as individual drugs (1) to achieve the largest possible sample size, (2) since nearly one third of subjects used more than one specific inhaled bronchodilator during pregnancy, and (3) due to the chemical similarities of the drugs.[32] It appears reasonable to choose metaproterenol at the current time for use during pregnancy, since the analysis of data derived from subjects using metaproterenol (constituting 83% of the subjects with asthma using any inhaled bronchodilator) produced similar results to the entire inhaled bronchodilator group in the present series. Subsequent to the onset of this study, several newer inhaled bronchodilators have been introduced that appear to be longer lasting and more β-selective than previously available inhaled bronchodilators.[32] Our data are consistent with the hypothesis that the use of any of the inhaled β-agonist bronchodilators is safe during pregnancy. However, further experience with the newer inhaled bronchodilators during pregnancy will be necessary before this hypothesis can be tested.

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6.34 CONGENITAL MALFORMATIONS

About 2 per cent of newborn infants have a major malformation. The incidence is as high as 5 per cent if one includes malformations detected later in childhood, such as abnormalities of the heart, kidneys, lungs, and spine. Malformations are more common among spontaneous abortuses; many of these are severe and may be the cause of the abortion. About 9 per cent of perinatal deaths are due to malformations. Treatment of malformations is one of the common reasons for the hospitalization of children.

A simple and arbitrary terminology has evolved for describing malformations. A *major malformation* has serious medical, surgical, or cosmetic consequences. A *minor anomaly* and a *normal variation* have no serious consequences and are differentiated on the basis that a minor anomaly occurs in 4 per cent or less of children of the same race, whereas a normal variation is more common. The use of 4 per cent as the point of differentiation is arbitrary. The incidence of features such as simian crease, clinodactyly of the fifth finger, extra nipples, Brushfield spots, and sacral dimple varies in each race (Table 6–16).

A *syndrome* refers to a recognized pattern of malformations considered to have a single and specific cause, such as the Holt-Oram syndrome, an autosomal dominant disorder with malformations of the heart and upper extremities. *Association* is used to indicate a pattern of malformations for which no specific etiology has been identified, such as the VATER association of vertebral, anal, tracheal, esophageal, and renal anomalies. A *morphogenic complex* (which has also been called an anomalad) comprises a primary malformation and its derived structural changes (see Chapter 29). The term does not specify a cause.

Etiology. In a prospective study of 18,155 newborn infants Holmes found 464 major malformations (2.6 per cent), 50 per cent of which were attributed to genetic abnormalities. Of the 18,155 infants, 0.1 per cent had malformations attributed to chromosomal abnormalities 0.1 per cent to single mutant genes, 0.8 per cent to multifactorial inheritance and 0.3 per cent for whom the pattern of inheritance is uncertain. The number of chromosomal abnormalities is less than the 0.6 per cent incidence of all types of chromosomal abnormalities in newborn infants because many of the common disorders, such as 47,XXY, 47,XYY, and 47,XXX, have no detectable physical characteristics in the newborn infant. Teratogens and other environmental factors were identified as a cause of malformations in 0.2 per cent of the infants or 8 per cent of all malformations, an incidence lower than many clinicians expect. Teratogens include drugs, maternal conditions such as diabetes mellitus; other environmental factors include amniotic constrictive bands and oligohydramnios. Twinning is associated with a higher incidence of malformations than that in singletons; the acardiac infant syndrome is an example of a malformation that occurs only in twins, specifically monozygous twins.

The causes of 42 per cent of the 464 major malformations were not detected. Malformations

TABLE 6–16 INCIDENCE OF MINOR ANOMALIES AND NORMAL VARIATIONS IN NEWBORN INFANTS*

PHYSICAL FEATURE	White infants (%) (N = 3989)	Black infants (%) (N = [illegible])
Third sagittal fontanel	3.1	9.8
Epicanthal folds, bilateral	1.4	1.0
Brushfield spots, bilateral	7.2	0.5
Preauricular sinus, left or right	0.8	5.9
Extra nipple, left or right	0.5	4.6
Umbilical hernia	0.7	6.1
Sacral dimple	4.8	0.6
Clinodactyly of both fifth fingers	5.2	4.5
Simian crease, both hands	0.7	0.5
Syndactyly of toes 2 and 3, left or right	1.7	2.3

*From Holmes, L. B.: The Malformed Newborn—Practical Perspectives. Boston, Developmental Disabilities Council, 1976.

of unknown cause include many types of intestinal atresia, imperforate anus, megaloureter, Goldenhar syndrome, absence of the pectoralis major muscle, omphalocele, cloacal exstrophy, and diaphragmatic hernia through the foramen of Bochdalek.

Underlying Mechanisms. The understanding of malformations has been derived principally from the study of animals. Basic abnormalities identified include (1) abnormal cell shape; (2) abnormalities of the collagens or of the proteoglycans, major constituents of the extracellular matrix; (3) errors in circulation during fetal development; and (4) lack of appropriate death of cells during morphogenesis. An example of abnormal cell shape is the defect in the Bergmann glial cells which normally provide the latticework for migration of neuronal cells. When they are defective due to the autosomal recessive gene *weaver* in the mouse, hypoplasia of the cerebellum results. Several types of Ehlers-Danlos syndrome have been identified by clinical and genetic studies in humans; at least 3 have been shown to be due to different defects in collagen metabolism. For example, in type VI the collagen is deficient in hydroxylysine, owing to a deficiency of lysyl hydroxylase; in type VII, there is an inability to convert procollagen to collagen; in type IV there is a lack of type III collagen.

The malformation *hemifacial microsomia* can be caused by a failure of the vascular supply to be transferred from the stapedial artery to the external carotid artery, a switchover that normally occurs during the 6th and 7th weeks of gestation in humans. Lack of appropriate death of cells between the developing long bones in a limb can lead to synostosis of these bones. For the palatal shelves to meet in the midline and fuse, there must be death of cells in the epithelium preceding the fusion of the underlying palatal mesenchyme.

Clinical Evaluation. Each child with a major or minor malformation deserves a thorough diagnostic evaluation. This includes a history of defects in other family members and of any untoward events during the pregnancy, as well as a thorough physical examination. In the examination it is helpful to use objective measurements when a physical feature seems too long, short, narrow, or wide. Many normal standards are included in Smith's *Recognizable Patterns of Human Malformation.* Chromosomal analysis by banding techniques should be obtained when there are multiple malformations, especially if the infant is mentally retarded, is stillborn, or dies soon after birth. Cells obtained from biopsies of skin, gonad, thymus, or spleen grown in tissue culture are preferable for such studies on a deceased infant rather than placing reliance on a blood sample obtained when the infant is moribund. The likelihood of finding a chromosomal abnormality in infants in the above categories is only 10 to 20 per cent, hence the clinician must be prepared to develop a differential diagnosis for other genetic and nongenetic causes of the malformations.

As noted, the same clinical signs or malformations may be caused by a variety of genetic accidents. Split-hand/split-foot syndrome, an unusual malformation in which there is a cleft in the middle of the hand, foot, or both due to lack of development of the middle digits and metatarsals and metacarpals, is such an example. The same deformity occurs in focal dermal hypoplasia, a multiple malformation syndrome, and in the autosomal dominant disorder in which the deformities are limited to the limbs.

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Orkin, R. W., Pratt, R. M., and Martin, G. R.: Undersulfated chondroitin sulfate in the cartilage matrix of brachymorphic mice. Devel. Biol. 50:82, 1976
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Smith, D. W.: Recognizable Patterns of Human Malformation. 2nd Ed. Philadelphia, W. B. Saunders, 1976.
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Tharapel, A. T., and Summitt, R. L.: A cytogenetic survey of 200 unclassifiable mentally retarded children with congenital anomalies and 200 normal controls. Hum. Genetics 37:329, 1977.
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Warkany, J: Congenital Malformations. Chicago, Year Book Medical Publishers, 1971.

6.35 GENETIC COUNSELING

Genetic counseling is a process of communication dealing with the human problems associated with the occurrence or risk of occurrence of a genetic disorder in a family. Those who should receive it can be divided into a majority who are unaware of their risks and a minority who request genetic information and counseling. The latter most commonly are couples whose first child has

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NOV - 2 1988

NDA 18-830

NAME OF DRUG: Tombocor (flecamide acetate) Tablets

SPONSOR: Riker

TYPE OF SUBMISSION: Periodic ADRs (6/11/88-9/10/88)

DATE OF SUBMISSION: 10/12/88

DATE OF REVIEW: 10/24/88

REVIEWER: Sughok K. Chun, M.D., HFD-110

A. Resume:

From spontaneous domestic sources

I. Initial Reports This Period

A. Serious Labeled

Manufacturing Report No.	Reaction Term
1. [redacted]	SYNCOPE ARRHYTHMIA VENTRICULAR

71 y/m;1 mo Rx Tombocor 200 mg for 1 mo & increased to 400 mg. Two days following the dose increase he experienced a syncopal episode with attendant fall and scalp laceration. When presented to the emergency room he had a wide-complex ventricular rhythm and no measureable blood pressure, precordial thump and cardiopulmonary resuscitation suceeded & achieved blood pressure 130/82, pulse 62, temperature 35.9.

Laboratory Data

	Blood glucose	pH	pCO2	pO2	Serum flecainide
On admission:	499 mg/dl	7.3	42	158	1.77 mcg/ml (normal .2-1.0)

2. [redacted] TACHYCARDIA VENTRICULAR
ECG ABNORMAL
HYPOTENSION

58 y/m on Flec for 22 yrs to control PVC's and runs of non-sustained ventricular tachycardia. Never had tachycardia been sustained. High dose propranolol had not given adequate

arrhythmia control and procainamide, while controlling the tachyarrhythmia, had not controlled the PVC's well and had resulted in a lupus-like syndrome. During a routine treadmill exercise test on 18JUN88 he developed evidence of very wide QRR complex tachycardia of non-sustained nature with two runs of 7 and 10 beats. Flec dose was reduced to 200 mg/day. Two days thereafter (19JUL88) the exercise test was repeated. On that occasion again, as before, the QRS widened with stress starting at 0.12 sec and progressing to well over 0.20 sec and a PR interval which reached 0.24 sec by the time stage 3 of stress was reached. At this point the tachycardia was more sustained. Exercise was terminated, the patient was light-headed and blood pressure had dropped to 100/80. As the patient lay down tachycardia was 150 to 160 bpm and the QRS became wider and wider. Gradually the patient lost consciousness, his eyes rolled back and CPR was begun. Within a few seconds consciousness returned. He had now broken from his V-Tach back to sinus rhythm. He was admitted to to hospital where he remained stable. He had experienced no angina either during the few days preceeding the test or during it. Mexilitine replaced flec, acebutolol replaced propranolol and on 22JUL88 he was put through the treadmill test again. This time the QRS widened to about .11 sec, but he reached quite high levels of exertion without difficulty. In questioning the wife, she recalled that several times over the past two years he had experienced syncope while exercising on his bicycle.

3. [redacted] TACHYCARDIA SUPRAVENTRICULAR

65 y/f was hospitalized for initiation of flec 100 mg bid for control of WPW syndrome. On the 3rd day of flec use she experienced recurrence of SVT (120/min.). The flec dose was then increased to 150 mg bid, but the SVT persisted, & proved to refractory to treatment with beta-blocker, verapamil, & finally to ventricular pacing She was transferred to a tertiary care hospital on the 7th day of flec therapy, last dose of flec given that morning. The following day ventricular pacing successfully terminated the tachycardia.

4. [redacted] SYNCOPE, VF

16 y/m was born with D-transposition of the great arteries & balloon atrial septostomy was performed immediately. At 6 wks of age the Mustard operation was carried out, but shortly afterward revision was required to correct baffle obstruction. From infancy he has had a variety of cardiac arrhythmia problems: intermittent compete heart block &

bradycardia for which a demand pacemaker was implanted (& which is functioning much of the time), & frequent, intractable episodes of AFlu with rapid HR, often requiring overdrive pacing or electrical cardioversion, & not controlled by QUN or PA. In June 1987 PA was d/ced, continued digoxin, & starting amiodarone. However the parents were wary of amiodarone, & flecainide 50 mg bid was begun. AFlu was still evident 9/4/87, & flec dose was increased to 100 mg bid 9/7/87. On 9/8/87 he participated in physical education activities in the morning, ran 1 lap around the baseball field & asked to be allowed to rest. His request was denied and required him to perform a dozen push-ups; he was unable to complete that task, & was then instructed to do a dozen sit-ups. He was observed by a companion to be flushed & breathing rapidly. After doing a few sit-ups he suddenly became pale & collapsed. His companion started CPR & paramedical help was called, arriving within 10 minutes. CPR & O2 were administered in transit & on arrival at the emergency room he was found to be in coarse VF. Several attempts to cardiovert following lidocain-epinephrine bolus IV were unavailing, but after bretylium-epinephrine bolus IV, cardioversion produced sinus rhythm, 55 min after admission, approximately 65 min after collapse. Supporting measures included ventilatory assistance with O2, subclavian venous catheter, & dopamine IV. He was transferred by helicopter to a hospital in [redacted] Neurologic sequelae are severe & persisting.

5. [redacted] VT, DEATH

68 y/m with a Hx of COPD and elevated blood sugar. He was hospitalized with an irregular heartbeat. He had runs of self-limited VT & was started on flec 100 mg daily on 723/8. He was doing well, however, prior to discharge on 7/25/88 he experienced another run of VT. He was kept in the hospital; flec was increased to 200 mg daily on the evening of 7/26/88 he went into VT and, despite resuscitation attempts, died. A Holter monitor which was in place at the time did not show torsade de pointes.

6. [redacted] PALPITATION HYPOESTHESIA

51 y/f with a Hx of HTN,idiopathic thrombocytopenic purpura (ITP), asthma, sulfur allergy, and mitral valve prolapse was started on flec 100 mg bid in November 1986. Several months later she was given a sustained release theophylline for bronchitis and developed palpitations that resulted in hospitalization. Cystitis occurred during the following months which was treated with erythromycin, but before the p.m. dose on the 1st day of therapy she had palpitations & was taken to an emergency room. Flec was still ongoing in August 1987 when

enalapril maleate was started. About February 1988 she ws treated for a dry eye with topical prednisolone/sulfacetamide and within several days she began to develop numbness over her entire body. Neurologist found no response to a pin prick. During this time the flec dose was reduced to 50 mg bid. About April 1988 she learned enalapril may cause the numbness she was experiencing and therefore stopped taking it. Four months after enalapril was stopped her body feeling is returning but she still has a numb throat resulting in spasms of throat muscles (breathing apparently not compromised but, she fears not being able to breath). Diazepam Rx was implemented about March 1988. Flec therapy continued throughout all events until 1Aug88. After 4 weeks off flec the pt reported the tongue numbness was gone.

7. [redacted] PALPITATION, NON SUS-VT, HEPATIC FUNCTION ABNORMAL, NAUSEA

55 y/f with Hx of MI 5 yrs ago, was being treated with amiodarone when flec was added. She has a VT that is easy to induce electrically. After 5 doses of flec (100 mg bid) she was admitted to an emergency room with VT (220 b/min) and palpitations. Cardioversion was required and diazepam was started. Elevated SGOT, SGPT, and alkaline phosphatase (levels of ~1000) were found at that time along with nausea but no pain. Amiodarone was continued & flec was stopped. Three days later the liver enzymes were in the 300 range and were still high after 2 wks. She was rechallenged with flec 3 wks after. After 3 doses (100 mg bid) the nonsus-VT developed and the liver enzymes started increasing. Flec was d/ced and she recovered.

8. [redacted] TACHYCARDIA, DEATH

Pt with Hx of COPD was receiving theophylline, flec, and a number of other concomitant medications. His cardiologist decreased the theophylline dose, then his pulmonologist increased the dose. The man developed tachycardia and died.

9. [redacted] SUICIDE ATTEMPT, DEATH

15 y/f consumed 60-70 flec 100 mg tabs this morning (8/23/88), and died. Symptoms and course prior to death are not known by the reporter at first contact, but will be supplied later.

B. Nonserious

Manufacturing Report No.	Reaction Term
1. [redacted]	BREAST PAIN
52 y/f,Flec and Isotretinoin for 2 wks. D/C of Isotretinoin showed improvement.	
2. [redacted]	IMPOTENCE
55 y/m,Flec for several mos.	
3. [redacted]	VISION ABNORMAL
58 y/m,Flec 200 mg/d for 1 wk and increased to 400 mg. Concomitant medication includes digoxin, dipyridamole, diltiazem and aspirin. Shortly after the dose increased he noticed blurred vision that seems to start about 2 hours after the dose and lasts about 2 hours but doesn't happen every day. He seems to be able to focus one eye at a time but not both of them together. After about 5 months of therapy the blurring of vision still occurs. Flecainide therapy continues.	
4. [redacted]	TACHYCARDIA
12 y/m,Flec for 2 yrs noted palpitation when changed Lot #.	
5. [redacted]	IDIOVENTRICULAR RHYTHM
After several weeks of therapy, the patient was undergoing a treadmill test when idioventricular rhythm occurred. Atropine was given which restored sinus rhythm. However, PVC's returned and lidocaine was started. Idioventricular rhythm once again was noted but the patient spontaneously returned to sinus rhythm.	
6. [redacted]	
65 m noticed tremor after 1 wk of Flec.	
7. [redacted]	ARTHRALGIA ANA ELEVATED
30 y/f,7 mos of Rx with fec developed polyarthralgia. Rh factor (-)	
8. [redacted]	HYPOESTHESIA
76 y/m,Flec for 2 wks. dechallenge & rechallenge (+)	
9. [redacted]	HYPERGLYCEMIA
50 y/f obese diabetic	
10. [redacted]	ALOPECIA
52 y/m	
11. [redacted]	URTICARIA
58 y/f developed urticaria after 18 mos Rx with Flec. Dechallenge (-)	
12. [redacted]	ECG ABNORMAL
45 y/m wide QRS	
13. [redacted]	ECG ABNORMAL
wide QRS	
14 [redacted]	NEUROPATHY
75 y/f. After 3 days of Flec rapid worsening of neuropathy was noted.	
15. [redacted]	ALOPECIA
83 y/f	

16. [redacted] ASTHENIA
15 y/f developed weakness in one arm.

17. [redacted] PULMONARY FIBROSIS
76 y/f with COPD and pulm fibrosis noticed acceleration of pulm fibrosis after 2 yrs Rx.

18. [redacted] ECG ABNORMAL
27 y/f, T-wave inversion after 3 wks Rx of Flec 100 bid

19. [redacted] ALOPECIA
37 y/m noted increased hair loss after 5 mos Rx.

20. [redacted] ARTHRALGIA
58 y/m after about 5 mos of therapy, he developed progressive tenderness & pressure-related pain in his feet, ankles & hands. He eventually had difficulty walking. Flec was stopped about 10 days ago and there has been essentially no change in the symptoms. He was taking no concomitant medication.

21. [redacted] TORSADE DE POINTS
58 y/m, recent aortic valve replacement, had episode of Torsade after 4th dose of PA. PA was d/ced and started on Fec 50 mg/bid for 4 days and increased to 100 mg bid. Following the 1st 100 mg dose he went into Torsade, lasting 60 seconds, resulting in syncope and transient apnea. Flec was discontinued. Subsequently, in an electrophysiologic study, Torsade was not inducible.

Comments:

The sponsor's narrative summary and analysis of 15 day reports are acceptable except congenital anomaly. [redacted] reported the case of an infant born with a large intracranial AV fistular, whose mother had taken flec during the first 7 wks of the pregnancy. Patent ductus arteriosus and patent foramen ovale were also present at birth; the infant was delivered prematurely at 31 weeks gestation because of polyhydramios and premature rupture of membranes. The Vein of Galen was successfully partially occluded to ameliorate the cardiovascular burden imposed by the fistula. Developmental definition of the intracranial blood vessels is established at an embryonic state later than the period of intrauterine exposure to flecainide occurring in this case, but a teratongenic effect of flecainide in this instance cannot, of course, be categorically excluded. To date the sponsor have catalogued 24 cases of pregnancy in women using flec during part or all of the gestation; 16 cases produced normal infants; in 9 of these flec was in use by the mother before conception and was continued throughout pregnancy, in 2 others flec was d/ced at 1 or 2 mos gestation, and in the other 5 flec use started in the second trimester or later. Three congenital anomalies have been reported prior to [redacted], an asymptomatic small interventricular septal defect, [redacted] a mild pes varus with metatarsus varus, and [redacted] a case of intracranial calcification with serious neurological deficit. No pattern of congenital defects has appeared. However, the incidence are higer and teratogenicity of flec should be re-evaluated. Two cases ADRs [redacted] raised a possibility of drug interaction with theophylline. There were similar cases in previous reports.

I called the sponsor Jeanne M. Fox, Sr. Regulatory Coordinator on 10/24/88 and asked her to relay my concern of teratogenicity of flec and possible drug interaction with theophylline to the Medical Dept. She will let me know their stand.

S K. Chun 11/2/88

Sughok K. Chun, M.D.

cc:Orig.
HFD-110
HFD-110/CSO
HFD-110/SChun
sh:11/01/88:1062h

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

REPORTS

October 12, 1988

3M

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir/Madam:

Pursuant to 21 CFR 314.80, enclosed is the Periodic ADR Report in duplicate for Tambocor® (flecainide acetate) NDA 18-830. There are 37 FDA-1639 forms in this submission, 30 of which are initial reports and 7 are follow-up reports.

The time period covered by this report is June 11, 1988 through September 10, 1988.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

:an

Dest Copy: Dr. S. Chun (HFN-110)

P011

ORIGINAL

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved. OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO	DA	YR.
[redacted]	68	M	07	26	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***VENTRICULAR TACHYCARDIA* Death**
This 68 y.o. man had a history of chronic obstructive pulmonary disease and elevated blood sugar. He was hospitalized with an irregular heartbeat. He had runs of self-limited ventricular tachycardia & was started on flecainide 100 mg daily on 23JUL88. He was doing well; however, prior to discharge on 25JUL88 he experienced another run of ventricular tachycardia. He was kept in the hospital; flecainide was increased to 200 mg daily. On the evening of 26JUL88 he went into ventricular tachycardia and, despite resuscitation attempts, died. A Holter monitor which was in place at the time did not show torsade de pointes.

13. RELEVANT TESTS LABORATORY DATA
None.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

THERAPY DATES *(From To)*
07/23/88 - 07/26/88

19. THERAPY DURATION
4 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
ASPIRIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See 87 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST. PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
7/28/88

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved. OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)* [redacted]

2. AGE YRS. ---

3. SEX M

4-6. REACTION ONSET: MO. -- DA. -- YR. --

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

TACHYCARDIA Death
This patien* had a history of chronic obstructive pulmonary disease. He was receiving theophylline, flecainide, and a number of other concomitant medications. His cardiologist decreased the theophylline dose, then his pulmonologist increased the dose. The man developed tachycardia and died.

8-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
CARDIAC DYSRHYTHMIA NOS

18. THERAPY DATES *(From To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

THEOPHYLLINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See 87 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG
[redacted]/18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
8/12/88

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [X] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [X] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6 REACTION ONSET MO	DA.	YR.
[redacted]	15	F	08	23	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
Overdose, Death
Mid-teenage girl consumed 60-70 flecainide 100mg tablets this morning (8/23/88), and died. Symptoms and course prior to death are not known by the reporter at first contact, but will be supplied later.

13. RELEVANT TESTS LABORATORY DATA
None known.

8-12 CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X OVERDOSE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 6-7 G

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: SUICIDE-DRUG/MEDICIN NEC

18. THERAPY DATES *(From To)*: 08/23/88 - / /

19. THERAPY DURATION: ONE DOSE

20 DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e g diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG: [redacted] /18-830

24b MFR CONTROL NO.: [redacted]

24c DATE RECEIVED BY MANUFACTURER: 8/23/88

24d REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25 15 DAY REPORT
[ ] YES [X] NO

25a REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314 80

V. INITIAL REPORTER *(In confidence)*

26 -26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b TELEPHONE NO. *(Include area code)*
[redacted]

26c HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

JUL 28 1988

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA # 18,830

DRUG: Tambocor (flecainide acetate) Tablets

SPONSOR: Riker

TYPE OF SUBMISSION: Periodic ADR Report (3/11/99 to 6/10/88

DATE OF SUBMISSION: July 19, 1988

DATE OF REVIEW: July 27, 1988

REVIEWER: Sughok K. Chun, M.D. HFD-110

INDEX OF 15-DAY REPORTS

Manufacturer's Control Number	Date of Submission	Reaction Term
[redacted]	05/10/88	Pancreatitis
[redacted]	06/14/88	Abdominal Pain Nausea/Vomiting
[redacted]	03/31/88	Cardiac Arrest
[redacted]	06/14/88	Hepatitis
[redacted]	05/04/88	Psychosis
[redacted]	04/25/88	Anemia Hemolytic
[redacted]	03/11/88	Upper Respiratory Tract Infection

NON SERIOUS ADR'S

Abnormal liver function 2, Alopecia 2, dematitis/pruritus 2, anemia and thrombocytopenia 1, nervous system, hyperlipemia/hyperglycemia 1, edema 1, pleurisy 1

\+ Literature Report
* Follow-up reports

TABULATION OF ALL FDA-1639's INVOLVING DEATH

15-DAY

1. [redacted]	Cardiac Arrest
2. [redacted]	Heptatitis Abdominal Pain Nausea/Vomiting

NON 15-DAY

1. [redacted]	ECG Abnormal
2. [redacted]	ECG Abnormal Hypotension
3. [redacted]	VT
4. [redacted]	VF
5. [redacted]	VF

NARRATIVE OF ACTION TAKEN

After review of ADRs received this quarter, the sponsor concluded that current U.S. prescribing information for flecainide acetate tablets continues to describe safety information appropriately and, therefore, is not in need of revision at this time.

Comments: No comment.

S. K Chun 7/28/88
Sughok K. Chun, M.D.

cc: Orig./NDA #18,830
HFD-110
HFD-110/CSO
HFD-110/SKC
ayg/07/28/88/0140a

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

REPORTS

July 19, 1988

3M

RECEIVED
CENTER FOR DRUG EVALUATION AND RESEARCH

JUL 25 1988

CENTRAL DOCUMENTS ROOM

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir/Madam:

Pursuant to 21 CFR 314.80, enclosed is the Periodic ADR Report in duplicate for Tambocor® (flecainide acetate) NDA 18-830. There are 32 FDA-1639 forms in this submission, 24 of which are initial reports and 8 are follow-up reports.

The time period covered by this report is March 11, 1988 through June 10, 1988.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

:an

Desk Copy: Dr. S. Chun (HFN-110)

RECEIVED
NATIONAL CENTER FOR DRUGS AND BIOLOGICS
JUL 25 1988
HFN-110

P010
ORIGINAL

110

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	78	M	04	20	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

*QRS WIDENING*Death
This 78 y.o. man had long history or chronic obstructive pulmonary disease and congestive heart failure. He was admitted to hospital for congestive failure and atrial fibrillation and runs of 2 to 4 beats of tachycardia. Various degrees of bundle branch block and ischemia were noted on EKG over the two weeks in hospital before flecainide was begun. He was taking theophylline, lasix, digoxin, potassium, hydralazine. Quinidine and hydralazine were started 4APR88 and mexilitine given between 6-11APR88. Procainamide was begun 11APR88 and continued throughout his course. Flecainide, 100mg bid was begun 15APR88 and increased to 200mg bid on 18APR without blood level determination and despite eject-

13. RELEVANT TESTS LABORATORY DATA

Echocardiogram 31MAR88 (upon admission) showed dilated cardiomyopathy, moderately decreased ejection fraction and mild pericardial effusion.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 400 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: ATRIAL FIBRILLATION, VENTRI PREMATURE BEATS

THERAPY DATES *(From To)*: 04/15/88 - 04/20/88

19. THERAPY DURATION: 5 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

QUINIDINE GLUCONATE	16 DAYS	HYDRALAZINE HCL	16 DAYS
FUROSEMIDE	16 DAYS	POTASSIUM CHLORIDE	
SODIUM CHLORIDE		PROCAINAMIDE HCL	16 DAYS
PHENERGAN W/CODEINE PHOSPHATE	6 DAYS	THEOPHYLLINE	>21 DAYS

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Please see above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/26/88

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

tion fraction of ~25%. On 20APR wide QRS complexes developed and he was transfered to the critical care unit where he died later that day. Needle biopsy of prostate had been performed on 18APR with addition of phenergan and codeine to his drug regimen.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTUREH

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	45	M	CH	NG	

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

*QRS WIDENING, HYPOTENSION*Death
A hospitalized male patient with 2-week history of cardiac arrest had been put on flecainide at that time (100mg bid). During the hospital course he developed wide QRS tachycardia and died within 24 hours of its onset. He was in hospital for electrophysiologic studies, but died before they were undertaken.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

THERAPY DATES *(From To)*: 03/07/88 - 03/21/88

19. THERAPY DURATION: 2 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Please see above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted]/18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/26/88

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE. Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)* [redacted]

2. AGE YRS. 68

3. SEX M

4.-6. REACTION ONSET: MO. [illegible] DA. 09 YR. 88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

VENTRICULAR TACHYCARDIA Death
On 1/29/88 this 68 year old man experienced an episode of ventricular fibrillation followed by cardiac arrest in his physician's office, was resuscitated & hospitalized. He was found to have suffered a myocardial infarction, developed congestive heart failure & pulmonary edema & ileus High frequency premature ventricular contractions appeared on 2/1/88, for which IV lidocaine was started. By 2/2/88 the arrhythmia had progressed to frequent bigeminy & couplets, & quinidine 200mg IM q6h was started + metaproterenol. Nasogastric tube was in use for suction due to ileus & not available for drug. Therefore, when the decision was made to initiate flecainide therapy, the rectal route was elected.

13. RELEVANT TESTS LABORATORY DATA

DATE	ROUTE ADMIN.	TIME POST-DOSE	FLECAINIDE PLASMA LEVEL (mcg/ml)
2/2	RECTAL #1	1/2 HOUR	0.14
2/2	RECTAL #1	1 HOUR	0.18
2/2	RECTAL #1	3.3 HOURS	0.11
2/2	RECTAL #1	12 HOURS	0.12

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From To)*: 02/02/88 - 02/09/88

19. THERAPY DURATION: 7 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG? [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

QUINIDINE SULFATE
PROCAINAMIDE HCL
PHENYTOIN SODIUM
METAPROTERENOL SULFATE
MEXILETINE HCL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

see #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTUPER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFAGTURER: 4/29/88

24d. REPORT SOURCE *(Check one)*: [ ] FOREIGN [ ] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT: [ ] YES [X] NO

25a. REPORT TYPE: [X] INITIAL [ ] FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL? [ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Flecainide 100mg dissolved in 15ml water was administered by retention enema q12h, & PVCs ceased to appear promptly after the first dose. On 2/3/88 quinidine was discontinued & procainamide (started 2/1/88) was decreased. Clonic & tonic seizures of the facial muscles & arms began 2/4/88, & by evening PVCs had reappeared at high frequency. Flecainide was increased to 100mg q8h rectally. On 2/5/88 flecainide administration was switched to nasogastric tube, 100mg q12h, & mexiletine was added. PVCs continued to be troublesome on 2/6/88, seizures persisted, & phenytoin was added to the regimen. The patient had remained comatose from the time of admission, & a "no code" order was issued on 2/7/88. Occasional PVCs were noted on 2/8/88. On 2/9/88 ventricular tachycardia

13. RELEVANT TESTS LABORATORY DATA

2/2	RECTAL #2	12 HOURS	0.20
2/3	RECTAL #4	8.5 HOURS	0.42
2/5	GASTRIC #1	12 HOURS	0.43
2/5	GASTRIC #2	12 HOURS	0.46
2/6	GASTRIC #3	12 HOURS	0.37

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 3)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
supervened, conversion was not attempted, and cardiac arrest & death ensued.

13. RELEVANT TESTS LABORATORY DATA
2/6 GASTRIC 84 12 HOURS 0.47

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c DATE RECEIVED BY MANUFACTURER

24d REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include [illegible] code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	30	F	02	??	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#UNRESUSCITATABLE VENTRICULAR FIBRILLATION*Death
The reporting physician happened to be in the hospital when he was called to the ER to see this 30 y.o. woman in ventricular fibrillation. No history was available except that she had reportably been taking 100mg flecainide bid for control of premature ventricular complexes. She could not be resuscitated and died. No flecainide plasma concentration was determined.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
None obtained.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

THERAPY DATES *(From/To)*
UNKNOWN - 02/??/88

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
None obtained

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/19/88

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	60	F	03	??	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

*UNRESUSCITATABLE VENTRICULAR FIBRILLATION*Death
The reporting physician was in the hospital when he was called to the ER to attend this 60 y.o. woman said to have been taking flecainide 100mg bid for about 3 months for control of premature ventricular complexes. She was also taking diuretic. For several days before being admitted in vent. fibrillation she was said to have experienced dizzy spells. Her plasma flecainide conc was 1.5 microgm/ml (N=0.2-1.0microgm /ml). She converted with lidocaine but after 24 hours off flecainide she developed VPC's which in only 4 minuted changed to V-Tach and Vent Fibrillation. She could not be resuscitated and died. Enzyme work in hospital seemed to rule out infarct as the initial event. K+=normal.

13. RELEVANT TESTS LABORATORY DATA
Plasma flecainide concentration elevated (see above).

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

THERAPY DATES *(From To)*
12/??/87 - 03/??/88

19. THERAPY DURATION
~ 3 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
FUROSEMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Patient was not considered to be suicidal.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/19/88

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

151

REPORTS

Riker Laboratories, Inc.

270-3A-01 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

3M

July 6, 1988

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experience which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/an

Enclosure: 15 Day Report
[redacted]

Certified Mail P 504 523 968

RECEIVED
JUL 18 1988
NATIONAL CENTER FOR BIOLOGICS

1988 JUL 14 AM 7:23
FOR DRUGS & BIOLOGICS

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910 0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	34	F	07	22	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

CARDIAC ARREST Death
This 34 y.o. woman had a complicated history of right lung aplasia, dextrocardia, left ventricular hypertrophy, and malignant arrhythmias for several years. She had undergone surgical correction of a patent ductus arteriosus. Previous anti-arrhythmic agents included mexiletine and prajmalium. On 7/15/86 flecainide was started at 100 mg daily with an increase to 200 mg daily after one week. On 7/22/86 the woman was admitted to the intensive care unit where several resuscitations were performed. The woman died on 7/22/86. Autopsy showed right lung aplasia, dextrocardia, surgical correction of patent ductus arterious, left dilatation with a heart weight of 530 gm and severe fibrosis in the

13. RELEVANT TESTS LABORATORY DATA

Results of autopsy are given in #7 above.
On admission (22JUL86) Quick value=18%, Hemoglobin=14.8g/dl.
On 27JUL86 hemoglobin was 6.4g/dl.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

INDICATION(S) FOR USE: ATRIAL FIBRILLATION, ATRIAL TACHYCARDIA, VENTRICULAR TACHYCARDIA

17. THERAPY DATES *(From To)*: 07/15/86 - 07/22/86

19. THERAPY DURATION: 7 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: [redacted] /18-83(

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/14/88

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

conducting system, especially in the sinus and AV-node. Moderate to severe pancreatic fibrosis was also seen. Death is believed due to the severe cardiomyopathy.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

'DICATION(S) FOR USE

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

.HERAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

25.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

25b. TELEPHONE NO. *(Include area code)*

25c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

25d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

REPORTS

Riker Laboratories, Inc.

270-3A-01 3M Center
St. Paul, Minnesota 55144
(612)736-5016

3M

July 6, 1988

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is a Follow-up Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experience which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/an

Attachments: Follow-up Report
-[redacted] (Initial sent 10/27/87)

Certified Mail P 504 523 967

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6 REACTION ONSET MO.	DA.	YR.
[redacted]	65	M	09	29	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

QRS-WIDENING, CARDIAC INSUFFICIENCY, ELEVATED SERUM CREATININE, POSSIBLE DRUG INTERACTION (AMIODARONE) Death
This 65 y.o. man has a history of ventricular tachycardia and ischemic cardiomyiopathy. He experienced several episodes of ventricular arrhythmia which required resuscitatic~ A pacemaker was implanted in 1986. The man was started on amiodarone bu did not respond to this therapy. Flecainide 200 mg daily was added to amiodarone 200 mg daily in early 1987. (Ejection fraction 35%) On 29SEP87 the man was hospitalized with cardiac insufficiency, compensated renal insufficiency, and QRS prolongation. Flecainide was discontinued, & the patient recovered following treatment in the intensive care unit.

13. RELEVANT TESTS LABORATORY DATA

Ejection fraction (prior to flecainide): 35%
29SEP87 Serum creatinine: 2 mg% (normal: 0.6-1.5 mg/100ml)
Plasma flecainide level: 1.43 mcg/ml
Amiodarone level: 0.48 mcg/ml
Digoxin level: 2.07 ng/ml

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

DICATION(S) FOR USE: VENTRICULAR TACH[illegible]RDIA

17. THERAPY DATES *(From To)*: 01/??/87 - 09/29/87

19. THERAPY DURATION: 9 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[X] YES [ ] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

AMIODARONE HCL
CAPTOPRIL
XIPAMIDE
ACETYLDIGOXIN
ISOSORBIDE DINITRATE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: [redacted]/18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/14/88

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

JUL 19 1988

NDA #18-8[illegible]

Name of Drug: Tambocor (flecainide acetate) Tablets

Sponsor: Riker

Type of Submission: ADR

Date of Submission: 07/01/88

Date of Review: 07/14/88

Reviewer: Sughok K. Chun, M.D. HFD-110

A. Resume:

*[redacted] DEPRESSIVE-PARANOID PSYCHOSIS
77 y/m developed depression, apathy, delusions of guilt, and lack of concentration after 2 wks Rx with Tambocor. He had no previous Hx of such symptoms. The man was referred to a psychiatric hospital. Clinical-neurological examinations and CAT scan could not reveal any explanation for the symptoms. EEG tracings, however, confirmed the psychosis by showing alpha rhythm and occasionally theta and beta rhythm and variations of wakefulness. Haloperidol was prescribed for 2 wks without satisfactory results. Flecainide was discontinued with abrupt improvement. EEG tracings 2 wks later showed normal signs of slow alpha rhythm, occasional theta rhythm, and little paroxysmal dysrhythmia.

[redacted]: CEREBRAL HEMORRHAGE, COLLAPSE, CONVULSION
This 49 y/m had a hx of mitral value replacement (1979) and atrial and ventricular dysrhythmias. He received disopyramide without success. Flec 150 mg daily was started with success in control of PVC's. About 3 wks after initiation of flec, the man suddenly collapsed. He was taken to the hospital and resuscitated. Two hrs after admission he suffered convulsions treated with clonazepam. Brainstem syndrome with status epilepticus was diagnosed. He was transferred to another hospital and was in coma (with cerebral edema verified by CAT scan and probably due to hypoxemia). He died on 08/18/85.

[redacted] CARDIAC ARREST (ASYSTOLE), RENAL FAILURE
This 79 y/m had a hx of two MIS requiring a pacemaker. He was experiencing PVCS (Lown IVb). He was admitted to the hospital where flec 200 mg daily was started. Renal function tests were within normal range. After 10 days he experienced a temporary electromechanical decoupling of the pacemaker with reversible asystole (cardiac arrest) and progressive

kidney failure. Flec level was 1.46 mcg/ml. Hemoperfusion with activated charcoal for 3 hrs removed only 35 mg flec despite clearance of 164-180 ml/min. (Literature report: ("Hamoperfusion bei Flecainidintoxikation"; Klin Wochenschr (1986) 64: 442-444.) Follow-up information shows that this man died on the day following the adverse experience and the hemoperfusion. Medical Hx: diabetes mellitus and renal impairment.

* [redacted] ERYTHEMA NODOSUM, FEVER
This 61 y/f had a Hx of CAD, diabetes mellitus, and myocardial insufficiency. She was treated with flec 100 mg/day because of malignant dysrhythmias, which couldn't be controlled by other antiarrhythmic drugs. After several mos of flec use she developed erythema nodosum with fever, and was hospitalized. Other causes of erythema nodosum could be excluded, and the disease remitted after flec was discontinued and cortisone was given. When flec was given again erythema nodosum reappeared, in spite of continuation of cortisone therapy.

* [redacted] CARDIAC ARREST
This 50 y/f had a Hx of CAD, anterior MI with pneumonia. She was started on flec 200 mg daily. After 11 mos of Rx, she suffered a cardiac arrest which required resuscitation. After hospitalization the woman experienced a generalized convulsion, probably due to hypoxemia. Oxygen, dopamine, and dobutamine were given and the woman recovered. She was discharged after 1 mo without any antiarrhythmic agent.

* [redacted] ECZEMA
This 72 y/m had a Hx of psoriasis. He was started on flec 200 mg daily. After 1 to 2 days, he developed eczema with pustules on his legs. He was hospitalized where flec was discontinued and cortisone administered. The eczema disappeared. No more information is available.

SK. Chun 7/19/88
Sughok K. Chun, M.D., 07/19/88

cc:
Orig. NDA #18-830
HFD-110
HFD-110/CSO
HFD-110/SKChun/19jul88

#0085R/mn

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

REPORTS

3M

July 1, 1988

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are two Follow-up Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox /cLH

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/an

Attachments: Follow-up Report
- [redacted] (Initial sent 5/22/87)
- [redacted] (Initial sent 10/27/87)

Certified Mail P 504 523 961

cc 7/14

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	79	M	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

CARDIAC ARREST (ASYSTOLE), RENAL FAILURE Death
This 79 y.o. man has a history of two posterior myocardial infarctions requiring a pacemaker. He was experiencing ventricular extrasystoles (Lown IVb). He was admitted to the hospital where flecainide 200mg daily was started. Renal function tests were within normal range. After ten days he experienced a temporary electromechanical decoupling of the pace maker with reversible asystole (cardiac arrest) and progressive kidney failure. Flecainide level was 1.46 mcg/ml. Hemoperfusion with activated charcoal for 3 hours removed only 35 mg flecainide despite clearance of 164-180 ml/min. [Literature report: "Hamoperfusion bei Flecainidintoxikation"; Klin Wochenschr (1986) 64: 442-444.]

13. RELEVANT TESTS LABORATORY DATA

Plasma flecainide level (after ten days of 200 mg daily): 1.46 mcg/ml
Flecainide clearance (after ten days of 200 mg daily): 164-180 ml/min.
On admission:
Hemoglobin 15.2 g% (normal 13-18)
Leucocyte count 8600/mcl (normal 4300-10,800)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

AILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

DICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: 10 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [x] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

MEDIGOXIN
SPIRONOLACTONE
THEOPHYLLINE
GLIBENCLAMIDE
ISOSORBIDE DINITRATE
FUROSEMIDE
ALLOPURINOL
ACETYLCYSTEINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24 NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted]/18,830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/14/88

24d REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [x] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25 15 DAY REPORT
[x] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [x] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80

REPORTS

Riker Laboratories, Inc.

270-3A-01 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

3M

July 1, 1988

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are five (5) Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox/GLF

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/an

Enclosure: 15 Day Reports

[redacted]

Certified Mail P 504 523 960

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	49	M	08	13	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

CEREBRAL HEMORRHAGE, COLLAPSE, CONVULSION Death
This 49 y.o. man had a history of mitral valve replacement (1979) and atrial and ventricular dysrhythmias. He received disopyramide without success. Flecainide 150 mg daily was started with success in control of PVC's. About 3 weeks after initiation of flecainide, the man suddenly collapsed. He was taken to the hospital and resuscitated (artificial respiration, external heart massage, heparin, verapamil, dobutamine, dopamine).Two hours after admission he suffered convulsions treated with clonazepam. Brainstem syndrome with status epilepticus was diagnosed. He was transferred to another hospital & was in coma (with cerebral edema verified by CAT scan & probably due to hypoxemia). He died on 19AUG85.

13. RELEVANT TESTS LABORATORY DATA

General hemorrhagic tendency (Quick's value below normal range).
Autopsy report showed encephalomalacia (softening of the brain).

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 150 MG

16. ROUTE OF ADMINISTRATION: ORAL

INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From To)*: 07/27/85 - 08/13/85

19. THERAPY DURATION: 18 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ACETYLDIGOXIN
HEPARIN SODIUM
DOBUTAMINE HYDROCHLORIDE
CLONAZEPAM
HYDROCHLOROTHIAZIDE/AMILORIDE HCL
PHENPROCOUMON
VERAPAMIL HCL
DOPAMINE
POTASSIUM CHLORIDE

23. OTHER RELEVANT HISTORY *(e.g diagnoses, allergies, pregnancy with LMP etc.)*

See 87 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 5514[illegible]-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/14/88

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80

15.1

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

JUN 27 1988

NDA 18-830

Name of Drug: TAMBOCOR (Flecainide Acetate) Tab

Sponsor: Riker

Type of Submission: ADR

Date of Submission: 6/14/88

Date of Review: 6/27/88

Reviewer: Sughok K. Chun, M.D. HFD-110

A. Resume:

[redacted] HEPATITIS, FULMINANT*

This 64 Y/M with CAD, CHF, COPD and previous MIs (2) was admitted to the hospital with severe nausea and abdominal discomfort. Flec 200 mg/day had been ongoing for about 19 mo; concomitant medications included furosemide, digoxin, theophylline, disopyramide & prednisone. On admission he had total bilirubin of 1.7, SGOT of 463, LDH of 1050, BUN of 36 and WBC of 13600. Two days later he had total bilirubin 4.6, SGPT of 6825, LDH of 3525, SGOT of 6105 and SGGT of 191. A hepatitis profile revealed positive reaction for anti-HAV, positive anti-HBS, and positive anti-HBC. On 4/21/88 (admitted on 4/19/88) he appeared much weaker, BP was 90/60 and by 12:17 p.m., he was without vital signs. The physician felt the hepatitis was probably secondary to flec even though the preliminary viral hepatits studies appeared positive.

S.K. Chun 6/27/88
Sughok K. Chun, M.D.

cc: Orig
HFD-110
HFD-110/CSO
HFD-110/SChun
c1b/6/27/88/0795C

REPORTS

Riker Laboratories, Inc.

270-3A-01 3M Center
St. Paul, Minnesota 55144

(612) 736-5016

3M

June 14, 1988

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experience which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/an

Enclosure: 15 Day Report
- [redacted]

Certified Mail P 504 523 949

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA	YR.
[redacted]	64	M	04	19	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

HEPATITIS, FULMINANT
This 64 y/o man with a history of coronary artery disease, left ventricular congestive failure, chronic obstructive lung disease and previous myocardial infarctions (2) was admitted to the hospital with severe nausea and abdominal discomfort. Flecainide therapy at 200 mg/day had been ongoing for about 19 months; concomitant medications included furosemide, digoxin, theophylline, disopyramide & prednisone. On admission he had total bilirubin of 1.7, SGOT of 463, LDH of 1050, BUN of 36 and white count of 13600. Two days later he had total bilirubin 4.6, SGPT of 6825, LDH of 3525, SGOT of 6105 and SGGT of 191. A hepatitis profile revealed positive reaction for anti-HAV, positive anti-HBS, and positive

13. RELEVANT TESTS LABORATORY DATA

See #7, above.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA, ATRIAL TACHYCARDIA

18. THERAPY DATES *(From To)*
09/ /86 - 04/20/88

19. THERAPY DURATION
19 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

PREDNISONE
DIPYRIDAMOLE
DISOPYRAMIDE
THEOPHYLLINE
IPRATROPIUM BROMIDE
DIGOXIN(LANOXIN)
ALBUTEROL
FUROSEMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
5/17/88

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*

[redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

anti-HBC. On 21Apr88 (admitted on 19Apr88) he appeared much weaker, his blood pressure was 90/60 and by 12:17 p.m. he was without vital signs. The physician felt the hepatitis was probably induced secondary to flecainide even though the preliminary viral hepatitis studies appeared positive.

The reporter also sent all his information to the FDA in the form of a letter and the death and discharge summaries.

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED MANUFACTURER

24d. REPORT SOURCE *(Check one)*

☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. IS DAY REPORT

☐ YES ☐ NO

25a. REPORT TYPE

☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

25.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?

☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

MAY 12 1988

MEDICAL OFFICER'S SHORT FORM REVIEW

NDA # 18,830

DRUG: Tambocor (flecainide Acetate)

SPONSOR: RIKER

TYPE OF SUBMISSION: Periodic ADR Report (12/11/87 - 3/10/88)

DATE OF SUBMISSION: April 12, 1988 DATE OF ASSIGNMENT: May 5, 1988

DATE OF REVIEW: May 9, 1988

REVIEWER: Sughok K. Chun, M.D. HFD-110

A. Resume: FDA 1639's

	U.S. Spontaneous	Clinical	Foreign Spontaneous	Total
Serious -				
Unlabeled (15-day)	11	3	8	22
Labeled	11	NA	NA	11
Nonserious	27	NA	NA	27
Total	49	3	8	60

ANALYSES OF DEATH

FDA 1639 Reports Submitted Containing Death as an Outcome

	U.S. Spontaneous	Clinical	Foreign Spontaneous	Total
Unlabeled (15-day)	1	0	3	4
Labeled	3*	NA	NA	3
Total	4	0	3	7

* Includes 1 "Death, Cause Unknown", which is arbitrarily included among "labeled" events.

2 deaths due to AMI, 1 death cardiomyopathy - sudden death. Three deatns were of a proarrhytemic nature.

Unlabled Events

[redacted]: Breast pain (left) 1 wk RX. D/C of RX pain disappeared.

[redacted]: Hypoglycemia within 7 - 10 days RX. liver function normal.

[redacted]: Hyperlipemia; cholestenol baseline 157-180, RX 1 yr 325 with triglyceride 585.

[redacted]: Muscle Atrophy.

S.K. Chun 5/12/88

Sughok K. Chun, M.D.

cc: Orig./NDA # 18,830
HFD-110
HFD-110/CSO
HFD-110/SKC
ayg/05/12/88/0111a

15.1

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

REPORTS

Pad

April 12, 1988

3M

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir/Madam:

Pursuant to 21 CFR 314.80, enclosed is the Periodic ADR Report in duplicate for Tambocor® (flecainide acetate) NDA 18-830. There are 38 FDA-1639 forms in this submission, 27 of which are initial reports and 11 are follow-up reports.

The time period covered by this report is December 11, 1987 to March 10, 1988.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

:an

Desk copy: Dr. S.K. Chun
HFN-110

C AL

110

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	61	F	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

BRADYCARDIA, VENTRICULAR TACHYCARDIA Death
Thir 61 y.o. woman was being treated with flecainide 300 mg daily for control of atrial fibrillation. After five days of therapy she developed spontaneous polymorphic ventricular tachycardia which was difficult to cardiovert. After 30 minutes, the woman recovered to an awakened st[illegible]. Flecainide level at this time was 0.9 mcg/ml. Fourteen hours later [illegible] woman developed bradycardia, polymorphic ventricular tachycardia died. The physician noted that the woman had underlying hypertro cardiomyopathy with normal systolic function.

13. RELEVANT TESTS LABORATORY DATA

Plasma flecainide level (following first episode of ventricular tachycardia) 0.9 mcg/ml [normal 0.2-1 mcg/ml]

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: ATRIAL FIBRILLATION

THERAPY DATES *(From/To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: 5 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST. PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 1/15/88

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO	DA.	YR.
[redacted]	23	F	01	12	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cause unknown
This 23 year old woman had been given prescription for flecainide sometime prior to 12/9/87 (date last filled) for a presumed cardiac arrhythmia not apparent on Holter monitoring. She had the empty flecainide container (originally 60 tablets) when she collapsed 1/12/88, immediately after swallowing 2 tablets. Paramedical team was called & she was taken promptly to hospital emergency room. On arrival she was still warm but apneic & pulseless. Blood sample drawn at once: plasma flecainide level was 5.2mcg/ml, ethanol .07mg/dl. Autopsy specimens 12 hours post mortem revealed whole blood flecainide level of 12.0mcg/ml and total gastric content of 160mg flecainide. Five drugs were being used concomitantly.

13. RELEVANT TESTS LABORATORY DATA

Post-mortem (< 1 hour?) Plasma Flecainide Level= 5.2mcg/ml (N = .2-1.0)
" " 12 hours Whole Blood " " = 12.0mcg/ml
" " " " Gastric Flecainide Content= 160mg
" " (< 1 hour?) Urine Flecainide Level= 30mcg/ml
Assays for other drugs were not performed.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- [X] OVERDOSE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: CARDIAC DYSRHYTHMIA NOS

THERAPY DATES *(From To)*: <12/9/87 - 01/12/88

19. THERAPY DURATION: 5+ WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

VERAPAMIL HCL
HYDROCHLOROTHIAZIDE
DOXYCYCLINE HCL
ATENOLOL
METRONIDAZOLE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 2/ 9/88

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID-INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	69	M	01	16	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#VENTRICULAR FIBRILLATION* Death
This very active 69 y/o man with a history of myocardial infarct (1976), atherosclerotic heart disease (5 years), & elevated serum cholesterol was started on flecainide acetate on 8JAN88 after having increasingly worsened exercise related arrhythmias starting in JUNE 87. On 8JAN88 he had mulitfocal PVCs, pairs and short runs of ventricular tachycardia during a treadmill test. Concomitant medication was cholestyramine. He was admonished NOT to exercise and return in one week. On 16JAN88 he apparently used his jacuzzi to relax after his exercises and was found dead in the jacuzzi. An autopsy was not allowed. The death certificate lists ventricular fibrillation with underlying ASHD as cause of death.

13. RELEVANT TESTS LABORATORY DATA

See #7, above.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

THERAPY DATES *(From To)*: 01/08/88 - 01/16/88

19. THERAPY DURATION: 9 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

CHOLESTYRAMINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 2/15/88

24d. REPORT SOURCE *(Check one)*

[ ] FOREIGN [ ] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT

[ ] YES [X] NO

25a. REPORT TYPE

[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

[ ] YES [ ] NO

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

ORIGINAL D

REPORTS

3M

March 31, 1988

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are two Follow-up Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/an

Attachments: Follow-up Report
- [redacted] (Initial sent 5/7/86)
- [redacted] (Initial sent 6/1/87)

Certified Mail P 504 523 883

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	80	M	03	21	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

CARDIAC ARREST, OCCURRED AT HOME 3/21/86 AT 6:55P WHILE EATING DINNER. PARAMEDICS ARRIVED WITHIN 15 MINUTES, FOUND HIM UNRESPONSIVE, CYANOTIC, WITH MILDLY DILATED PUPILS, AND IN VENTRICULAR FIBRILLATION. PATIENT WAS RESUSCITATED TO SUPRAVENTRICULAR TACHYCARDIA AT RATE OF 160/MINUTE, SYSTOLIC PRESSURE OF 90MM, BUT NO SPONTANEOUS RESPIRATION. HOSPITALIZED WITH DIAGNOSIS OF ISCHEMIC HYPOXIC ENCEPHALOPATHY DUE TO CARDIAC ARREST. CARDIAC RHYTHM REVERTED TO NORMAL SINUS RHYTHM. REMAINED UNRESPONSIVE, DECEREBRATE & FLACCID, ON RESPIRATOR. LIFE SUPPORT SYSTEMS WERE DISCONTINUED 4/3/86, AND THE PATIENT DIED AT 5:35P.
TAMBOCOR 100MG Q12H, STARTED 12/5/85, WAS CONTINUED UNTIL 4/1/86.
3/21/88: Treatment Indication changed.

13. RELEVANT TESTS LABORATORY DATA

12/9/86: PLASMA FLECAINIDE LEVEL 0.71 MCG/ML
1/13/86: PLASMA FLECAINIDE LEVEL 0.45 MCG/ML
1/13/86: HOLTER ECG REVEALED 91% SUPPRESSION OF VENTRICULAR ECTOPY.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: PAROX VENTRIC TACHYCARD

THERAPY DATES *(From/To)*: 12/05/86 - 04/01/86

19. THERAPY DURATION: 80 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ESTROGEN	3 MONTHS	POTASSIUM	3 MONTHS
FUROSEMIDE	3 MONTHS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

MYOCARDIAL INFARCT, 1975. NONSUSTAINED EPISODIC VENTRICULAR TACHYCARDIA SINCE 1983. EXPERIENCED SYNCOPAL EPISODE 11/29/85 WITH VENTRICULAR FIBRILLATION. ELECTROPHYSIOLOGIC TESTING 12/5/85 REVEALED INDUCED VENTRICULAR TACHYCARDIA, CYCLE LENGTH 230 MSEC, RESULTING IN SYNCOPE. TAMBOCOR 100MG Q12H STARTED 12/5/85; REPEAT EPS 12/9/85 SHOWED INDUCED V-TACH WITHOUT SYNCOPE, CYCLE LENGTH PROLONGED TO 340 MSEC.
PROSTATIC CARCINOMA WITH METASTASES, DATE OF DIAGNOSIS UNKNOWN.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG: [redacted]/18-830

24b. MFR CONTROL NO: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 3/21/88

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	80	M	03		21

8.-12. CHECK ALL APPROPRIATE TO REACTION 86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
#CARDIAC ARREST#, OCCURRED AT HOME 3/21/86 AT 6:55P WHILE EATING DINNER. PARAMEDICS ARRIVED WITHIN 15 MINUTES, FOUND HIM UNRESPONSIVE, CYANOTIC, WITH MILDLY DILATED PUPILS, AND IN VENTRICULAR FIBRILLATION. PATIENT WAS RESUSCITATED TO SUPRAVENTRICULAR TACHYCARDIA AT RATE OF 160/MINUTE, SYSTOLIC PRESSURE OF 90MM, BUT NO SPONTANEOUS RESPIRATION. HOSPITALIZED WITH DIAGNOSIS OF ISCHEMIC HYPOXIC ENCEPHALOPATHY DUE TO CARDIAC ARREST. CARDIAC RHYTHM REVERTED TO NORMAL SINUS RHYTHM. REMAINED UNRESPONSIVE, DECEREBRATE & FLACCID, ON RESPIRATOR. LIFE SUPPORT SYSTEMS WERE DISCONTINUED 4/3/86, AND THE PATIENT DIED AT 5:35P.
TAMBOCOR 100MG Q12H, STARTED 12/5/85, WAS CONTINUED UNTIL 4/1/86.

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
12/9/86: PLASMA FLECAINIDE LEVEL 0.71 MCG/ML
1/13/86: PLASMA FLECAINIDE LEVEL 0.45 MCG/ML
1/13/86: HOLTER ECG REVEALED 91% SUPPRESSION OF VENTRICULAR ECTOPY.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [ ] NA

15. DAILY DOSE
200MG

16. ROUTE OF ADMINISTRATION
ORAL

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [X] NO [ ] NA

17. INDICATION(S) FOR USE
CARDIAC DYSRHYTHMIA NOS

THERAPY DATES *(From/To)*
12/05/86 - 04/01/86

19. THERAPY DURATION
80 DAYS

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
ESTROGEN
FUROSEMIDE
POTASSIUM

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
MYOCARDIAL INFARCT, 1975. NONSUSTAINED EPISODIC VENTRICULAR TACHYCARDIA SINCE 1983. EXPERIENCED SYNCOPAL EPISODE 11/29/85 WITH VENTRICULAR FIBRILLATION. ELECTROPHYSIOLOGIC TESTING 12/5/85 REVEALED INDUCED VENTRICULAR TACHYCARDIA, CYCLE LENGTH 230 MSEC, RESULTING IN SYNCOPE. TAMBOCOR 100MG Q12H STARTED 12/5/85; REPEAT EPS 12/9/85 SHOWED INDUCED V-TACH WITHOUT SYNCOPE, CYCLE LENGTH PROLONGED TO 340 MSEC.
PROSTATIC CARCINOMA WITH METASTASES, DATE OF DIAGNOSIS UNKNOWN.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-13-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/ 2/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [X] STUDY
- [ ] LITERATURE
- [X] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

NOTE. Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

ORIGINAL

REPORTS

3M

March 16, 1988

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are two (2) Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/an

Enclosure: 15 Day Reports
- [redacted]
- [redacted]

Certified Mail P 504 523 868

RECEIVED
MAR 25 1988
HFN-110
NATIONAL CENTER FOR DRUGS AND BIOLOGICS

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: ... 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS (In Confidence)	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	79	F	03		87

7. DESCRIBE REACTION(S) (Underline single most important clinical event or reaction term)

COMPLETE HEART BLOCK, SEPTICEMIA Death

This 79 y/o woman with trifasicular heart block and ventricular tachycardia was placed on flecainide acetate therapy at 400 mg/day. Within 48 hours of starting flecainide she developed complete heart block with a ventricular rate of 40 bpm. A temporary pacing wire was inserted prior to permanent pacing but 7 days after insertion she died from staphylococcal septicemia. Flecainide continued until death.

8-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (Give manufacturer and lot no. for vaccines biologics)

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 400 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES (From To): / / - / /

19. THERAPY DURATION: UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat reaction)
NONE KNOWN

23. OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with LMP etc.)

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER (Include Zip Code)
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 2/26/88

24d. REPORT SOURCE (Check one)
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

5 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER (In confidence)

26-26a. NAME AND ADDRESS OF REPORTER (Include Zip Code)
[redacted]

26b. TELEPHONE NO (Include area code)

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

3M

March 4, 1988

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experience which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Enclosure: 15 Day Report
- [redacted]

Certified Mail P 504 523 863

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2 AGE YRS.	3 SEX	4-6 REACTION ONSET MO	DA	YR
[redacted]	43	M	10	25	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

CARDIAC ARREST, MYOCARDIAL INFARCTION
Patient was a 43 year old man with history of congestive heart failure & cardiomyopathy since 1985, & alcoholism. On 10/13/87 he was admitted to hospital for acute cardiac decompensation. Flecainide 200mg bid was started as treatment for Lown IVb cardiac dysrhythmia; dose was reduced to 100mg bid after 2 days. On 10/16/87 cardiac arrest occurred, & resuscitation measures were unsuccessful. The physician interpreted the terminal ECG as showing evidence of an acute anterior wall myocardial infarction, which in his opinion was the cause of death.

13. RELEVANT TESTS LABORATORY DATA

8-12 CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From To)*: 10/22/86 - 10/25/86

19. THERAPY DURATION: 4 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGITOXIN
CAPTOPRIL
FUROSEMIDE
ISOSORBIDE DINITRATE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a IND NDA NO. FOR SUSPECT DRUG: [redacted] /18-830

24b MFR CONTROL NO: [redacted]

24c DATE RECEIVED BY MANUFACTURER: 2/16/88

24d REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b TELEPHONE NO *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612) 736-5016

REPORTS

February 22, 1989

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor®(flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are two (2) Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/an

Enclosure: 15 Day Reports
[redacted]

fln 316

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	90	M	01	20	89

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

GRANULOCYTOPENIA, ANEMIA Death
This 90 y o. man had a history of recent hospitalizations, starting with casting for a fractured heel complicated by cellulitis.He was readmitted in late December 1988 with respiratory insufficiency, acute myocardial infarction & ventricular arrhythmias.Flecainide and digoxin were started at this time. Chest x-rays showed bilateral infiltrate. White blood count and temperature were normal. On 15JAN89 he was readmitted when he fractured his hip by falling in the shower. WBC upon admission was 6.7 with a normal differential. On 16JAN89 he underwent surgery to repair his hip fracture. He did well until 20JAN89 when his WBC dropped from 6.8 to 1.5 in 24 hours. A repeat WBC showed 1.4. On 21JAN89 WBC was 1.0

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

	late DEC88	15JAN89	19JAN89	20JAN89	21JAN89
WBC count	normal	6.7	6.8	1.5	1.2
granulocyte ct.				200	0%segs;4%basophil
platelet ct.					251
hemoglobin					9.7

II. SUSPECT DRUG(S) INFORMATION

3. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

5. DAILY DOSE
UNKNOWN

6. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

18. THERAPY DATES *(From To)*
12/??/88 - 01/21/89

19. THERAPY DURATION
1 MONTH

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

FUROSEMIDE
CEFTRIAXONE SODIUM
DIGOXIN
NIFEDIPINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
[redacted]/18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
2/15/89

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 1 REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFW-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

with no granulocytes. All medications were discontinued but the WBC did not improve. A bone marrow biopsy revealed no early cellular forms of either red or white cell precursors. Broad spectrum antibiotics were restarted. Despite aggressive antibiotic therapy, the man was found dead in his hospital bed on 27JAN89. It is not known whether cause of death was of cardiac origin or infectious disease. An autopsy was not performed.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. [illegible] / REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

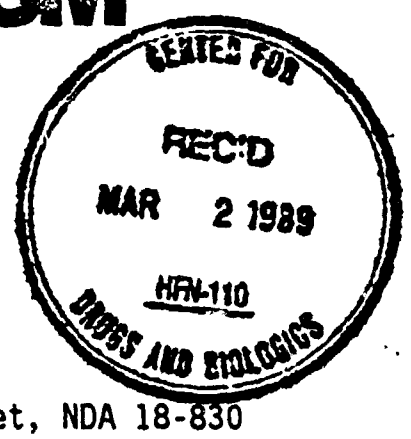
26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

REPORTS

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

3M



February 13, 1989

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is a Follow-up Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/an

Attachments: Follow-up Report
- [redacted] (Initial sent 9/16/88)
(Follow-up sent 12/19/88)

Certified Mail P656 012 662

CL-3/02

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-736)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1985

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	F	07	27	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ARTERIOVENOUS FISTULA, INTRACRANIAL (CONGENITAL ANOMALY)
The mother is a highly intelligent 32 year old black woman who has mitral valve prolapse & palpitations. She had been taking flecainide 100mg/day for several months before this pregnancy was discovered at 7 weeks gestation; flecainide was discontinued then, & no anti-arrhythmic therapy was used throughout the remainder of the gestation. She developed polyhydramnios during the 6th month, resulting in premature rupture of membranes, followed by amnionitis with fever & evidence of fatal distress. The infant was delivered by C-section at 31 weeks, 7/27/88, a girl weighing 1515g. Chest Xray showed evidence of pneumonia treated with antibiotic; hypoxia was corrected by oxygen, & the infant

13. RELEVANT TESTS LABORATORY DATA

7/28/88 - Cardiac catheterization reveals Patent Ductus Arteriosus with small left-to-right shunt & Patent Foramen Ovale.
8/25/88 - ECG monitoring: normal sinus rhythm with conducted & non-conducted premature atrial complexes, occasional atrial extrasystolic bigemeny; marked right atrial enlargement & biventricular hypertrophy.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X CONGENITAL ANOMALY

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: 100 MG

16. ROUTE OF ADMINISTRATION: UNKNOWN

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From To)*: 12/23/87 - 02/03/88

19. THERAPY DURATION: 7 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Mother is Gravida 2, Para 2. First pregnancy was normal, normal product

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED MANUFACTURER: 2/ 7/89

24d. REPORT SOURCE *(Check one)*: ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT: ☒ YES ☐ NO

25a. REPORT TYPE: ☐ INITIAL ☒ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

appeared to be progressing well by the 5th day of life. A ductus murmur was audible at birth & ECG displayed P-waves of 9mm amplitude; catheterization confirmed a minimally patent ductus arteriosus. At 5 days of age ECG still showed high-amplitude QRS signal, interpreted as representing biventricular hypertrophy.
8/11/88: Infant requiring only low oxygen concentration now, tube-fed & showing weight gain. Premature atrial contractions began to appear a few days ago, & digoxin was started 8/10/88. Echocardiogram shows no no cardiac enlargement, chest Xray shows mild pulmonary congestion, ECG shows 5mm P-waves.
8/22/88: A large intracranial arteriovenous fistula was discovered by

13. RELEVANT TESTS LABORATORY DATA

Computerized tomography & magnetic resonance imaging (cranial): large intracranial arteriovenous fistula evident.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN. OR PROLONGED. INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From-To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15-DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 3)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

computerized tomography & magnetic resonance imaging; although a bruit was not audible; this lesion is credited with causing the observed evidence of biventricular hypertrophy & pulmonary vascular congestion. On 8/19/88 partial occlusion of the Vein of Galen was accomplished, using several balloons; the procedure was well tolerated. Nasogastric tube feeding is continuing. Present weight: 1350g. No evidence of peripheral edema. Blood pressure 61/37.
12/12/88 Follow-up: At four months of age the infant is alive and gaining weight, but exhibits evidences of severe neurological deficit.
Follow-up: The baby died 1/31/89, aged 6 months. Death was attributed to sepsis & congestive heart failure; autopsy was not allowed.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines & biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From, To)*

19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT ☐ YES ☐ NO

25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA # 18-830:
Name of Drug: Tombucore Tablets
Sponsor: Riker
Type of Submission: Periodic ADR Report (9/11/88-12/10/88)
Date of Submission: 1/13/89
Date of Review: 1/30/89
Reviewer: Sughok K. Chun, M.D. HFD-110

A. Resume:

I. Initial Reports This Period

A. Serious Labeled

Manufacturing Report NO.	Age/Sex	Duration of Rx	Reaction Term
[redacted]	35/m	6 wks	Hepatic Function abnormal
[redacted]	71/f	3 days	Transaminase increased
[redacted]	76/m	5 days	Hepatic Function abnormal Nausea/Vomiting
[redacted]	17/f Drug & Alcohol abuse	1 day	Convulsions, Fever, VT, AV Block
[redacted]	75/m	3 doses	VF, Death
[redacted]	64/f	30 mos	VT
[redacted]	60/m	few wks	VT, ECG abnormal (QRS .17")
[redacted]	12/m	20 days	Syncope, Hypotension, VT AV Block
[redacted]	55/m	3 wks	Agranulocytosis

11/23/88: WBC 4500, PMN 60%
12/05/88: PMN 600/cu.mm.--less than 400/cu.mm.
12/08/88: PMN 100/cu.mm.
12/09/88: PMN 0/cu.mm.
12/06/88: Bone Marrow: sparse myelocytes, few granulocytes, otherwise OK

B. Nonserious

Manufacturing Report No.	Age/Sex	Duration of Rx	Reaction Term
[redacted]	53/f	2 yrs	Drug Interaction-Diltiazem, Tremor, Twitching, Arrhythmia
[redacted]	68/f	6 wks	Vision abnormal (enhanced peripheral perception)
[redacted]	2/f	4 yrs	Palpitation
[redacted]	22/m	?	Recurrent SVP due to WPW
[redacted]	34/f	2 days	Sinus Arrest 4-5"
[redacted]	79/m	1 yr	Hepatic Function abnormal Hepatitis. LFT returned to normal while cont. Rx with Flecainide
[redacted]	53/f	3 days	Pulm Edema drug interaction with Metaprolol
[redacted]	59/m	1 wk	Paroxysmal Nocturnal Dysonea drug interaction (Propanolol)
[redacted]	45/f	3 mos	Weitht Increase, Facial Puffiness, Bradycardia possible Hypothyroidism
[redacted]	?/f	?	Sinus Node Dysfunction, drug intercation (Digoxin)
[redacted]	50/m	2 mos	Hypertension, Urinary Retention BPH ?
[redacted]	76/m	12 days	Pericarditis
[redacted]			Pacemaker Function Abnormal increased Threshold
[redacted]	12/m	3 wks	Blurred Vision Improved with D/C
	12/m	3 wks	Headache, Dizziness, Blurred Vision

[redacted]	49/m	6 mos	Hyperlipemia, Hypothyroidism
[redacted]	85/f	1 mo	Sinoatrial Arrest,
[redacted]	17/f	7 mos	Pruritus, Unrelated to Flec.
[redacted]	?/?	?	Leukopenia, WBC increased after D/C
[redacted]	?/m	?	Abnormal LFT

The volume of U.S. Spontaneous reports in the Twelfth Quarter is essentially unchanged from the last quarterly report, and there are no reports deriving from clinical studies. Foreign reports are also absent this quarter.

After review of the ADRs received this quarter, the sponsor concluded that current U.S. Prescribing information for flecainide acetate tab continues to describe safety information appropriately and, therefore, is not in need of revision at this time.

The reviewer concurred with this conclusion.

S K. Chun 1/31/89
Sughok K. Chun, M.D.

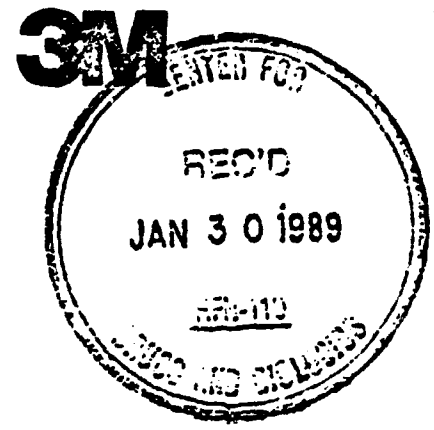
CC: Original
HFD-110
HFD-110/CSO
HFD/110/SKChun/1/30/89
0084d/lah/1/30/89

REPORTS

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

January 13, 1989



Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir/Madam:

Pursuant to 21 CFR 314.80, enclosed is the Periodic ADR Report in duplicate for Tambocor® (flecainide acetate) NDA 18-830. There are 37 FDA-1639 forms in this submission, 32 of which are initial reports and 5 are follow-up reports.

The time period covered by this report is September 11, 1988 through December 10, 1988.

Sincerely,

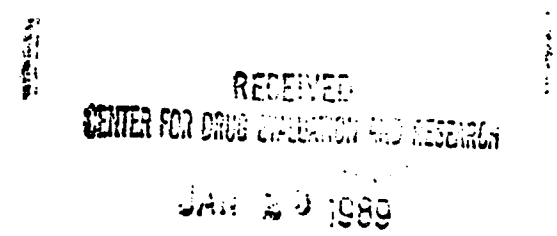
Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Affairs Coordinator

:an

Desk Copy: Dr. S. Chun (HFN-110)

P072



110

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	17	F	09	20	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

SEIZURES, FEVER, VENTRICULAR TACHYCARDIA, AV BLOCK Death
This 17 y/o girl with a history of alcohol abuse and hospitalization 2 years previously for drinking (chug-a-lug contest) one quart of liquor was admitted to the hospital at 22:20 hours on 20Sep88. LSD was taken earlier in the evening followed by about 20 mixed tablets (flecainide acetate, nifedipine, and dipyridamole) at some time prior to admission to ER. She was treated with lavage and activated charcoal. About 20 minutes after admission she developed seizures (tonic/clonic to status epilepticus) which were treated with 40 mg diazepam. No response occurred over 45 min. period. Additional treatment of epinephrine and calcium chloride. Temperature was 105.2 F at 02:45 hours. About then

13. RELEVANT TESTS LABORATORY DATA

See #7, above.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- [X] OVERDOSE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: ?

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: SUICIDE-DRUG/MEDICIN NEC

18. THERAPY DATES *(From To)*: 09/20/88 - 09/20/88

19. THERAPY DURATION: ONE DOSE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NIFEDIPINE
DIPYRIDAMOLE
ALCOHOL, ETHYL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 9/21/88

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

she was coded for 2 hours for ventricular tachycardia/atrioventricular block. She died at 07:30 hours on 21Sep88. A tox screen was negative for alcohol.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
17. INDICATION(S) FOR USE	
18. THERAPY DATES *(From To)*	19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)* ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER
25. 15 DAY REPORT ☐ YES ☐ NO	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	76	M	11	29	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

VENTRICULAR FIBRILLATION Death
This 76 y.o. woman had experienced chronic atrial fibrillation for about 6 months. She had been known to have hypertrophic myocardiopathy. She was hospitalized with plans to begin flecainide 100mg/day, electrocardiovert and discharge the patient. She received three 100 mg tablets of flecainide at 12 hr intervals when, about 6 hours after her last dose she was found in ventricular fibrillation. Shock "converted" her to an ineffective, wide complex tachycardia, but the patient expired.

13. RELEVANT TESTS LABORATORY DATA

Potassium concentration in serum was normal during hospitalization.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
200MG	ORAL

17. INDICATION(S) FOR USE
ATRIAL FIBRILL/FLUTTER

18. THERAPY DATES *(From To)*	19. THERAPY DURATION
11/28/88 - 11/29/88	3 DOSES

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN
NIFEDIPINE
PROPRANOLOL HCL
FUROSEMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
[redacted] /18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
11/30/88	[ ] FOREIGN [ ] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
[ ] YES [X] NO	[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

25b. TELEPHONE NO. *(Include area code)*

[redacted]

25c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

25d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO	DA.	YR.
[redacted]	16	F	08	23	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Overdose, Death
Mid-teenage girl consumed 60-70 flecainide 100mg tablets this morning (8/23/88), and died. Symptoms and course prior to death are not known by the reporter at first contact, but will be supplied later.
11/14/88: Overdose occurred at about 3 AM, time of death not clearly established. Post mortem blood sample was obtained at 8:30 AM. Flecainide plasma level was determined to be 7.2mcg/ml.

13. RELEVANT TESTS LABORATORY DATA

@ 5 hours post-dose: plasma flecainide = 7.2mcg/ml

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X OVERDOSE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

5. DAILY DOSE: 6.6 G

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: SUICIDE-DRUG/MEDICIN NEC

18. THERAPY DATES *(From To)*: 08/23/88 - / /

19. THERAPY DURATION: ONE DOSE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
S PAUL, MN 55144-1000

24a. IND./NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 11/14/88

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

REPORTS

3M

November 7, 1988

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are two (2) Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/an

Enclosure: 15 Day Reports
- [redacted]
- [redacted]

Certified Mail P 656 012 605

RECEIVED
NOV 13 1988
HFN-110
CENTER FOR DRUGS AND BIOLOGICS

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1985

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	M	05	09	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***HEMORRHAGE* Death**
This elderly man had a history of congestive heart failure and arrhythmias. He was taking flecainide and a number of concomitant medications including danthron. He was hospitalized four times from February through May 1986. During his hospitalization in May, he developed upper GI distress which his physician diagnosed as esophageal varices. Following surgery, the man's wife (who reported this case) found him "dying in a pool of blood". He was transfered to the intensive care unit where he died on 09MAY86. According to his wife, the man died from "ruptured viscera, probably accelerated by danthron".

13. RELEVANT TESTS/LABORATORY DATA

None.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

DICATION(S) FOR USE: CARDIAC DYSRHYTHMIA NOS

18. THERAPY DATES *(From To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DANTHRON W/CALCIUM DOCUSATE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

DATE RECEIVED Y MANUFACTURER: 10/24/88

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [ ] HEALTH PROFESSIONAL [x] CONSUMER

25. 15 DAY REPORT
- [x] YES [ ] NO

25a. REPORT TYPE
- [x] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

25.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

17.1

REPORTS

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612) 733-8824

July 10, 1989

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Reports
Tambocor® (flecainide acetate),
NDA 18-830

Dear Sir/Madam:

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Gene L. Harris

Gene L. Harris
Sr. Regulatory Coordinator

GLH/ddap

Enclosures: 15-Day Reports - [redacted]

Certified Mail P 818 965 791

CENTER FOR DRUG
REC'D
JUL 20 1989
HFD-110
EVALUATION AND RESEARCH

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	10	10	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***SEPTIC SHOCK* death**
This patient was enrolled in a clinical study of flecainide, amiodarone, and propafenone. Study protocol involved treatment with the three agents in random order. This patient had a history of ischemic heart disease and dilated cardiomyopathy. The patient took propafenone as the first drug in the study and was then switched to flecainide 200 mg/day. On 10OCT85, 129 days after enrolling in the study, the patient died of septic shock.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR (UNIT SIZE UNSPECIFIED)/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
CARDIAC DYSRHYTHMIA NOS

18. THERAPY DATES *(From/To)*
??/??/85 - 10/10/85

19. THERAPY DURATION
<129 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
[redacted] /18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
6/21/89	[X] FOREIGN [X] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
[X] YES [ ] NO	[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	06	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***NEOPLASM* Death**
This patient was enrolled in a clinical study of flecainide, amiodarone, and propafenone. Study protocol involved treatment with the three agents in random order. This patient had a history of ischemic heart disease. On 24SEP84 the patient started taking flecainide as the first drug in the study. On 13JUN86, 627 days after enrolling in the study, the patient died of cancer.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- [X] CANCER

13. RELEVANT TESTS LABORATORY DATA
None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR (UNIT SIZE UNSPECIFIED)/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
CARDIAC DYSRHYTHMIA NOS

18. THERAPY DATES *(From To)*
09/24/84 - 06/13/86

19. THERAPY DURATION
627 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
6/21/89

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	03	17	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#GASTRIC HEMORRHAGE* Death
This patient was enrolled in a clinical study of flecainide, amiodarone, and propafenone. Study protocol involved treatment with the three agents in random order. This patient had a history of dilated cardiomyopathy. On 13MAR86 the patient started taking flecainide 200 mg/day as the first drug in the study. On 17MAR86, 5 days after enrolling in the study, the patient died of gastric hemorrhage.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR (UNIT SIZE UNSPECIFIED)/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: CARDIAC DYSRHYTHMIA NOS

18. PY DATES *(From/To)*: 03/13/86 - 03/17/86

19. THERAPY DURATION: 5 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/21/89

24d. REPORT SOURCE *(Check one)*
[x] FOREIGN [x] STUDY [ ] LITERATURE
[x] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[x] YES [ ] NO

25a. REPORT TYPE
[x] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

19-1

3M Riker
3M Health Care Group

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000

(612) 733-8824

REPORTS

December 10, 1989

3M

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate),
NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experience which occurred in association with the use of the subject product.

Sincerely,

Gene L. Harris

Gene L. Harris
Sr. Regulatory Coordinator

GLH/kjn

Enclosure: 15-Day Report - [redacted]

Sent via Certified Mail Article Number P 818 965 877

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	69	F	04	10	89

7. DESCRIBE REACTION(S)

MYOCARDIAL INFARCTION, VENTRICULAR FIBRILLATION* Death
This 69 y.o. man had a complicated medical history of diabetes, hypertension, angina pectoris, cerebral infarction and myocardial infarctions in 1981, 1983, and 1987. She experienced ventricular fibrillation after her myocardial infarction and was started on flecainide 200 mg/day in 1987. On 28MAY89 she was hospitalized (cause unknown). On 10APR89 she collapsed in her hospital bed. She developed ventricular fibrillation; despite resuscitation attempts for one hour, the woman died. Cause of death is listed as acute myocardial infarction. The reporter suspects that the concomitant medication of digoxin may have contributed.

8.-12. CHECK ALL APPROPRIATE:

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR FIBRILLATION

18. DATES OF ADMINISTRATION (From/To): ??/??/87 - 04/10/89

19. DURATION OF ADMINISTRATION: ? YEARS

20. DID REACTION ABATE AFTER STOPPING DRUG? [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? [ ] YES [ ] NO [X] NA

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ASPIRIN
POTASSIUM CHLORIDE
GLIBENCLAMIDE
DIGOXIN
FUROSEMIDE
BUMETANIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR. CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 12/ 5/89

24d. REPORT SOURCE *(Check all that apply)*: [X] FOREIGN [ ] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

'AY REPORT? [ ] YES [ ] NO

25a. REPORT TYPE: [X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL? [ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

FORM FDA 1639 (7/86) PREVIOUS EDITION MAY BE USED

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612) 733-8824

REPORTS

3M

November 20, 1989

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate),
NDA 18-830

Dear Sir/Madam:

Enclosed are six Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Gene L. Harris

Gene L. Harris
Sr. Regulatory Coordinator

GLH/kjn

Enclosure: 15-Day Report - [redacted]

Sent via Certified Mail Article Number P 818 965 870

11/30

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	1	M	--	--	--

7. DESCRIBE REACTION(S)

BRADYCARDIA, CARDIAC ARREST Death
This 13 month old boy had structural heart disease consisting of ventricular septal defect, transposition of the great arteries & subpulmonary stenosis. He was initially treated with digoxin; other antiarrhythmic agents were tried unsuccessfully.At the age of 5 months, flecainide oral solution 4.2mg/kg/day was added to digoxin therapy. This combination was successful in maintaining sinus rhythm. At the age of 13 months, the boy experienced supraventricular tachycardia in association with an upper respiratory tract infection. He was hospitalized; intravenous adenosine was unsuccessful but IV flecainide restored sinus rhythm. IV flecainide 2mg/kg was given 24 hours later when supraventricular tachycardia

13. RELEVANT TESTS LABORATORY DATA

Flecainide level (one hour before death)=1.203 mcg/ml (normal 0.2-1)
Digoxin level (one hour before death) =0.7 mcg/l (normal 0.8-22)

8.-12. CHECK ALL APPROPRIATE:

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR (UNIT SIZE UNSPECIFIED)/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: SUPRAVENTRICULAR ARRHYTH

18. DATES OF ADMINISTRATION (From/To): UNKNOWN - UNKNOWN

19. DURATION OF ADMINISTRATION: 7 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

b. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

See 8? above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR. CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 11/ 3/89

24d. REPORT SOURCE *(Check all that apply)*
[ ] FOREIGN [ ] STUDY [X] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

AY REPORT?
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S)

recurred; this was not successful in terminating the arrhythmia. After 45 minutes, IV flecainide 1mg/kg was given which restored sinus rhythm; however, bradycardia and cardiac arrest occurred. The boy was resuscitated. Flecainide level was 1.203mcg/ml (normal 0.2-1). One hour later the boy again experienced bradycardia and died despite resuscitation and temporary pacing.
Literature reference: Priestley KA. Sudden death associated with flecainide in children with structural congenital heart disease. UNPUBLISHED

8.-12. CHECK ALL APPROPRIATE.

- ☐ PATIENT DIED
- ☐ REACTION TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. DATES OF ADMINISTRATION (From/To)

19. DURATION OF ADMINISTRATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND NDA. NO. FOR SUSPECT DRUG

24b. MFR. CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check all that apply)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

)AY REPORT?
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved. OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	--	--	--

7. DESCRIBE REACTION(S)

BRADYCARDIA, APNEA, CYANOSIS, CARDIAC ARREST Death

The 8 month old boy had a medical history of structural heart disease consisting of Ebstein's anomaly. He was treated with IV flecainide, followed by maintenance oral flecainide at home. The dose was increased to 5.7mg/kg/day because of low plasma flecainide levels. He was admitted to the hospital four days later in sinus rhythm with mild heart failure. Flecainide level was 0.588 mcg/ml (normal 0.2-1). Five days later he developed bradycardia (heart rate 30 beats/min), apnea and cyanosis. He was resuscitated and flecainide was discontinued. 48 hours later he died from cardiac arrest. [Literature reference: Priestley KA. Sudden death associated with flecainide in children with structural congenital heart

13. RELEVANT TESTS LABORATORY DATA

Flecainide level (at admission) = 0.588 mcg/ml (normal 0.2-1)

8.-12. CHECK ALL APPROPRIATE.

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR (UNIT SIZE UNSPECIFIED)/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
SUPRAVENTRICULAR ARRHYTH

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

18. DATES OF ADMINISTRATION *(From/To)*
UNKNOWN - UNKNOWN

19. DURATION OF ADMINISTRATION
2 WEEKS

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to trea reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55.44-1000

24a. IND NDA. NO. FOR SUPPLEMENT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
11/ 3/89

24d. REPORT SOURCE *(Check all that apply)*
[ ] FOREIGN [ ] STUDY [X] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

AY REPORT?
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

DESCRIBE REACTION(S)
disease. UNPUBLISHED]

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE:

- ☐ PATIENT DIED
- ☐ REACTION TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. DATES OF ADMINISTRATION (From/To)

19. DURATION OF ADMINISTRATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND NDA. NO. FOR SUSPECT DRUG

24b. MFR. CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check all that apply)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

JAY REPORT?
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOW-UP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

FORM FDA 1639 (7/86) PREVIOUS EDITION MAY BE USED

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	F	--	--	--

7. DESCRIBE REACTION(S)

CONGESTIVE HEART FAILURE, CARDIAC ARREST Death

This 9 month old girl had a structural heart disease consisting of surgically corrected congenital transposition of the great arteries, ventricular septal defect, and Ebstein's anomaly. She was initially treated with oral digoxin and intravenous verapamil. At three weeks of age she experienced a recurrance of her arrhythmia. She was started on IV flecainide and later switched to oral flecainide. Three weeks later she experienced supraventicular tachycardia; flecainide level was 0.121 mcg/ml (normal 0.2-1). She was treated with IV flecainide and switched to oral flecainide and diuretics. Flecainide level at the age of seven months was 0.284 (mcg/ml). Flecainide was increased over the next two

13. RELEVANT TESTS LABORATORY DATA

Flecainide level (three weeks after initiation of therapy) 0.121 mcg/ml
Flecainide level (six months after initiation of therapy) 0.284 mcg/ml

8.-12. CHECK ALL APPROPRIATE:

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR (UNIT SIZE UNSPECIFIED)/FLECAINIDE ACETATE

15. DAILY DOSE: 30 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: SUPRAVENTRICULAR ARRHYTH

18. DATES OF ADMINISTRATION (From/To): UNKNOWN - UNKNOWN

19. DURATION OF ADMINISTRATION: 8 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR. CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 11/ 3/89

24d. REPORT SOURCE *(Check all that apply)*

[ ] FOREIGN [ ] STUDY [X] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

24e. MAY WE HAVE COPY OF THIS REPORT?

[X] YES [ ] NO

25a. REPORT TYPE

[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S)

months from 22.5 mg/day to 30 mg/day. At the age of nine months, the patient was admitted to the hospital in congestive cardiac failure without supraventricular tachycardia. Thirteen hours later she suffered cardiac arrest and died. [Literature reference: Priestley KA. Sudden death associated with flecainide in children with structural congenital heart disease. UNPUBLISHED]

8.-12. CHECK ALL APPROPRIATE:

- ☐ PATIENT DIED
- ☐ REACTION TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

18. DATES OF ADMINISTRATION (From/To)

19. DURATION OF ADMINISTRATION

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND NDA. NO. FOR SUSPECT DRUG

24b. MFR. CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check all that apply)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

DAY REPORT?
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

FORM FDA 1639 (7/86) PREVIOUS EDITION MAY BE USED

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612) 733-8824

REPORTS

November 8, 1989

3M

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor™ (flecainide acetate),
NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Gene L. Harris

Gene L. Harris
Sr. Regulatory Coordinator

GLH/kjn

Enclosure: 15-Day Report - [redacted]

Sent via Certified Mail Article Number P 818 965 855

11/22

ORIGINAL

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	53	M	07	28	88

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

MYOCARDIAL INFARCT; SEIZURES; MORBID DREAMS; IMPOTENCE* Death
This 53 y/o man had a history of myocardial disease(infarct - 1974) and a coronary artery bypass in OCT87. About 6 weeks post bypass flecainide acetate therapy was started at 300 mg/day by his personal physician. Two weeks later his surgeon stopped flecainide but then several weeks later the personal physician restarted flecainide. Soon after initiation of flecainide therapy he began having morbid dreams & became impotent. He is reported to have had one or more grand mal seizures during the course of the next few months. He sustained "a heart attack" and died 28JUL88.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: **300 MG**

16. ROUTE OF ADMINISTRATION: **ORAL**

17. INDICATION(S) FOR USE: **CARDIAC DYSRHYTHMIA NOS**

18. THERAPY DATES *(From To)*: **11/ /87 - 07/28/88**

19. THERAPY DURATION: **9 MONTHS**

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 10/24/89

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☒ CONSUMER

25. 15-DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612) 733-8824

REPORTS

3M

November 8, 1989

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

RECEIVED
DIVISION OF EPIDEMIOLOGY
AND SURVEILLANCE
89 NOV 15 AM 2:15

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate),
NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Gene L. Harris

Gene L. Harris
Sr. Regulatory Coordinator

GLH/kjn

Enclosure: 15-Day Report - [redacted]

CENTER FOR
REC'D
NOV 17 1989
HFN-110
DRUGS AND BIOLOGICS

Sent via Certified Mail Article Number P 818 965 867

ORIGINAL

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	63	M	04	??	89

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***VENTRICULAR TACHYCARDIA, CARDIAC ARREST, BRADYCARDIA* Death**
This 63 y.o. man was taking flecainide 300 mg/day for at least three years. He decreased his dose on his own after hearing the preliminary results of the CAST study. The next day he experienced ventricular tachycardia of 180 beats/minute which was successfully converted. The following day cardiac arrest occurred; he was resuscitated, but bradycardia ensued and he died that day. 18OCT89 Follow-up information: This man had a history of Wolff-Parkinson-White syndrome and a cardioversion in January 1989. He refused electrophysiology testing.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR 150 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: **300 MG**

16. ROUTE OF ADMINISTRATION: **ORAL**

17. INDICATION(S) FOR USE: **CARDIAC DYSRHYTHMIA NOS**

18. THERAPY DATES *(From To)*: **04/??/86 - 04/??/89**

19. THERAPY DURATION: **3+ YEARS**

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23 OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See 7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: **10/18/89**

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 5-DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612) 733-8824

October 9, 1989

3M

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate),
NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Gene L. Harris

Gene L. Harris
Sr. Regulatory Coordinator

GLH/kjn

Enclosure: 15-Day Report - [redacted]

Sent via Certified Mail Article Number P 818 965 849

10/18

ORIGINAL

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	61	M	03	22	89

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

SORE THROAT* SUDDEN DEATH, CAUSE UNKNOWN
Wife reports that this 61 y.o. gentleman had had hypertension for many years and "PVC's". He had been taking the medications shown below for years, but 4-5 days prior to death was prescribed flecainide acetate tablets (100mg b.i.d.). Following start of the latter, he developed a sore throat and died suddenly. She recalls that the physician told her that a valve in his heart closed causing his sudden death. Further information and the name of the physician has been requested to facilitate further investigation.

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
200 MG	ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
03/17/89 - 03/22/89	4-5 DAYS

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

TRIAMTERENE, HYDROCHLOROTHIAZIDE YEARS **ATENOLOL** YEARS
TIMOLOL MALEATE YEARS

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Please see #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
9/15/89

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☒ CONSUMER

24e. 5-DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

NDA 19-930

Memorandum of Telephone Conversation
Wednesday, September 20, 1989

SEP 20 1989

Between:

Robert Temple, M.D., Director
Office of Drug Evaluation I

and

Representatives of Riker
Florence Wong
Ed Basile, Attorney, Outside Counsel
Mike Cullen, Director of Clinical Research
Moss Duvall, General Counsel

The Riker representatives had a number of concerns about the upcoming Advisory Committee, but it was not easy to determine what they were. They seemed to be concerned that certain recommendations the Advisory Committee might make would put them in a difficult position. For example, they thought the Advisory Committee might recommend approval of a claim in supraventricular tachycardia with a requirement that phase 4 studies be developed to see whether the drug was dangerous or not and whether the mortality was increased in the treated patients. They thought they would be in a difficult liability position if that occurred. They also were concerned that if the recommendation was that the drug was too dangerous to be used in supraventricular arrhythmias, it might become their duty to warn physicians who were using the drug that way that they should not do so.

I expressed some skepticism regarding their perceived need to warn physicians about uses outside the package insert, as these had occurred often in the past, generally without intervention by drug companies. It is well known that uses outside the package insert for flecainide and encainide were quite common and I had noticed no attempt to warn. For not clear reasons, in any event, the present situation was deemed potentially different. I said I could not tell what the outcome of the session would be but that I thought the advice the Committee was likely to give would be based on a clear weighing of the benefits and risks of any particular use in any particular patient group. Thus if they were to recommend that approval be granted for a limited population of patients with supraventricular tachycardia that would represent their explicit view that the available data allowed the conclusion that the risk, as estimated based on current data, was acceptable. Any phase 4 studies they suggested would probably be directed at a wider group, i.e., a group that would not be included in labeling based on present data (or the uncertainty felt by present data.) Again I emphasized that I was not predicting the outcome of the meeting but that I thought the discussion the Committee would have would make clear what the basis for their recommendation was. It did not seem likely to me that Riker would be confused or placed in difficult position.

Robert Temple

Robert Temple, M.D.

cc:
Orig. NDA
HFD-100/Chron File
HFD-100/Drug File
HFD-101/Botstein
HFD-110/CSO
HFD-110/Lipicky
[illegible]:jp:1/3/90:Wang #2666d
Revised:RT:jp:10/4/89(2)

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612) 733-8824

REPORT

September 28, 1989

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Reports
Tambocor® (flecainide acetate),
NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Gene L. Harris

Gene L Harris
Sr. Regulatory Coordinator

GLH/kjn

Enclosure: 15-Day Reports - [redacted]

RECEIVED
DIVISION OF EPIDEMIOLOGY
AND SURVEILLANCE
89 OCT -4 PM 6:45

Sent via Certified Mail Article Number P 818 965 420

10/10

ORIGINAL

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

ATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	02	06	89

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#SYNCOPE, CARDIAC ARREST* Death
This man was admitted to the hospital in late December 1988 after feeling ill due to his "heart condition" of several years. He was given flecainide and a number of other agents (not identified) and discharged from the hospital in early January 1989. The man felt much better and returned to the hospital for a check-up on 03FEB89. He was told that his condition was much improved. On 06FEB89 he collapsed and was transported to the hospital where he regained consciousness. On 07FEB89 he suffered a heart attack and died.

13. RELEVANT TESTS/LABORATORY DATA

None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR (UNIT SIZE UNSPECIFIED)/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: CARDIAC DYSRHYTHMIA NOS

18. THERAPY DATES *(From/To)*: 12/??/88 - 02/06/89

19. THERAPY DURATION: 2 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 9/ 8/89

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [X] CONSUMER

'AY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612) 733-8824

REPORTS

3M

August 23, 1989

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate),
100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject product.

Sincerely,

Gene L. Harris

Gene L. Harris
Sr. Regulatory Coordinator

GLH/kjn

Enclosure: 15-Day Report - [redacted]

Sent via Certified Mail Article Number P 818 965 392

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	F	07	09	89

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***CARDIAC ARREST* Death**
This 70 y.o. woman had a complicated medical history of hypertension, congestive heart failure, diabetes, cerebrovascular accident, chronic obstructive lung disease, and possible myocardial infarction. On 05JUL89 EKG recordings showed extrasystoles and runs of 6 to 8 beats. Flecainide 200 mg/day was started. On 09JUL89 the woman experienced cardiac arrest and died. The physician believes that the woman died from complications due to her underlying diseases with the possibility of proarrhythmia.

13. RELEVANT TESTS LABORATORY DATA
None.

8-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS, VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
07/05/89 - 07/09/89

19. THERAPY DURATION
4 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
ISOSORBIDE DINITRATE **FUROSEMIDE**

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
8/18/89

24d. REPORT SOURCE *(Check one)*
- [X] FOREIGN [ ] STUDY [ ] LITERATURE
- [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 5-DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

REPORTS

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612) 733-8824

3M

August 3, 1989

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate),
NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject product.

Sincerely,

Gene L. Harris

Gene L. Harris
Sr. Regulatory Coordinator

GLH/ddap

Enclosure: 15-Day Report - [redacted]

Sent via Certified Mail Article Number P 818 965 847

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	04	25	89

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

CARDIAC ARREST Death
Patient's age, history, condition being treated are not presently reported. It is reported that "During the 3 months prior to death the patient was prescribed flecainide acetate tablets extensively for heart-related difficulties". He is reported to have died on 25APR89 of cardiac arrest.
Further information is being sought.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR (UNIT SIZE UNSPECIFIED)/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: UNKNOWN

18. THERAPY DATES *(From To)*: 01/25/89 - 04/25/89

19. THERAPY DURATION: 3 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 7/20/89

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [x] CONSUMER

25. 15 DAY REPORT
[x] YES [ ] NO

25a. REPORT TYPE
[x] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

AUG 10 1989

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICERS REVIEW

NDA #18-830

Name of Drug: Tambocor tablets

Sponsor: Riker

Type of Submission: ADR

Date of Submission: 8/1/89

Date of Review: 8/10/89

Reviewer: Sughok K. Chun, M.D. HFD-110

[redacted]

VENTRICULAR TACHYCARDIA, CARDIAC ARREST, BRADYCARDIA Death with decreased dose.

This 63 y/m was taking flecainide 300 mg day for at least three years. He decreased his dose on his own after hearing the preliminary results of the CAST study. The next day he experience ventricular tachycardia of 180 beats/minute which was successfully converted. The following day cardiac arrest occurred; he was resuscitated, but bradycardia ensued and he died that day. No further information is available.

S.K. Chun 8/10/89
Sughok K. Chun, M.D.

cc: ~~Orig~~. NDA
HFD-110
HFD-110/CSO
HFD-110/SChun
ml:8/10/89:#0550a

REPORTS

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000

3M

August 1, 1989

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Reports
Tambocor® (flecainide acetate),
NDA 18-830

Dear Sir/Madam:

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Gene L. Harris

Gene L. Harris
Sr. Regulatory Coordinator

GLH/ddap

Enclosures: 15-Day Reports -

Sent via Certified Mail Article Number P 818 965 811

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT IDINITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	63	M	04	??	89

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

VENTRICULAR TACHYCARDIA, CARDIAC ARREST, BRADYCARDIA Death
This 63 y.o. man was taking flecainide 300 mg/day for at least three years. He decreased his dose on his own after hearing the preliminary results of the CAST study. The next day he experienced ventricular tachycardia of 180 beats/minute which was successfully converted. The following day cardiac arrest occurred; he was resuscitated, but bradycardia ensued and he died that day. No further information is available.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR 150 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
CARDIAC DYSRHYTHMIA NOS

18. THERAPY DATES *(From To)*
04/??/86 - 04/??/89

19. THERAPY DURATION
3+ YEARS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See 7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
7/13/89

24d. REPORT SOURCE *(Check one)*
- [X] FOREIGN [ ] STUDY [ ] LITERATURE
- [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(in Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	05	22	89

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***CARDIAC ARREST* DEATH**
This man was taking flecainide when he discontinued upon hearing the news reports of 25APR89. On 18MAY89, he collapsed with cardiac arrest. He was started again, but had sufferred brain damage from which he died on 22MAY89.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*
UNKNOWN - 05/18/89

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND./NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
7/20/89

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

2211

Regulatory Affairs
3M Pharmaceuticals

3M Center Bldg. 270-3A-01
St. Paul, MN 55144-1000
(612) 733-8824

REPORTS

3M

June 8, 1990

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate),
100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject product.

Sincerely,

Gene L. Harris

Gene L. Harris
Sr. Regulatory Coordinator

GLH/kjn

Enclosure: 15-Day Report - [redacted]

6/21/90

Sent via Certified Mail Article Number P 818 965 965

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approval: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	62	F	??	??	90

7. DESCRIBE REACTION(S)

"MYOCARDIAL INFARCTION" Death
This 62 y.o. woman had been taking flecainide acetate 200 mg/day successfully for the past three years for control of ventricular extrasystoles. She experienced a myocardial infarction and died before being transported to the hospital No further information is available.

8.-12. CHECK ALL APPROPRIATE:

- [x] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

18. DATES OF ADMINISTRATION (From/To)
??/??/87 - ??/??/90

19. DURATION OF ADMINISTRATION
3 YEARS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those ... reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
5/28/90

24d. REPORT SOURCE *(Check all that apply)*
[x] FOREIGN [ ] STUDY [ ] LITERATURE
[x] HEALTH PROFESSIONAL [ ] CONSUMER

... 15 DAY REPORT?
[x] YES [ ] NO

25a. REPORT TYPE
[x] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
( ) -

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

FEB 27 1990

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA #18-830

Name of Drug: Tambocor (flecainide acetate) tablets

Sponsor: 3M Riker

Type of Submission: Annual ADR Report (12/11/88 - 12/10/)

Date of Submission: February 22, 1990

Date of Review: February 26, 1990

Reviewer: Sughok K. Chun, M.D. HFD-110

This Periodic ADR Report includes 102 FDA 1639 forms, 95 of which are initial reports and 7 are follow-up reports.

DISTRIBUTION OF FDA 1639's*

	U.S. Spontaneous	Literature	Foreign Spontaneous	Total
Serious -				
Unlabeled (15-day)	19	5	16	40
Labeled	33	NA	NA	33
Nonserious	69	NA	NA	69
TOTAL	121	5	16	142

*There were no clinical study events reported in this report period.

Figure 1 displays graphically the annual numbers of adverse drug experiences reported during the first four years of marketing under the U.S. NDA.

The rate of decline in the number of U.S. spontaneous reports observed in the 3rd year extended itself through the 4th year of marketing experience, a not unexpected trend.

The most startling and remarkable set of events evolved from the broadcast of the CAST results April 25, 1989. A considerable number of pts precipitatel, discontinued use of flecainide shortly after the news was released. The results of the abrupt cessations of flecainide use included sudden deaths, resuscitated cardiac arrests, and recurrences of the cardiac arrhythmias which had originally prompted the flecainide prescription. The proportionate contribution of these post-treatment events during this reporting period is seen in figure 2.

The volume of reports in all categories continued to decline during this reporting period. Of the total of 142 reports, 21 (15%) derived form ADRs occuring to pts subsequent to their discontinuation of flecainide following the announcement of the CAST results at the end of April, two of them from Germany and 19 domestic USA. All told, reports of 50 instances of this class reached the company, of which 29 were not submitted as 1639 reports.

FDA 1639 REPORTS SUBMITTED CONTAINING DEATH AS AN OUTCOME*

	U.S. Spontaneous	Literature	Foreign Spontaneous	Total
Unlabeled(15-day)	6	3	7	16
Labeled	17	NA	NA	17
TOTAL	23	3	7	33

*There were no clinically study events reported in this report period.

Thirty-three reports in which death was the outcome are included in this annual report. Ten of these are of the post-CAST revelation post-treatment-withdrawal class, two submitted as 15-Day Reports, one from Germany and one from the USA; the other eight are non-15-Day Reports, all from the USA. Although the Company has received reports of another sixteen incidents of that class in which death was the outcome, those reports did not qualify for submission as 1639 reports.

The largest single class was composed of ten deaths occurring to pts shortly after discontinuation of flecainide use consequent on the CAST results revelation. In seven of these cases the immediate cause of death was not determined, although it is a justifiable presumption that death was of a cardiac nature; in the other three cases fatal cardiac dysrhythmia was documented.

Of the remaining 23 incidents, 5 resulted from deliberate overdose. [redacted] reports the death of an infant as a final consequence of sever congenital cardiovascular abnormalities. Total bone marrow failure in a 90 year old man, probably consequent to overwhelming post operative infection, accounted for the death reported in [redacted]. Four additional cases of death of undetermined cause, unrelated to the post-CAST post-treatment-withdrawal class detailed above, were reported. Myocardial infarction was credited with causing the deaths of the pts cited in [redacted] and [redacted] Eight cases of fatal cardiac arrest are included in this report, two of which belong to the post-CAST post-treatment-withdrawal class. Three cases of fatal cardiac arrest occurred in infants with structural heart disease reported in an as yet unpublished paper. The case reported in [redacted] and listed as "pharyngitis" was actually an instance of sudden death of undetermined cause in which pharyngitis was the only recognized disease condition immediately prior to death. The deaths reported in [redacted] and [redacted] one due to fatal neoplastic disease and the other credited to massive gastric hemorrhage, occurred in pts of unknown age and sex who had been enrolled in a three-drug anti-arrhythmic clinical study, and cannot be reasonably connected with the study drugs.

NARRATIVE OF ACTION TAKEN

Upon review of the accumulated adverse drug experience reports of the first four years of marketing, the inclusion of "Alopecia," "Peripheral Neurophathy" and "Cardiac Arrest" in the list of adverse drug experiences in the next revision of the Tambocor full prescribing information has been proposed.

S.K. Chun, 2/27/90
Sughok K. Chun, M.D. HFD-110

cc: Orig. NDA
HFD-110
HFD-110/CSO
HFD-110/SChun
ml:2/27/90:#2053a

Figure 1: NDA REPORTABLE FLECAINIDE TABLET CASES

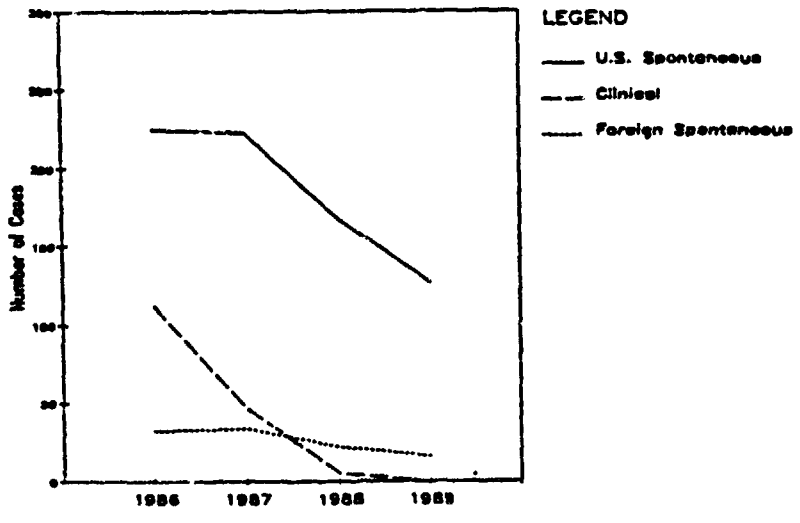
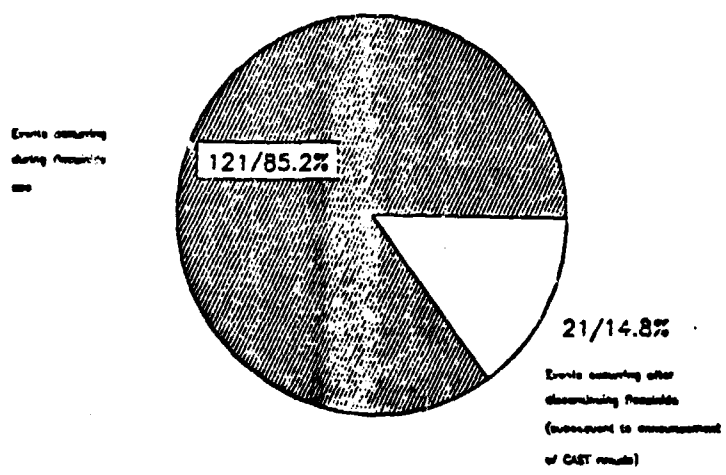


Figure 2:

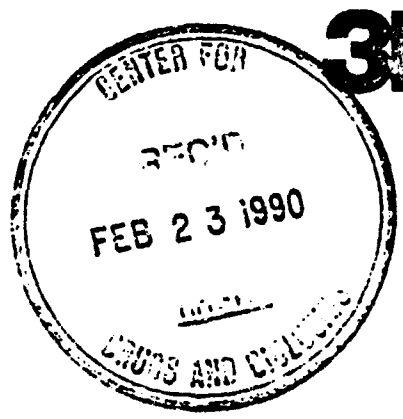
ADVERSE DRUG EXPERIENCE REPORTS



Regulatory Affairs
3M Pharmaceuticals

3M Center Bldg. 270-3A-01
St. Paul. MN 55144-1000
(612) 733-8824

ORIGINAL REPORTS



February 22, 1990

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir/Madam:

Pursuant to 21 CFR 314.80, enclosed is the Periodic ADR Report in duplicate for Tambocor® (flecainide acetate) NDA 18-830. There are 102 FDA 1639 forms in this submission, 95 of which are initial reports and 7 are follow-up reports.

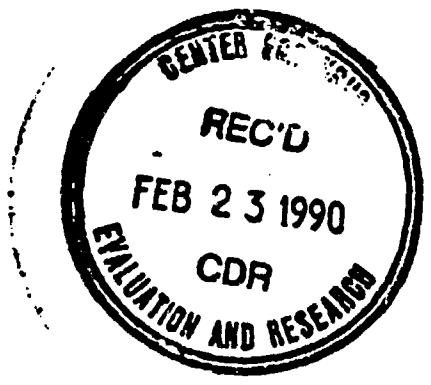
The time period covered by this report is December 11, 1988 through December 10, 1989.

Sincerely,

Gene L. Harris
Sr. Regulatory Coordinator

GLH/kjn

Desk copy: Dr. SK Chun (HFN-110)



F-013
110

2/26/90

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved. OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO	DA.	YR.
[redacted]	85	F	10	22	88

7. DESCRIBE REACTION(S)

***OVERDOSE* Death**
An investigation of a death in [redacted] is proceeding which may be related to the use of flecainide acetate.
This 85 y/o woman with a history of a cerebrovascular accident in April 1988 was started on flecainide acetate on 21Oct88. The next day she was found dead at 9:30am and it was determined she had taken about 20 100 mg tablets of flecainide. An autopsy was conducted about 24 hours later and a blood sample collected at that time from the inferior vena cava showed a flecainide level of 50.3 mcg/ml. Flecainide concentration in gastric contents was 116 mg(total) and in liver was 452 mcg/g. The cause of death was listed as flecainide intoxication.

8.-12. CHECK ALL APPROPRIATE.

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X **OVERDOSE**

13. RELEVANT TESTS/LABORATORY DATA

Please see #7 above.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: **2000 MG**

16. ROUTE OF ADMINISTRATION: **ORAL**

17. INDICATION(S) FOR USE: **UNKNOWN**

18. DATES OF ADMINISTRATION (From/To): **10/22/88 - 10/22/88**

19. DURATION OF ADMINISTRATION: **ONE DOSE**

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: [redacted] **/18-830**

24b. MFR. CONTROL NO: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: **1/ 4/89**

24d. REPORT SOURCE *(Check all that apply)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT?
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE. Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26c. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	65	M	01		89

7. DESCRIBE REACTION(S)

Death, cause unknown
This 65 y/o man with a long history of ventricular arrhythmias and recent sustained ventricular tachycardia was started on flecainide acetate 100mg bid in January 1989. Concomitant medication was digoxin. About 2 weeks after therapy started he was found slumped over in his yard dead. The physician suspects a heart attack but the actual cause of death was not objectively substantiated.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE:

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

DATES OF ADMINISTRATION (From/To): 01/ /89 - 01/ /89

19. DURATION OF ADMINISTRATION: 2 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144 1000

24a. IND NDA NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR. CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 3/ 6/89

24d. REPORT SOURCE *(Check all that apply)*

[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT?

[ ] YES [X] NO

25a. REPORT TYPE

[X] INITIAL [ ] FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

FORM FDA 1639 (7/86) PREVIOUS EDITION MAY BE USED

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	32	F	--	--	--

7. DESCRIBE REACTION(S)

VENTRICULAR FIBRILLATION - Death
This 32 y.o. woman had a several year history of idiopathic hypertrophic subaortic stenosis when she began experiencing paroxysmal atrial fibrillation, especially when she had been ingesting ethanol. Eliminating ethanol consumption resolved the matter, but gradually the atrial condition began appearing spontaneously. For reason of side effects/lack of efficacy the patient was unable to take disopyramide, sustained release procainamide, or quinidine. Good control was obtained with 100mg flecainide bid, but gradually PAF "broke through". The dose of flecainide was increased until, after 3 months on the drug, she was stabilized on 200mg bid (400mg/day). She was found slumped in the shower one day

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE.

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: 400 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: ATRIAL FIBRILLATION

18. DATES OF ADMINISTRATION (From/To): 01/10/89 - 04/10/89

19. DURATION OF ADMINISTRATION: ~3 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR. CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 3/27/89

24d. REPORT SOURCE *(Check all that apply)*: ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 5 DAY REPORT? ☐ YES ☒ NO

25a. REPORT TYPE: ☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S)

and seen by the emergency crew who found her in ventricular fibrillation from which she could not be resuscitated. Her physician recalled that flecainide serum concentrations obtained a week before death were within reasonable therapeutic range, but (unusual) the QRS had shown no widening despite control of the arrhythmia. The patient was receiving no other medication.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE.

- ☐ PATIENT DIED
- ☐ REACTION TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. DATES OF ADMINISTRATION *(From/To)*

19. DURATION OF ADMINISTRATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND NDA NO. FOR SUSPECT DRUG

24b. MFR. CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check all that apply)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT?
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	55	F	04		89

7. DESCRIBE REACTION(S)

***DEATH* Cause Unknown**
This 55 y/o woman was being treated with flecainide acetate at 100 mg bid. Her brother reported that she died "just prior" to the media announcement of 25Apr89 regarding change in indication. The only other information given was that she had been treated for 2-3 years and there were no concomitant medications.

8.-12. CHECK ALL APPROPRIATE:

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: CARDIAC DYSRHYTHMIA NOS

18. DATES OF ADMINISTRATION (From/To): / /?? - 04/ /89

19. DURATION OF ADMINISTRATION: 2-3 YEARS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR. CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/24/89

24d. REPORT SOURCE *(Check all that apply)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☒ CONSUMER

25. 15 DAY REPORT?
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

REFUSED TO TELL

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

FORM FDA 1639 (7/86) PREVIOUS EDITION MAY BE USED

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	48	M	06	12	89

7. DESCRIBE REACTION(S)

DEATH, OVERDOSE
This 48 y.o. man with a history of exercise induced arrhythmia was started on flecainide acetate therapy in 1986 for premature ventricular contractions. Concomitant medication was enalapril maleate & allopurinol. His present dose was 400 mg/day. On the day of death (12JUN89) it was estimated he should have had 12 100 mg tablets left, but they were all gone. A serum flecainide level obtained 16 hours postmortem was about 52.5 mcg/ml (normal is 0.2-1.0 mcg/ml).

13. RELEVANT TESTS LABORATORY DATA

See #7, above.

8.-12. CHECK ALL APPROPRIATE:

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- [X] **OVERDOSE**

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: **400 MG**

16. ROUTE OF ADMINISTRATION: **ORAL**

17. INDICATION(S) FOR USE: **VENTRI PREMATURE BEATS**

18. DATES OF ADMINISTRATION (From/To): **/ /86 - 06/12/89**

19. DURATION OF ADMINISTRATION: **3+ YEARS**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ENALAPRIL MALEATE **ALLOPURINOL**

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted] **/18-830**

24b. MFR. CONTROL NO: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: **6/14/89**

24d. REPORT SOURCE *(Check all that apply)*: ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT? ☐ YES ☒ NO

25a. REPORT TYPE: ☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1 PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	46	F	05	12	89

7 DESCRIBE REACTION(S)

SUDDEN DEATH, CAUSE UNKNOWN
This 46 year old woman had medical history of myocardial infarction at age 30, and again 3/1/88. Holter monitoring in March '89 revealed a ventricular tachycardia that was classified as potential lethal. For that reason flecainide 50mg bid was added to her medication regimen (digoxin, diltiazem, hydrochlorthiazide). Her subsequent course was benign, until the 25APRIL89 NIH announcement of the CAST Trial results caused her physician to advise her to discontinue flecainide on 5/2/89, substituting quinidine 300mg bid. On awakening 5/12/89 she turned off her alarm clock and promptly expired.

13 RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE:

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15 DAILY DOSE: 100 MG

16 ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: PAROX VENTRIC TACHYCARD

18 DATES OF ADMINISTRATION (From/To): 03/09/89 - 05/02/89

19 DURATION OF ADMINISTRATION: 8 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22 CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN
DILTIAZEM HCL
HYDROCHLOROTHIAZIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

See #7 above

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24 NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a IND/NDA NO. FOR SUSPECT DRUG: [redacted]/18-830

24b. MFR CONTROL NO.: [redacted]

24c DATE RECEIVED BY MANUFACTURER: 7/18/89

24d REPORT SOURCE *(Check all that apply)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT?
[ ] YES [X] NO

25a REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b TELEPHONE NO. *(Include area code)*: [redacted]

26c HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFH-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO	DA.	YR
[redacted]	---	M	05		89

7. DESCRIBE REACTION(S)

DEATH, CAUSE UNKNOWN
This man had been on flecainide acetate therapy for about one year when the physician determined the need to change therapy due to the change in indication for flecainide. The flecainide dose was tapered down and stopped. The weekend intervened before another drug was started; he worked in the yard on Sunday and died that day.

8.-12. CHECK ALL APPROPRIATE:

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
CARDIAC DYSRHYTHMIA NOS

18. DATES OF ADMINISTRATION (From/To)
/ / - / /

19. DURATION OF ADMINISTRATION
ONE YEAR

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR. CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
5/23/89

24d. REPORT SOURCE *(Check all that apply)*
- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [X] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT?
- [ ] YES [X] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

FORM FDA 1639 (7/86) PREVIOUS EDITION MAY BE USED

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	56	M	05	05	89

7. DESCRIBE REACTION(S)

SUDDEN DEATH, CAUSE UNKNOWN
This 56 y.o. man had history of coronary bypass surgery in the past. In DEC88 he underwent coronary angioplasty. He was judged to be in Class II failure. A 24 hour Holter in JAN89 showed more than 28 runs of bigemini and trigeminy and several runs of sustained ventricular tachycardia. On about 3MAY89 at his physician's direction he stopped taking flecainide, which he had taken since JAN/FEB89, and was to have another Holter one week thereafter. However, two days after discontinuation (i.e. ~5MAY89) he was found dead.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE:

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS, VENTRICULAR TACHYCARDIA

18. DATES OF ADMINISTRATION (From/To): JAN89 - 05/03/89

19. DURATION OF ADMINISTRATION: ~4 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*
Please see #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR. CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/18/89

24d. REPORT SOURCE *(Check all that apply)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT?
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	05	01	89

7. DESCRIBE REACTION(S)

SUDDEN DEATH, CAUSE UNKNOWN
This patient stopped flecainide upon hearing the news 25APR89. Died suddenly 6 or 7 days thereafter. One of 3 such cases in this practice of 3500 patients -- 300-400 of which are estimated to be taking flec.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE:

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) RX: VENTRICULAR ARRHYTHMIA

18. DATES OF ADMINISTRATION (From/To): UNKNOWN - 04/25/89

19. DURATION OF ADMINISTRATION: UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG: [redacted]/18-830

24b. MFR. CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/22/89

24d. REPORT SOURCE *(Check all that apply)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT?
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4. REACTION ONSET MO.	DA.	YR.
[redacted]	----	M	05	19	89

7. DESCRIBE REACTION(S)
VENTRICULAR FIBRILLATION; DEATH
This man stopped taking flecainide upon hearing the 25APR89 news reports. Two weeks later he collapsed with ventricular fibrillation and died.

8.-12. CHECK ALL APPROPRIATE:
- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. DATES OF ADMINISTRATION (From/To)
UNKNOWN - 04/25/89

19. DURATION OF ADMINISTRATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR. CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
5/22/89

24d. REPORT SOURCE *(Check all that apply)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT?
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

FORM FDA 1639 (7/86) PREVIOUS EDITION MAY BE USED

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1 PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	48	F	05	18	89

7 DESCRIBE REACTION(S)

SUDDEN DEATH, CAUSE UNKNOWN
This 48 y.o. woman had history of myocardial infarction 5-6 yrs ago with coronary artery bypass. Ventricular tachycardia since then was not controlled with quinidine or procainamide, but had been on flecainide the past 18mos with good control and tolerance. Discontinued flecainide with news announcement and put on quinidine. Patient died suddenly 2 weeks later.

8.-12. CHECK ALL APPROPRIATE:

- [x] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13 RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15 DAILY DOSE
UNKNOWN

16 ROUTE OF ADMINISTRATION
ORAL

17 INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

DATES OF ADMINISTRATION (From-To)
UNKNOWN - 05/18/89

19. DURATION OF ADMINISTRATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24 NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a IND NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR. CONTROL NO.
[redacted]

24c DATE RECEIVED BY MANUFACTURER
5/25/89

24d. REPORT SOURCE *(Check all that apply)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT?
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE. Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26-25a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1 PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	15	M	03	20	89

7 DESCRIBE REACTION(S)

***OVERDOSE* Death**
This 15 y/o male was despondent because he broke up with his girl friend He swallowed 10-15 flecainide acetate 100 mg tablets from his father's prescription bottle. he had no history of suicide attempts and he did not leave a note. Autopsy found healthy organs with no cause of death identified; the stomach contained brown fluid with white flecks. Postmortem samples were obtained about 11 hours following death. Flecainide levels were as follows: Heart blood - 10.6 mcg/ml; gastric contents - 11.4 mg(total); liver - 145 mcg/g.

13 RELEVANT TESTS LABORATORY DATA
See 7, above.

8.-12. CHECK ALL APPROPRIATE.

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

X **OVERDOSE**

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15 DAILY DOSE	16. ROUTE OF ADMINISTRATION
10-15 TABS	**ORAL**

17 INDICATION(S) FOR USE
UNKNOWN

18 DATES OF ADMINISTRATION (From/To)	19. DURATION OF ADMINISTRATION
03/20/89 - 03/20/89	**ONE DOSE**

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21 DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22 CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*
See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24 NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a IND NDA. NO. FOR SUSPECT DRUG	24b. MFR. CONTROL NO.
[redacted] /18-830	[redacted]

24c DATE RECEIVED BY MANUFACTURER	24d REPORT SOURCE *(Check all that apply)*
8/11/89	☐ FOREIGN ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

15 DAY REPORT?	25a REPORT TYPE
☐ YES ☒ NO	☒ INITIAL ☐ FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

FORM FDA 1639 (7/86) PREVIOUS EDITION MAY BE USED

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	69	F	05	12	89

7. DESCRIBE REACTION(S)

DEATH, CAUSE UNKNOWN
This 69 y.o. woman had long history of chronic obstructive pulmonary disease, cor pulmonale, hypertension and had had heart failure in MAR89. The patient also had hypercholesterolemia. For ventricular bigeminy she had received several antiarrhythmics, but could not tolerate them, when she was started on 14APR89 on flecainide 100mg tablets bid. She tolerated these well and responded well to them. Ongoing medications included theophylline, digoxin, furosemide, probucol and diclofenac. On 5MAY89 following announcement of Cardiac Arrhythmia Suppresion Trial results flecainide was discontinued and replaced with quinidine. On 12MAY89 she was found dead in bed.

13. RELEVANT TESTS LABORATORY DATA

On 31MAR89 plasma digoxin was normal at 1.3. On 14APR89 serum potassium was normal at 4.4.

8.-12. CHECK ALL APPROPRIATE:

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: **200 MG**

16. ROUTE OF ADMINISTRATION: **ORAL**

17. INDICATION(S) FOR USE: **VENTRI PREMATURE BEATS**

DATES OF ADMINISTRATION (From/To): **04/14/89 - 05/12/89**

19. DURATION OF ADMINISTRATION: **1 MONTH**

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

PROBUCOL
DIGOXIN
DICLOFENAC SODIUM
THEOPHYLLINE
FUROSEMIDE
QUINIDINE SULFATE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

Please see #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG: [redacted] **/18-830**

24b. MFR. CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: **9/ 2/89**

24d. REPORT SOURCE *(Check all that apply)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT?
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1 PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	73	F	06	05	89

7 DESCRIBE REACTION(S)

DEATH, CAUSE UNKNOWN
This 73 y.o. woman had long history of heart disease treated on 07JUL88 with mitral valve replacement.She received dipyridimole, digoxin, triamterene/hydrochlothiazide, and potassium supplement. About MAR89 she was given flecainide 100mg bid for arrhythmia (type uncertain) and thereafter grew very tired. On 05JUN89, while alone in the bathroom she died. No autopsy was obtained.

13 RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE.

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: **200 MG**

16. ROUTE OF ADMINISTRATION: **ORAL**

17 INDICATION(S) FOR USE: **CARDIAC DYSRHYTHMIA NOS**

18. DATES OF ADMINISTRATION (From/To): **03/??/89 - 06/05/89**

19. DURATION OF ADMINISTRATION: **3-4 MOS**

20 DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22 CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIPYRIDAMOLE
DIGOXIN
TRIAMTERENE, HYDROCHLOROTHIAZIDE
POTASSIUM CHLORIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

Please see #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24 NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a IND NDA NO. FOR SUSPECT DRUG: [redacted] **/18-830**

24b. MFR. CONTROL NO.: [redacted]

24c DATE RECEIVED BY MANUFACTURER: **8/18/89**

24d. REPORT SOURCE *(Check all that apply)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [X] CONSUMER

15 DAY REPORT?
[ ] YES [X] NO

25a REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26 -26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

NOTE: Required of manufacturers by 21 CFR 314.80

FORM FDA 1639 (7/86) PREVIOUS EDITION MAY BE USED

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-			

7. DESCRIBE REACTION(S)

DEATH, CAUSE UNKNOWN
Initial information suggests a child (age not specified) died about DEC87 while being treated with flecainide acetate. Further information is being sought.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE.

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines & biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15. DAILY DOSE: **UNKNOWN**

16. ROUTE OF ADMINISTRATION: **UNKNOWN**

17. INDICATION(S) FOR USE: **UNKNOWN**

18. DATES OF ADMINISTRATION (From/To): **/ / - ??DEC87**

19. DURATION OF ADMINISTRATION: **UNKNOWN**

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG: [redacted] **/18-830**

24b. MFR. CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: **9/20/89**

24d. REPORT SOURCE *(Check all that apply)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☒ CONSUMER

15 DAY REPORT?
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOW-UP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1 PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3 SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	06	??	89

7 DESCRIBE REACTION(S)

SUDDEN DEATH, CAUSE UNKNOWN
While on a speaking engagement reporter was approached by a physician (identity unknown) who told of a male patient who was discontinued from flecainide acetate tablets in JUN89 and died suddenly 5 to 7 days later. It is unlikely that any further information will be obtained.

Case is also referred to in a news article of 11SEP89: Doctors Decry Drug 'Panic' Story. Medical World News. page 16.

8.-12. CHECK ALL APPROPRIATE.

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13 RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

15 DAILY DOSE
UNKNOWN

16 ROUTE OF ADMINISTRATION
ORAL

17 INDICATION(S) FOR USE
UNKNOWN

18 DATES OF ADMINISTRATION (From/To)
UNKNOWN - 06/??/89

19. DURATION OF ADMINISTRATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22 CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23 OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*
Patient had originally been put on flecainide after electrophysiological studies showed that drug to control his arrhythmia.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24 NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a IND NDA NO FOR SUSPECT DRUG
[redacted] /18-830

24b MFR CONTROL NO.
[redacted]

24c DATE RECEIVED BY MANUFACTURER
9/13/89

24d REPORT SOURCE *(Check all that apply)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25 15 DAY REPORT?
[ ] YES [X] NO

25a REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

25-25a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

25b TELEPHONE NO *(Include area code)*
[redacted]

25c HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

25d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1 PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	23	F	10	30	89

7 DESCRIBE REACTION(S)

***SUICIDE* Death**
This 23 y.o. woman was started on flecainide about a year ago as prophylactic treatment of cardiac arrhythmia related to mitral valve prolapse, but was told to discontinue flecainide a while back. On 30OCT she was found dead. The body showed signs that she had suffered some sort of assault several days earlier. Forensic toxicologic investigation revealed the presence of flecainide in blood, stomach contents & liver, in amounts greater than would be accounted for by a normal therapeutic dose (see item 13, Lab. Data). No other drugs were detected. It is estimated that the samples were collected 24-48 hours post mortem.

13 RELEVANT TESTS LABORATORY DATA

Post mortem flecainide concentrations, 24-48 hours post mortem:
Cardiac blood: 13.4mcg/ml* (therapeutic range: 0.2-1.0mcg/ml)
Liver: 173mg/kg
Stomach contents: 123mg in 60ml.
***Concentration of flecainide in blood always increases post mortem.**

8.-12. CHECK ALL APPROPRIATE:

- [X] PATIENT DIED
- [ ] REACTION TREATED WITH Rx-DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR 100 MG TABLET/FLECAINIDE ACETATE

20 DID REACTION ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO ☒ NA

15 DAILY DOSE	16. ROUTE OF ADMINISTRATION
?	ORAL

17. INDICATION(S) FOR USE

CARDIAC DYSRHYTHMIA NOS, MITRAL VALVE DISORDER

DATES OF ADMINISTRATION (From To)	19. DURATION OF ADMINISTRATION
/ / - / /	UNKNOWN

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24 NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

3M PHARMACEUTICALS
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a IND NDA NO. FOR SUSPECT DRUG	24b MFR CONTROL NO.
[redacted] /18-830	[redacted]

24c DATE RECEIVED BY MANUFACTURER	24d REPORT SOURCE *(Check all that apply)*
11/15/89	☐ FOREIGN ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

25c. 15 DAY REPORT?	25a. REPORT TYPE
☐ YES ☒ NO	☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b TELEPHONE NO *(Include area code)*

[redacted]

26c HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

☐ YES ☐ NO

26d ARE YOU A HEALTH PROFESSIONAL?

☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

HFN-410

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DAT 8/26/85
FROM: Ray Lipicky, M.D		OFFICE ODRR
TO: Robert Temple, M.D.		DIVISION HFN-110
SUBJECT: Flecainide Approval		Page 1 of 4

SUMMARY

I have read your memo of 8/20/85 and related materials to the flecainide approval and have had a brief discussion with Dr. Chen who was not entirely satisfied with my answers and will be contacting you to express her point of view.

I am embarrassed by your having had to pull all of that death information and pro-arrythmia information together into some digestable form. My apologies for that.

I don't see a real relationship to dose in the crude numbers. About 4.1% of deaths due to proarrhythmia were at doses less than 400 mg (i.e. 200 or 300 mg), 45% were at doses of 400 mg, and 14% were at doses greater than 400 mg (i.e., doses of 500 or 600 mg). Of course one would like to know the population at risk at those doses and the data has not been broken out that way for all patients. There is some information though.

The red binder has Riker's response to some questions I raised, a rather global look, but the question entitled "what phenomena are observed if the recomended dose titration regimen is not followed?". My overall interpretation of that analysis is that rapid, early increases in dose or large early doses is the culprit. The daily dose at steady state doesn't seem to matter.

SIGNATURE	DOCUMENT NUMBER
Ray Lipicky Page 4 of 4	

FORM FD 2034 (6-76)

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DAT 8/25/88
FROM: Ray Lipicky, M.D.		OFFICE ODRR
TO: Robert Temple, M.D.		DIVISION HFN-110
SUBJECT: Flecainide Approval Page 2 of 4		

SUMMARY

In fact, figure 1 (% of ongoing patients) says to me, that all of the action is early and after the first couple of weeks no real differences are observable. This doesn't really make sense to me ~~but~~ so it did not become a point to focus on. But I think is data that makes early dosing (amount or change) an likely a candidate as dose alone. Moreover, it says that the likelihood of a proarrhythmic event at 200 mg is about as big as at 600 mg. Also doesn't make sense. I guess I believe neither because it has not been adequately defined.

The red jacket and safety update should answer your questions about 057 amended. Another review has not been done (if you disagree we will do one).

I am comfortable with the labelling indication as written. I am not sure any idea I have is any better than the one you have composed. Some obvious problems exist.

a) Defining life-threatening is not really possible. Sustained VT in a normal

SIGNATURE	DOCUMENT NUMBER
Ray Lipicky Page 2 of 4	

FORM FD 1034 (6/76)

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DAT. 8/25/86
FROM: Ray Lipicky, M.D.		OFFICE ODRR
TO: Robert Temple, M.D.		DIVISION HFN-110
SUBJECT: Flecainide approval		Page 3 of 34

SUMMARY

heart is not necessarily life threatening and non-sustained VT in a patient with a tight mitral stenosis could be devastating with each bout. Clearly there is no cited phrase that covers all possibilities.

b) Q am not sure it is not an over-reaction to an uncontrolled set of observations. One could say for "for symptomatic ventricular arrhythmias that deserve therapy" and go on to develop words that contrast treatment benefit/risks in some obvious categories such as asymptomatic uniform VPBs and contrasted to symptomatic uniform VPBs contrasted to symptomatic multiform VPBs in the presence of known structural heart disease in smokers, who are obese and have an elevated lipid profile, etc.

c) The litany of possible circumstances is infinite and one can only get agreement at absolute limits. In between the limits, experts disagree a lot.

d) Q guess all in all Q view the labelling as constructed as alarmist.

SIGNATURE Ray Lipicky Page 3 of 34	DOCUMENT NUMBER

FORM FD-2034-(6/76)

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 8/25/85
FROM: Ray Lipicky, M.D.		OFFICE ODRR
TO: Robert Temple, M.D.		DIVISION HFN-110
SUBJECT: Flecainide approval Page 4 of 4		

SUMMARY

However, I must agree I am confused and alarmed. I have no reasonable alternative to suggest.

I have no suggestion, at the moment, as to what studies would be required to loosen the label. I would prefer to wait until after the October arrhythmia guideline meeting, the December CR committee meeting, amiodarone approval and encainide, mexiletine approval (not necessarily in that chronological order) before making any definative statement. At first blush, several controlled clinical trials (mortality endpoints) in serious and benign arrhythmias will be necessary.

I probably have not helped much. I do believe flecainide is approvable. You, I and the entire medical community are struggling with unknowns. No one knows why to use an antiarrhythmic, how to use them, or exactly how to develop them. However, no one (especially me) thinks they should not be available. "Alarmist" labeling is an appropriate middle road given the circumstance. I am not convinced it is correct.

SIGNATURE	DOCUMENT NUMBER
Ray Lipicky Page 4 of 4	

FORM FD 203 (6-76)

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

Date : SEP 6 1985

From : Director
Office of Drug Research and Review/HFN-100

Subject: Flecainide, NDA 18-830

To : Acting Director
Division of Cardio-Renal Drug Products/HFN-110

Your memo of August 25, 1985 does convey the difficulty of the labeling decision with respect to flecainide. There is only one point I would like to review and that is the possibility that there is a dose-response relationship for pro-arrhythmic deaths. In the available data most instances of pro-arrhythmic events, fatal and non-fatal, and deaths that could have represented pro-arrhythmic events, occurred at relatively high doses of 400 mg or more. I do not believe that proves the existence of a dose response relationship because in most of the trials 400 mg was the starting dose and there was no opportunity to examine the lower dose. Nonetheless, and taking that into account, of 14 designated pro-arrhythmic deaths, ten used doses of 400 mg or more. Considering all of the designated pro-arrhythmic events (other than the increased VPBs) I count 27 of the 38 such events (most of them worsening of ventricular tachycardia) to have involved doses of 400 mg or more, not counting the events that occurred in study 057 amended. Considering other arrhythmic in hospital deaths that were not considered pro-arrhythmic events, seven of the eight were on doses of least 400 mg. Taking the out of hospital deaths, other than those attributed to pro-arrhythmic events, 12 of the 22 patients who sustained such events were on at least 400 mg. I am not sure of the doses the pro-arrhythmia 057 patients on the amended protocol were getting, but, as very few of them received doses as high as 400 mg, it may be safely presumed that they were not receiving 400 mg. The pro-arrhythmia rate was about 10% in study 057 amended, only slightly lower then that in the 028 and 057 protocols but none of the patients in these studies died, as contrasted with the 14 pro-arrhythmia patients who died in the course of the 028 and 057 protocols when higher doses were routinely used.

I certainly would not be prepared to argue that this proves that the higher doses are more likely to cause fatal pro-arrhythmic events, or that this information excludes the possibility that the rate of rise of the dose (as opposed to the final dose itself) is the critical measurement in making the 057 amended dosing regimen safer than the regimens used in 028 and 057. Nonetheless, I think it seems safest to say at this point that one should try to use both a relatively low starting dose and a relatively low maximum dose of 400 mg where possible. It is noticeable that in the 057 amended study, less than 10% of patients actually needed to be titrated to doses beyond 300 mg. It is possible, I suppose, that the success rate would have been higher if higher doses had been used but the higher doses were not used even though the protocol allowed doses of up to 400 mg.

I certainly agree that most of the serious problems that emerged with flecainide did emerge early and, fortunately, because patients were hospitalized at this time in the 057 protocol, it was possible to treat most of them successfully. This in fact is one of the important sources of my view that only serious arrhythmias suitable for treatment in a hospital should be treated with flecainide. It is not easy to believe that patients with lesser severities of arrhythmias could be hospitalized for the more than one week period of time needed to titrate flecainide properly and I would be very concerned about the introduction of large numbers of patients to the drug in any other manner. Obviously, as we know from the flecainide/quinidine comparison, clinical trials in a relatively well population can be carried out in an outpatient setting without significant risk. The difference arises when you move from a study involving a 2-3 hundred people to marketing status where you involve many thousands. My concern is that if we were to encourage treatment of patients with less severe arrhythmias, among the many thousands of patients whose therapy was initiated would be some unnecessary morbid events. In any case, additional data will be arising from the CAPS study, and perhaps from trials that Riker will be interested in carrying out, in patients with less severe arrhythmias.

Robert Temple, M.D.

cc:
Orig. NDA 18-830
HFN-110 CSO
HFN-1[illegible] Division File ✓

CDRR/RTemple/md
8-29-85 CORRed
F/T: md/9/3/85

6.1

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

Date : AUG 20 1985

From : Director
Office of Drug Research and Review/HFN-100

Subject: Flecainide, NDA 18-830

To : Acting Director
Division of Cardio-Renal Drug Products/HFN-110

I. Introduction

I have completed my look at flecainide and, as you forewarned, it poses some very difficult problems, many of them more related to the use of anti-arrhythmic drugs in general than to flecainide specifically. These include:

1. The best designed studies were not in the patient population most likely to benefit from the drug.

   The best evidence of anti-arrhythmic effectiveness and comparability or superiority to alternative agents comes from patients with "benign" VPBs (benign in that, prior to study, the patients had not arrested, even if non-sustained VP was fairly often seen on Holter). We know that flecainide is a wonderfully effective suppressor of VPB's, complets, and non-sustained VP, superior to quinidine and disopyramide in the single short term studies carried out and, undoubtedly, superior in long-term use as well, as the effects do not seem to diminish over time in the open studies. We do not know, of course, whether this effectiveness is of value in enhancing survival, as no anti-arrhythmic agent, including flecainide has been shown to decrease mortality in such patients. Even these short term studies show that flecainide can cause CHF and serious brady-arrhythmias and, occasionally, serious new ventricular arrhythmias.

2. The controlled studies in patients with frequent VPBs were very short and, while of adequate size for an effectiveness study, they were not long enough or big enough to assess adequately the potential for

pro-arrhymicity and other adverse effects in this population. The longer-term uncontrolled extensions of these trials added to the evidence of the short-term study suggesting a pro-arrhythmic potential (see below for details) and an ability to cause other problems such as sinus node dysfunction and brady-arrhythmias and heart failure, but these potentials cannot be evaluated adequately because of the lack of a control population.

3. Studies in seriously ill patients show that flecainide can both suppress life-threatening arrhythmias and cause them. The uncontrolled nature of these studies (probably unavoidable, and, in any event, standard practice) leaves uncertainty about the "net benefit". The studies certainly show, however, that many patients who unequivocally were at risk of death from their arrhythmia (sustained VT, often with a history of need for resuscitation, i.e., a "history of sudden death") were helped by flecainide, based on decreased episodes of hemodynamically unstable VT or on loss of VT-inducibility on PES testing. On the other hand there is little doubt that some seriously ill patients are harmed by the drug, with fatal consequences in some cases.

4. Attempts to reduce the pro-arrhythmic risk by dosage adjustment seem at least partially successful, and perhaps have been fully successful, but it is difficult to know this from the studies carried out.

During the early stages of evaluation of flecainide in seriously ill patients (virtually all had documented sustained, hemodynamically important VT) a major problem developed, viz, a cluster of patients who seemed to deteriorate substantially, either developing new arrhythmias or arrhythmias that proved more difficult or impossible to reverse despite prompt medical management in a sophisticated environment. After an interruption of studies a new dosing regimen, with lower starting dose, slower titration, and a lower top dose was developed, with a clearly better outcome in the very ill patients of protocol 057 amended. The difference in final dose between the two regimens, is not large and needs interpretation. The sponsor emphasizes the lower top dose of 400 mg vs. 600 in the early studies. But while the early studies did use up to 600 mg, most patient got only 400 mg and many problems were seen at that dose. The new regimen allowed up to 400 mg but in fact only 7 of 96 patients received that much, the rest stopping at 300 mg or less. Study 057 amended does appear to support the new regimen up to 300 mg but it seems likely that the safety of the 400 mg dose has not really been explored.

5. It is of interest that Winkle and Mason's experience with encainide is quite similar to the flecainide experience [Am. Heart J, 1981, 102:

857-864]. In 90 patients with sustained VT/VF, they found 10 (11%) early (very early, these are more impressive than the flecainide cases in that respect) serious new ventricular arrhythmias, many a polymorphic wide complex VT like that seen with flecainide. Among 47 patients without a history of sustained, hemodynamically important VT, they found one (2%) case of new VT needing resuscitation.

II. Evaluation of Proarrhythmic Events and Mortality Experience

The following analysis is based on Riker's written presentation to the Cardio-Renal Advisory Committee in June 1984 (a very excellent and candid exposition, I think) and Dr. Chun's review. The SBA is not helpful in this matter and needs to be revised.

A. Summary of pro-arrhythmic events and deaths by Study

1. Study 030 - 35 entered

Patient 030-02-001 DC flec because of 3 1/2-fold increase in VPB (not persuasive)

No deaths
No serious pro-arrhythmic events
Pro-Arrhythmic Rate = 0/35
Mortality = 0/35

2. Study 032 - 141 received flecainide
118 finished 2 weeks

a. Pro-arrhythmic events
032-08-006 (7d, 600 mg) New VT - not fatal
032-17-017 (7d, 400 mg) New NSVT - not fatal
032-05-009 - minor increase, about 50% - (not persuasive)
032-17-021 - single ECG showed marked increase over baseline Holter

b. Death
032-06-004 - Died of VT 36 hr after last dose (not persuasive)

c. Other events, not fatal, not considered pro-arrhythmic, but leading to discontinuation
032-02-23 - junctional bradycardia, syncope
032-06-14 - bradycardia, junctional rhythm, fainting

Overall rate, drug-related events = 5/141
new VT rate = 2/141
new sustained VT = 1/141
Mortality = 1/141

3. Study 060 - 32 patients

1 SD while dancing following nearly two weeks of treatment
1 episode of VF after possible AMI

Event rate = 2/25
Mortality Rate = 1/25

4. Study 031 - 29 patients

No pro-arrhythmic events
1 SD at 25 months (not persuasive)

Pro-arrhythmia rate = 0/29
Mortality = 1/29

5. Study 033 - 198 patients

a. Pro-arrhythmic events

*033-13-015 (7d, 400 mg) on Quin in 032, no hx of VT, found in continuous VT
033-14-006 (3 mos, 300 mg) Hx NSVT, but got VT on Quin, always PES-inducible. VT/VF after aprindine started-fatal-(not persuasive)
*033-17-012 (22d, 400 mg) Hx 3-beat; developed difficult to reverse VT with prolonged QT (0.42→0.54). Similar event on procainamide.
*033-04-009 (3d, 300 mg) sinus pause and junctional escapes and bradycardia
*033-07-008 (6 wk, 300 mg) new SVT with angina
*033-16-005 (8 wk, 400 mg) sinus arrest with slow junctional escape rhythm
*033-12-024 (31d, 600 mg) second degree AVB
*033-01-002 (3 mos, 400 mg) sick sinus synd.

b. Deaths

033-06-005 (30d, 400 mg) - Off flec x 5 days
033-06-98 (8 1/2 mos, 400 mg) - Prog CHF, then VT/VF (not persuasive, too long a period on drug)

033-02-001 (16 mos, 400 mg) found dead - (too late to be persuasive)
*033-02-007 (21d, 200 mg) - Asystole, no hx VT
033-06-007 (6 mos, 400 mg) - Died in sleep
033-11-002 (15 1/2 mos, 200 mg) - Died in sleep
033-13-008 (2 mos, 400 mg) - Collapsed at ballpark
*033-17-005 (4d, 400 mg) - Collapsed at picnic with resistant VT, no prior hx VT

The * marks those cases of death or arrhythmia that seem reasonably likely to be flecainide-related, and in particular, occurred early in the course of treatment (all within 8 weeks). In this relatively well population, with no history of cardiac arrest, an early sudden death in the absence of apparent AMI must be considered a possible pro-arrhythmic event. How life-threatening second degree AV block or slow junctional rhythmias are could be debated, and in this closely observed population, they did no lasting harm, but in a non-hospitalized, outpatient VPB population they represent a real risk.

Rate of pro-arrhythmic event (*) = 9/198

Rate of new VT or early SD/VT (*) 4/198
Rate of new VT or any SD/VT = 12/198

Without a control, of course, it is not possible to tell whether this is more or less than expected. Note also that only about 120 of the patients stayed on flecainide for a long period and that none of the suspect events involved doses above 400 mg per day.

6. Studies 028 and 057 prior to amendment.

Unlike the trials described above, patients in these studies were very sick. Nearly all had VT, often with history of resuscitation. In study 028, e.g., 198 of 228 patients had history of VT, 82 of them sustained VT and 40 "survivors of sudden death". Nearly all had failed to respond to other treatment. Study 057 had, if anything, even sicker patients, 38/39 significnt VT, 25/39 CHF. In study 057, only 30 patients were really treated with flecainide for any length of time, the other 9 being part of a multi-drug evaluation.

a. Pro-arrhythmic or possibly pro-arrhythmic events

These are analyzed in detail in Vol. 2 of the June submission for the Advisory Committee. Aside from 1 case

- Dr. Lipicky

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a. Pro-arrhythmic or possibly pro-arrhythmic events

These are analyzed in detail in Vol. 2 of the June submission for the Advisory Committee. Aside from 1 case

of increased VPBs there were 24 events considered possibly pro-arrhythmic by investigators, 9 of them fatal.

1) Fatal

Case	Daily Dose	Time	Prior VT	Prior Arrest	Prior MI	Prior CHF	EF	Event
028-12-101	600	7d	+	+	+	+	17%	VT/VF
028-14-112	400	5d	+	+	+	+	30%	Bradycardia
028-14-132	400	3d	+	+	+	+	25%	VT/VF
028-14-133	400	3d	+	+	+	+	12%	VT/VF
028-34-103	400	11d	+	+	+	+	28%	VT/VF
028-42-101	500	2d	+	0	+	+	15-18%	VT
028-43-003	400	5d	+	+	+	+	30%	VT
028-43-005	600	4d	+	+	+	+	20%	VT/VF
*028-72-103	200	4d	+	+	+	-	35%	VT

*Low dose and dose held prior to VT

What is striking about all of the cases is that they were early in the course of flecainide therapy and that patients could not be resuscitated even with prompt care and a history of resuscitability. Except for the last case, which seems unlikely to represent a flecainide-caused event, the doses were 400 mg (5), 500 mg (1), or 600 mg (2).

Several other deaths were arrhythmic and in-hospital, or out of hospital:

Case	Daily Dose	Time	Prior VT	Prior Arrest	Prior MI	Prior CHF	Event
in-hosp 028-14-114	250	6 mos	+		+	+	AMI, VT/VF, E-M dissoc.
in-hosp*028-14-123	500	5d	+	+	+	+	VT, not resusc
028-02-104	200	13 1/2 mos	+		+	+	Unobserved death
028-07-105	300	7 mos	-	-	+	-	Unobserved death
028-14-120	200	2 mos	+		-	-	Died during boat accident
028-55-101	400	1 1/2 mos	+		+	+	Collapse, ? VT/VF
*028-59-101	400	4 d	-	-	+	-	Collapsed at tennis
028-74-102	300	5 mos	+		-	-	Collapsed, 3 MI

Two of the deaths (*), while less well observed than the ones above, were early and occurred in a patient who had been resuscitable before (14-123) or who had never had VT (59-101).

They should, in my view, be added to the list of reasonably likely pro-arrhythmic deaths.

The 10 reasonably likely deaths occurred mostly in patients with prior history of VT (9/10) and prior arrests (8/10), a history of AMI (10/10) and CHF (9/10), and doses of 400-600 mg/day.

2) Non-fatal pro-arrhythmic events

Case	Daily Dose	Time	Prior VT	Prior Arrest	Prior MI	Prior CHF	Event
028-13-101	400	2 1/2 mos	+		+	?	Brady, Torsades, inc. QT
028-21-101	600	15 d	+		+	+	PES ind VT, harder convert
028-26-004	200	1 dose	+	+	+	-	VF harder to convert
028-26-010	200	9d	+		+	-	New morph VT, inc. QT
*028-26-011	300	7d	+		+	+	More freq VT
*028-27-002	300	4d	+		+	+	Rec. VT
028-28-004	300	4d	+		-	+	VT/VF; no VF before
028-33-103	400	7d	+		+	+	New, strange VT on PES
028-37-001	400	3d	+		+	+	Inc freq sust VT
028-37-003	400	9d	+	+	+	-	PES-ind VT degen to VF
028-44-103	400	3d	+		+	-	VT on exercise testing
028-44-104	400	3d	+		+	-	New wide VT, collapse
028-44-105	200	4d	+		+	+	New wide VT
028-87-101	400	1 1/2d	+		-	+	New polymorph VT
028-WD-101	600	32d	-	-	-	-	New VT, no Hx
028-14-129	400	1d					3° A-V block

*not clearly any change

Overall, counting 10 reasonably likely proarrhythmic deaths and all but two of the non-fatal cases (Two cases listed on page 212 of the June submission, case 13-001 and 14-130 say "prcarrhythmic events" occurred, but neither case appears in any list I could find so these are not counted),

Rate of pro-arrhythmic events	24/228
Overall arrhythmic mortality	17/228

The latter figure must be looked at in light of the substantial early drop-out rate; 139 of the 228 patientsd dropped out after an average of 2.3 months of treatment.

b. Non-arrhythmic cardiac deaths

There were 5 patients who had CF/low output deaths, not persuasively related to flecanide in every case,sometimes with arrhythmias complicating matters, and one patient who died of an AMI

Overall cardiac mortality = 23/228

Study 057:

a. Pro-arrhythmic events

1. Fatal

Case	Daily Dose	Time	Prior VT	Prior Arrest	Prior MI	Prior CHF	EF	Event
057-02-204	400	10d	+	-	+	+	46	New wide complex VT
057-02-205	300	24d	+	-	+	+	24	New wide complex VT
057-03-003	400	13d	+	+	+	+	28	VT/VF unresusc.
057-06-007	200	60d	+	+	+	+	24	Arrest at home
057-08-005	500	12d	+	+	-	+	?	VT/VF unresusc.

Again, these were early in the course of therapy and, along with some of the 028 cases, were perceived by the investigators as possibly drug-related and suggestive of a significant problem with induction of arrhythmias and/or a great increase in difficulty of resuscitation.

Other arrhythmic deaths included

Case	Daily Dose	Time	VT	Arrest	MI	CHF	Event
057-02-206	200	7 mos	+	+	-	+	SD, Holter never freed of V
057-02-201	(can't find record or details)						

2. Non-fatal pro-arrhythmic events

Case	Daily Dose	Time	VT	Arrest	MI	CHF	Event
057-10-004	600	3d	+		-	-	VT on ex test, reversed with difficulty
057-10-002	300	2d					Second degree A-V block

The rate of possible proarrhythmic events, omitting case 02-206, but counting A-V block was thus:

Pro-arrhythmic events = 7/30
Overall arrhythmic mortality = 6/30

b. Non-arrhythmic deaths

There appear to be no additional deaths

7. Study 035

It is hard to compare the extent of illness of these patients with patients in other trials. They did not need a history of VT but did need at least 500 VPBs per 24 hr, at least 5 VPBs in any one minute and at least one complet (or longer). That does not seem to be a very bad prognosis group, depending on other factors (history of recent AMI, etc.). While the patients do not seem to have been included in the pro-arrhythmia evaluation, several represent possible flecanide provoked arrhythmias.

a. Arrhythmic deaths

Case	Dose	Time	Prior VT	Prior Arrest	Prior MI	Prior CHF	Event
035-EN-03-203	400	4d	-	-	-	+	VT/VF, unresusc in hospital
035-EN-03-016	400	1d	+	+	+	+	VT harder to reverse
035-EN-03-006	300	8 mos	+	-	-	-	VT, Torsade
035-EN-03-209	300	14 mos	-	-	+	-	Chest pain and SD
035-EN-03-105	400	1 mo	-	-	+	-	Respir problem, collapse, possible AMI
035-EN-03-024	400	6d	+	+	+	+	Chest pain, death, probable AMI

One patient died of cancer.

At least the first 3 cases are potentially flecainide related, one of them having no prior history of VT/VF but developing it 4 days after flecainide and unresuscitable in the hospital.

Possibly Proarrhythmic rate 3/66
Mortality, cardiac 6/66

8. Study 057 amended

This study, by using a lower dose, slower titrating, and blood level monitoring, should be able to define a safe way to use flecainide, if there is one.

a. Pro-arrhythmic events

1) Fatal

No such events were identified.

2) Non-fatal

Ten patients were felt to have had proarrhythmic events, none fatal and generally less serious than those in studies 028 and 057. Nine had had prior sustained VT, one only non-sustained VT. Other details of history (dose, time) were not immediately available, although 7 of the 10 had the event during initial hospitalization. There were also two cases of third degree AV block. Doses in the study were not allowed to exceed 400 mg and most (all but 7) of the 66 patients discharged from the hospital had doses of 300 mg or less.

The events were:

Case	Event
057-06-104	Increased VPBs and NSVT
057-11-101	Increased VPBs and NSVT
057 ?	Increased VPBs and NSVT - late
057-01-102	VT more difficult to convert
057-01-105	VT more difficult to convert
057 ?	Arrhythmia (?) more difficult to convert
057-26-107	More easily induced sust VT, pacing needed
057-26-113	More easily induced NSVT, changed morphology
057-26-102	Inducible VT on PES, recurred next day
057-63-101	New spontaneous VT, diff't from baseline
057-12-113	Third degree A-V block
057-12-115	Third degree A-V block

b. Deaths

The June 1984 presentation lists 9 deaths (9.4%), 6 sudden deaths and 3 AMIs. Only 5 of these are detailed in the June 84 Vol, which contains a January 84 report on study 057 amended.

Case	Dose	Time	Prior VT	Prior Arrest	Prior MI	CHF	Event
057-01-101	400	2 1/2 mos	+	+	+	-	Collapsed while gambling
057-07-101	300	70d	+	+	+	+	SD at home
057-07-103	200	13d	+	-	+	+	Probable AMI
057-12-110	200	23d	NS			+	SD
057-31-102	?	about 3 mos	+	+	+	+	Probable AMI

If we accept all possible cases, and high degree block as pro-arrhythmic we have a rate of:

Proarrhythmia rate = 12/96 (12 1/2%)
Mortality rate = 9/96 (11%)

B. Overall summary of mortality and pro-arrhythmic events

1. Patients with history of VT and other evidence of severe cardiac disease (CFH, history AMI).

Study	Cardiac Mortality	Possible Pro-Arrhyth. fatal + NF (conduction problems)	Fatal Pro-Arrhyth.
028	23/228	24/228	10/228
057	6/30	7/30	5/30
057 Amend	9/96	10/96 (2)*	0/96

*2 cases third degree AV block

Let me emphasize that these are relatively gross numbers, uncorrected for time on therapy, etc. Follow-up for studies 028 and 057 is longer than 057 amended, for example, since they started earlier. On the other hand, the most recent follow-up for the 96 patients in 057 amended includes a mean duration of 8 months for the roughly 50% still in the study. Moreover, the most interpretable events are the early ones, which can be compared for the 3 studies.

What seems fairly striking is that the early, troubling fatal pro-arrhythmic events of studies 028 and 057 have not been seen in 057 amended; in fact, even the non-fatal events are rather less impressive. The subsequent experience with 057 amended has been similar, I gather, but I would like to see the safety update, or a more detailed review of it. (It should be reflected in the SBA too).

2. Patients without sustained VT and with less evidence of severe cardiac disease.

Study	Cardiac Mortality	Possible Pro-Arrhyth. fatal + NF (conduction problems)	Fatal Pro-Arrhyth.
030	0/35	0/35	0/35
032	1/141	3/141 (2)	0/141
060	1/25	?	?
031	1/29	0/29	0/29
033	9/198	4/198 (4)	2/198
035	6/66	3/66	3/66

While it is not possible to identify each event as flecainide-related or not, it is likely that some of the early serious arrhythmias seen in studies 033 and 035 were flecainide-related, principally because they arose shortly after therapy initiation in patients with no history of such arrhythmias. Of the 10 events, a rate of about 3% of exposed patients, only one occurred with a dose of less than 400 mg, although that could be misleading, as 400 mg was the lowest dose used. Whether lower doses would yield a better result is therefore not known.

There were, in addition, in these studies 6 cases of second or third degree A-V block, bradycardia/junctional rhythms with syncope, sinus pause, etc.).

III Conclusions

Despite its proarrhythmic potential, its ability to worsen CHF, and its ability to cause SA and AV block, flecainide has a role in the treatment of patients with life-threatening arrhythmias. With the recommended slow titration, limiting dose to 300-400 mg per day, and carrying out early therapy in hospital, it can manage some patients not treatable

with available agents, as evidenced by suppression of PES-induced VT/VF and prevention of recurrent spontaneous VT.

Although flecainide is very effective in suppressing VPBs, available data do not support its use in patients without life-threatening arrhythymias. While these patients are at a lesser risk of harm from flecainide than patients with serious arrhythmias, as much as 3% of them were worsened in trials to date. In the absence of clear evidence of benefit from flecainide (or other agents) in this setting, the limited evidence available cannot support approval and requires specific wording in labeling to discourage this use. It is possible future trials can amend this conclusion. (In the revised labeling given below you will note that whether non-sustained VT is "life-threatening" is left unclear. That was deliberate; physicians will have to decide for themselves.) While the above may moot the question, the proposed use of up to 600 mg per day in these patients, bears examination. The added response to such doses is small and they should probably not be used unless blood levels on 400 mg are shown to be quite low.

IV. Action

A. Letter to Riker (to follow paragraph 2)

We have completed review of this application as submitted with draft labeling. Before the application may be approved, however, it will be necessary to revise labeling substantially, in accord with the enclosed revised draft and, in addition, as follows:

1. Indications and Usage

At the present time, we believe flecainide should be indicated only for patients with life-threatening arrhythmias because of its pro-arrhythmic and other adverse potentials and should not be recommended for use in less severe arrhythmias. While the likelihood of provoking a new or more serious arrhythmia is greatest in patients with the most severe arrhythmias, it is in these patients that anti-arrhythmics, including flecainide, can offer a clear benefit, as indicated by an ability to suppress episodes of recurrent sustained ventricular tachycardia and inducibility of arrhythmias by programmed electrical stimulation.

Although it does so less frequently than in patients with serious arrhythmias, flecainide can have a pro-arrhythmic effect and cause worsened heart failure and conduction defects

in patients who do not have serious arrhythmias; there is no evidence that treatment of these lesser arrhythmias, such as frequent ventricular premature beats, has a favorable effect on mortality or sudden death. Additional study of flecainide in patients with these arrhythmias, including further and longer-term comparison with alternative agents, will be needed before use in such patients can be recommended. It also seems important to study doses below 400 mg, as most of the pro-arrhythmic events seen in patients without severe disease occurred at doses of 400 mg.

This section of labeling should therefore be revised to read:

Indications and Usage

Flecainide is indicated for the suppression of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

In view of its pro-arrhythmic effects (see Warnings) available data are too limited to support the use of flecainide in rhythm disturbances of lesser severity, such as frequent ventricular premature beats. No antiarrhythmic agent, including flecainide, has been shown to have a favorable effect on mortality or sudden death in these conditions.

The effects of flecainide in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

Because most serious adverse effects of flecainide (pro-arrhythmic effects, A-V block of greater than first degree, marked bradycardia, exacerbation of heart failure) appear early in treatment and require close monitoring, patients should be hospitalized during initial titration of flecainide.

2. Clinical Pharmacology

Labeling as proposed includes almost no information about what the drug does and the information on plasma levels is both very brief and not optimally located in the metabolism section. We suggest the following paragraph to be added to the electrophysiology section:

Flecainide causes a dose-related and blood-level related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, flecainide has been successful 30-40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.00 ug/ml may be needed to obtain the maximal therapeutic effect; most patients, however, need only 0.4-0.6 ug/ml. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 ug/ml. Plasma levels above 0.7-1.0 ug/ml are more likely to cause cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to pro-arrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

3. Warnings

The most critical warning is that concerning pro-arrhythmic effects. It should be the first warning, should be in dark print, and should be used to emphasize the need to limit dosage, monitor patients closely, titrate carefully, and be particularly careful in fragile patients. We suggest the following language:

Pro-arrhythmic effects

Flecainide, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such pro-arrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g. tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of flecainide, about 75% of pro-arrhythmic events were new or worsened ventricular tachyarrhythmics, the remainder being increased frequency of PVCs or new supraventricular arrhythmias (including sinus bradycardia).

In patients with complex arrhythmias it is often difficult to distinguish a spontaneous variation in the patient's

underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Among patients with serious arrhythmias (ventricular tachycardia, often sustained), frequently accompanied by heart failure and low ejection fraction, a history of acute myocardial infarction, and an episode of cardiac arrest requiring resuscitation, there has been an approximately 12% frequency of serious proarrhythmic effects. In earlier studies, where doses of 400 mg per day were used to initiate therapy, about 50% of these proarrhythmic events ended fatally, with patients proving impossible to resuscitate despite prompt medical attention. In more recent studies in the same population, using smaller initial doses and slow titration, with most patients not exceeding a dose of 300 mg/day, although pro-arrhythmic events have continued to be reported at a 10% rate, none have ended fatally.

Patients with less serious arrhythmics (chronic VPCs) have experienced a lower rate of proarrhythmic events, about 3%, but some were serious.

The relatively high frequency of pro-arrhythmic events in patients with ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of these patients with flecainide be started in the hospital.

The cardiac conduction warning does not give an adequate indication of the frequency of such events, except to describe them as rare. In fact, they do not seem rare by any reasonable definition, especially in the VT population. Among the 354 patients in studies 028, 057, and 057 amended, there was one case of second degree block (057-10-002), 4 cases of third degree block (057-54-102, or 057-12-112, 057-12-115, and 028-14-129), and 5 cases of sinus pause, exit block, or bradycardia (028-11-102, 028-14-102, 028-14-11[illegible], 028-20-103, 028-28-014), for an overall incidence of 10/354, or about 3%, not including bundle branch block.

There has also been at least one patient reported with prolonged QT, bradycardia and Torsade de Pointes (028-13-001) and others with VT (028-26-010). The frequency of true QT (or JJ) prolongation should be calculated and added to labeling.

4. Adverse Reactions

The discussion on page 11, indicating lower ADR rates in study 057 amended than in study 032, may be correct but has major problems. First, it is peculiar to compare studies when you could compare doses within studies. Patients in study 032, for example, h[illegible] both 400 and 600 mg dosages; did ADRs differ in the two dosage groups? Patients in study 057 amended had doses ranging from 200-400 mg; were dose-related differences seen? And did results in 057 amended differ from 057, a study of similar design and the same investigators, but that used higher doses? All of these comparisons are far more plausible than the one chosen.

B. Other Actions

1. I am revising the SBA to reflect the analyses above, but I am not making the entire repair. The safety information section is seriously deficient, giving no flavor of the pro-arrhythmic episodes, no hint that anyone died because of the drug, etc. Reviews and submission by Riker have reasonable summaries of this material, so that it should not be hard to get it together. The safety part of Vol. 1 of the June 84 submission to the Advisory Committee is a good start. We might simply attach as an appendix the Death's summary in Vol. 2.

2. The safety update needs to be reviewed specifically with respect to new pro-arrhythmic events in study 057 amended. Also, I would like to see the actual update when the package is returned.

3. We need to consider what additional data could support removal of the "non-indication" for non-life-threatening arrhythmias.

4. The suggested labeling is a major potential step toward revising labeling for this entire class of drugs. I need your candid comments on the entire analysis and labeling scheme.

Robert Temple, M.D.

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

Date: MAR · 6 1988

To: David Banks
Division of Drug Advertising and Labeling, HFN-244

From: Sughok K. Chun, M.D.
Division of Cardio-Renal Drug Products, HFN-110

Subject: Advertising of Tombocor (flecainide acetate), NDA 18-830, 3M-Riker

The bold heading "for most patients, the better choice" is probably a true statement. As Adv stated "noncardiac side effects" are less than quinidine, procainamide, disopyramide, tocainide, mexilitine or encainide. However, there was no comparative side effect studies to document. Beta-blockers (modest anti-arrhythmics) have different side effects which are also mild.

The problem of flecainide is adverse effect on heart, which is listed in Table and numerated well in WARNING in the labeling but not on advertising.

These serious "cardiac adverse effects" should be balanced on "noncardiac adverse effects" on Adv.

The statement in the 1st paragraph ". . . and she experienced none of the problems characteristic of arrhythmic therapy" better be deleted or modified. Each antiarrhythmic included flecainide has different and/or similar adverse effects in some population that this statement is misleading.

Sughok K. Chun, M.D.

This is a little late to mean anything. You are right in flagging the comparison. There is no head-to-head data anywhere. The emphasis on symptoms is inappropriate. The risk of flecainide is death, not undiagnosed symptoms. The ~~[illegible]~~ ad is misleading. Sorry our response is so late.

Lynne

JUN 20 1989

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA #18-830

Name of Drug: TAMBOCOR (flecainide acetate) Tablets

Sponsor: Riker Laboratories, Inc.

Type of Submission: New Corresp.

Date of Submission: 6/09/89

Date of Review: 6/15/89

Reviewer: Sughok K. Chun, M.D. HFD-110

A. Resume:

The submitted data from the 23 pts in the randomized trial assigned to flecainide active drug or placebo who died or had cardiac arrest, from the Cardiac Arrhythmia Suppression Trial (CAST) is reviewed.

DESCRIPTION OF DEATH OR ARREST

	Sudden Death	poss. AMI	pulm edema	others	Total
Flecainide Rx	9 *	2	2	3	17
placebo Rx	2 **	1	1	2	6

* 1 pt died within 1 day flecainide Rx during D/B period.

** 1 pt died 1 day of plcb Rx after open flecainide titration period.

B. Comments:

I called the sponsor (Dr. Richard Wilson, Director of Medical Affairs) on 6/15/89 and asked him how many pts died during open dose titration and after off medication periods. He'll try to obtain an information from [redacted] and forward to us.

S K Chun 6/20/89
Sughok K. Chun, M.D. 6/20/89

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-110/SKC/mn
#0223R

June 9,

NDA 18-930

Summary of Information on Flecainide and Flecainide Placebo Patients Who Died or Had Non-fatal Cardiac Arrests During Double-Blind Phase of CAST Study

Flecainide Patients

Patient Number	Age	Sex	Study Rx	Hx CHF	Hx AP	Hx Prior MI	Ejec Frac (%)	Date Qual MI	Concurrent Drugs[1] BB	CA	Dig	Diur	Start Study Rx	Stop Study Rx	Daily Dose	Taking Study Rx	Date Death or Arrest	Description of Death or Arrest
1	73	M	F	N	Y	Y	45	07/27/88	Y/Y	Y/Y	Y/Y	Y/Y	10/03/88	01/07/89	200	Y	01/07/89	Death; arrhythmia
2	42	M	F	N	Y	Y	50	06/02/87	Y/Y	Y/Y	N/N	N/N ✓	07/01/87	07/06/87	300	Y	07/06/87 △	Death; non-arrhythmic
3	62	M	F	Y	N	Y	39	04/29/87	N/N	Y/Y	N/N	Y/Y	10/26/87	11/12/87	300	Y	11/12/87 ×	Death; non-arrhythmic
5	66	M	F	N	Y	N	30	12/17/87	N/N	Y/Y	Y/Y	Y/Y	01/08/88	02/15/88	300	Y	02/15/88 *	Death; arrhythmia
10	69	M	F	Y	Y	N	51	08/19/87	Y/Y	Y/Y	Y/Y	Y/Y	09/21/87	12/17/87	200	Y	12/17/87 ×	Death; non-arrhythmic
11	60	F	F	N	N	N	44	11/07/87	N/N	N/N	N/N	N/Y	01/19/88	11/04/88	200	Y	11/04/88 *	Death; arrhythmia
12	62	M	F	Y	Y	Y	40	08/14/87	N/Y	Y/Y	N/Y	Y/Y	10/02/87	11/17/87	100	Y	11/17/87 *	Death; arrhythmia
13	68	M	F	Y	Y	N	43	08/01/88	N/N	Y/Y	N/N	N/N	12/08/88	03/14/89	200	Y	03/14/89 *	Death; arrhythmia[2]
14	62	M	F	Y	N	Y/N[3]	40	06/14/87	N/N	N/N	N/N	Y/Y ✓	07/03/87	07/03/87	300	Y	07/03/87 *	Death; arrhythmia
16	74	M	F	N	N	Y	46	08/20/87	Y/N	Y/N	N/N	N/N	10/01/87	08/10/88	300	Y	08/10/88 *	Death; arrhythmia
17	60	F	F	Y/N[4]	N	N	32	11/26/87	N/N	N/N	Y/N	Y/Y	01/27/88	03/31/88	---	N	07/23/88 (1)	Non-fatal arrest (on procainamide)
18	70	M	F	N	Y	Y	33	03/10/88	N/N	Y/Y	N/N	N/N	03/29/88	05/09/88	200	Y	05/09/88 *	Death; arrhythmia
19	63	F	F	Y	N	Y	30	10/11/87	N/N	N/N	Y/Y	Y/Y	10/13/88	10/20/88	200	Y	10/20/88 (2)	Death; non-cardiac
20	68	M	F	Y	Y	Y	39	09/10/87	N/Y	Y/Y	Y/N	N/N	10/01/87	10/16/87	200	Y	10/16/87	Death; non-arrhythmic
21	74	M	F	N	Y	Y	40	05/07/87	N/N	Y/Y	Y/Y	N/N	10/22/87	02/19/89	200	Y	02/19/89[5][6]	Non-fatal arrest; arrhythm
22	69	M	F	Y	Y	Y	47	11/15/87	N/N	Y/Y	Y/N	Y/N	01/15/88	06/06/88	200	Y	06/06/88 *	Death; arrhythmia

Flecainide Placebo Patients

4	60	M	P	N	N	N	38	10/30/87	Y/Y	N/N	Y/Y	Y/Y	11/25/87	12/20/88	200	Y	12/20/88 *	Death; arrhythmia
6	77	F	P	Y	N	Y	34	03/05/88	N/N	Y/Y	Y/Y	Y/Y	08/04/88	09/23/88	---	N	02/09/89	Death; cause unknown
7	62	M	P	N	Y	N	49	03/24/88	N/N	N/N	N/N	Y/Y	06/06/88	09/14/88	---	N	09/17/88 *	Death; non-arrhythmic
8	57	F	P	N	Y	N	37	02/24/86	Y/Y	Y/Y	N/N	Y/Y	07/21/87	09/10/87	200	Y	09/10/87 △	Death; non-arrhythmic
9	69	M	P	N	Y	N	55	07/06/87	N/N	N/Y	N/N	N/N	08/14/87	01/11/88	---	N	09/26/88 (4)	Death; cause unknown
15	73	F	P	N	N	N	50	12/06/88	N/N	N/N	Y/Y	Y/Y ✓	02/01/89	02/02/89	200	Y	02/02/89 *	Death; arrhythmia
23	71	M	P	N	N	Y	30	01/23/89	N/Y	Y/Y	N/Y	Y/Y	02/16/89	?	200	?	03/27/89	Death; cause unknown

Just AH flare. Elevation on plcb 9/13.

[1] Concurrent at baseline/concurrent at time of event

[2] Investigator classification: death, arrhythmia (Data and Safety Monitoring Board classification not available)

[3] Patient 14: computer printout states no prior MI, physician summary states prior MI

[4] Patient 17: computer printout states no prior CHF, physician summary states prior CHF

[5] Patient 21: computer printout states non-fatal cardiac arrest on 2/27/89; physician summary states non-fatal arrest on 2/19/89 and patient death on 2/27/89 while on open label flecainide.

(1) cwVT → Pulm edema. VAs disappeared at CABG, LV aneurysmectomy
(2) ruptured abd. aneurysm
(3) Candida septicemia. — d.c. life myelog ↓ anemia.
(4) resp failure — severe COPD

* Sudden death
△ Possible AMI
× Pulm. edema.

6.1

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

ORIGINAL

REPORTS

3M

May 14, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/he

Enclosure - [redacted]

Certified Mail P 648 917 221

5/27

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1985

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	M	04	09	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cerebrovascular accident
Patient (70-year-old male) with ventricular arrhythmia was being treated with flecainide 100 mg b.i.d. On April 7, 1986, patient suffered a massive cerebrovascular accident and was hospitalized. He died on 04/09/86.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*: 12/10/85 - 04/09/86

19. THERAPY DURATION: 120 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NITROGLYCERIN	120 DAYS	NITROGLYCERIN	120 DAYS
FUROSEMIDE	120 DAYS	POTASSIUM CHLORIDE	120 DAYS
NIFEDIPINE	120 DAYS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
History of nonsustained ventricular tachycardia, ~~coronial sclerotic~~ Arteriosclerotic heart disease, myocardial infarction, congestive heart failure (Class I) cardiomyopathy, and angina (Class II).

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/11/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 5 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS (In Confidence)	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	79	M	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, bradycardia, ECG abnormal. Increased pacing threshold. Patient (male, 79 years) with severe CAD and recent myocardial infarction. Also "moderately" reduced kidney function (serum creatinine 1.4-1.5 mg %). Patient digitalized and treated with Tambocor (flecainide acetate) 100 mg b.i.d. for 12 days. During this time no signs of bradycardia or QRS widening. Since therapy was inadequate, propranolol 5 mg was added. Within 2 days, bradycardia and increasing QRS widening occurred. A ventricular pacemaker was ineffective, although properly placed, and the patient died.

13. RELEVANT TESTS/LABORATORY DATA

Serum creatinine, 1.4 to 1.5 mg %

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [x] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: 14 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?

- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

PROPRANOLOL 2 DAYS DIGOXIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Patient had coronary artery disease.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
275-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 3/31/86

24d. REPORT SOURCE *(Check one)*

- [x] FOREIGN [ ] STUDY [ ] LITERATURE
- [ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 5 DAY REPORT

- [x] YES [ ] NO

25a. REPORT TYPE

- [ ] INITIAL [x] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

- [ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

6.1 REPORTS

ORIGINAL

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

3M

May 7, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are eight Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

One of the reports, [redacted] is a followup report. The initial report is also attached.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure - [redacted] (initial)
(followup)

[redacted]

Certified Mail P 648 917 220

5/19

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	75	M	12	21	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
#VENTRICULAR FIBRILLATION, DEATH#
ON 21DEC85 PATIENT WAS AT HOME WHEN WIFE FOUND HIM UNRESPONSIVE AND WITHOUT RESPIRATIONS. THE RESCUE SQUAD FOUND HIM IN VENTRICULAR FIBRILLATION WHICH RESPONDED TO CARDIOVERSION. HE WAS TRANSPORTED TO THE HOSPITAL WHERE IT WAS DETERMINED HE HAD SEVERE NEUROLOGICAL DAMAGE AND SUPPORT WAS WITHDRAWN AFTER 2 DAYS.
(THIS SECTION AND DIAGNOSES WERE REVISED 01MAY86 FROM THAT OF REPORT DATED17JAN86 BASED ON NEW INFORMATION JUST RECEIVED.)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
NO AUTOPSY PERFORMED. CPK'S REMAINED NORMAL THROUGHOUT.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [x] NO [ ] NA

15. DAILY DOSE
100MG

16. ROUTE OF ADMINISTRATION
ORAL

INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [x] NA

18. THERAPY DATES *(From/To)*
9/3/85 - 12/21/85

19. THERAPY DURATION
109 DAYS

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
AMIODARONE
POTASSIUM CHLORIDE
NIFEDIPINE
FUROSEMIDE
NITROGLYCERIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
HISTORY: MI, CHF (CLASS II), ANGINA (CLASS II), PERIPHERAL VASCULAR DISEASE, ASHD, FIRST DEGREE AV BLOCK, RBBB, PVC'S, SUSTAINED VENTRICULAR TACHYCARDIA, NONSUSTAINED VENTRICULAR TACHYCARDIA, VENTRICULAR FIBRILLATION AND SYNCOPE.

DIAGNOSIS: VENTRICULAR FIBRILLATION

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/29/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [x] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[x] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [x] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	75	M	12	21	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Myocardial infarction
Patient suffered a myocardial infarction at home on 12/21/85. He was transported to the hospital but never regained consciousness and was found to be "brain-dead". On 12/23/85 he was removed from the respirator and pronounced dead.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Unknown

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor^{R}/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
100 mg	Oral	☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE Ventricular tachycardia

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
9/3/85 to 12/21/85	109 days

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

amiodarone/ - -
furosemide/Lasix -
potassium chloride/ - -
nitroglycerin/Nitrobid -
nifedipine/ - -

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)* History: MI, CHF (Class II), angina (Class II), peripheral vascular disease, ASHD, first degree AV block, RBBB, PVC's, sustained ventricular tachycardia, nonsustained ventricular tachycardia, ventricular fibrillation and syncope. Diagnosis: Myocardial infarction.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-15-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
NDA 18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
4/7/86	☐ FOREIGN ☒ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
☒ YES ☐ NO	☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	56	M	02	18	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

APLASTIC ANEMIA, DEATH
ONSET ABOUT TWO WEEKS AFTER INITIAION OF TAMBOCOR THERAPY FOR VENTRICULAR ECTOPIC ARRHYTHMIA, WITH RAPID DOWNHILL COURSE; DIED 3/14/86.
(NB: PRIOR TO FLECAINIDE TREATMENT, PT KNOWN TO HAVE LEUKEMIA AND HAD MANIFESTED BONE MARROW ABLATION SECONDARY TO ANTILEUKEMIC DRUGS.)

13. RELEVANT TESTS/LABORATORY DATA

3/5/86: SGOT 323; SGPT 450; ALK. PHOS. 266; HGB 10 G/DL; HCT 30; WBC 5000/CU.MM.
3/6/86: WBC 1600/CU.MM.; PLATELETS 9000/CU.MM.; BONE MARROW HYPOPLASTIC PANCYTOPENIA PERSISTED & PROGRESSED THEREAFTER.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300MG

16. ROUTE OF ADMINISTRATION: ORAL

INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*: 02/4/86 - 03/4/86

19. THERAPY DURATION: 1 MONTH

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DISOPYRAMIDE	>1 MONTH	PROCAINAMIDE HCL	>1 MONTH
PHENYTOIN	3 WEEKS	DIGOXIN	3 WEEKS
HEPARIN SODIUM	3 WEEKS	SODIUM WARFARIN	3 WEEKS
TICARCILLIN/CLAVULANATE	10 DAYS	TOBRAMYCIN	10 DAYS
VANCOMYCIN HCL	1 WEEK	CEFTAZADIME	1 WEEK
DOXEPIN HCL	>1 MONTH	RANITIDINE	1 MONTHH

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

PATIENT HAD ACUTE MYELOGENOUS LEUKEMIA; PRIOR THERAPY INCLUDED COURSES OF 6 MERCAPTOPURINE, CYTOSAR, & OTHER CYTOTOXIC AGENTS. DEVELOPED SYMPTOMATIC VENTRICULAR ECTOPIC BEATS , POORLY CONTROLLED BY PRONESTYL + NORPACE, DILANTIN OR DIGOXIN. TAMBOCOR 100MG BID IMPROVED CONDITION, BUT COMPLETE CONTROL OF ARRHYTHMIA ACHIEVED WHEN TAMBOCOR DOSE WAS RAISED TO 150MG BID AFTER 4 DAYS AT 100MG BID. SEPSIS SUPERVENED WHEN BONE MARROW FAILED, & ANTIBIOTIC THERAPY WAS UNAVAILING. CEREBROVASCULAR ACCIDENT 3 MONTHS EARLIER. FINAL HOSPITALIAZTION 1/28/86 FOR MULTIPLE PULMONARY EARLIER, AND COURSE WAS FURTHER COMPLICATED BY MULTIPLE PULMONARY

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/22/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	38	M	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#Death#
Patient (38-year-old male) with supraventricular fibrillation due to primary cardiomyopathy and a previous myocarditis had been treated with disopyramide and quinidine plus verapamil, which were all unsuccessful. The family physician referred the patient to the cardiologist who prescribed flecainide 100 mg b.i.d. plus metoprolol 50 mg t.i.d. After about one week on this medication the ECG was normal. During the night following the ECG check, the patient died at home.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [x] NA

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

INDICATION(S) FOR USE
ATRIAL FIBRILLATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

18. THERAPY DATES *(From/To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
1 WEEK

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
METOPROLOL 1 WEEK

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
None.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-8[illegible]0

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
3/26/86

24d. REPORT SOURCE *(Check one)*
- [x] FOREIGN [ ] STUDY [ ] LITERATURE
- [ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [x] YES [ ] NO

25a. REPORT TYPE
- [x] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]		80	M	03	21

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#CARDIAC ARREST#, OCCURRED AT HOME 3/21/86 AT 6:55P WHILE EATING DINNER. PARAMEDICS ARRIVED WITHIN 15 MINUTES, FOUNS HIM UNRESPONSIVE, CYANOTIC, WITH MILDLY DILATED PUPILS, AND IN VENTRICULAR FIBRILLATION. PATIENT WAS RESUSCITATED TO SUPRAVENTRICULAR TACHYCARDIA AT RATE OF 160/MINUTE, SYSTOLIC PRESSURE OF 90MM, BUT NO SPONTANEOUS RESPIRATION. HOSPITALIZED WITH DIAGNOSIS OF ISCHEMIC HYPOXIC ENCEPHALOPATHY DUE TO CARDIAC ARREST. CARDIAC RHYTHM REVERTED TO NORMAL SINUS RHYTHM. REMAINED UNRESPONSIVE, DECEREBRATE & FLACCID, ON RESPIRATOR. LIFE SUPPORT SYSTEMS WERE DISCONTINUED 4/3/86, AND THE PATIENT DIED AT 5:35P.
TAMBOCOR 100MG Q12H, STARTED 12/5/85, WAS CONTINUED UNTIL 4/1/86.

8.-12. CHECK ALL APPROPRIATE TO REACTION 86

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

12/9/86: PLASMA FLECAINIDE LEVEL 0.71 MCG/ML
1/13/86: PLASMA FLECAINIDE LEVEL 0.45 MCG/ML
1/13/86: HOLTER ECG REVEALED 91% SUPPRESSION OF VENTRICULAR ECTOPY.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE 200MG

16. ROUTE OF ADMINISTRATION ORAL

INDICATION(S) FOR USE CARDIAC DYSRHYTHMIA NOS

17. THERAPY DATES *(From/To)* 12/05/86 - 04/01/86

18. THERAPY DURATION 80 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [X] NO [ ] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ESTROGEN
FUROSEMIDE
POTASSIUM

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

MYOCARDIAL INFARCT, 1975. NONSUSTAINED EPISODIC VENTRICULAR TACHYCARDIA SINCE 1983. EXPERIENCED SYNCOPAL EPISODE 11/29/85 WITH VENTRICULAR FIBRILLATION. ELECTROPHYSIOLOGIC TESTING 12/5/85 REVEALED INDUCED VENTRICULAR TACHYCARDIA, CYCLE LENGTH 230 MSEC, RESULTING IN SYNCOPE. TAMBOCOR 100MG Q12H STARTED 12/5/85; REPEAT EPS 12/9/85 SHOWED INDUCED V-TACH WITHOUT SYNCOPE, CYCLE LENGTH PROLONGED TO 340 MSEC.
PROSTATIC CARCINOMA WITH METASTASES, DATE OF DIAGNOSIS UNKNOWN.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG 18-830

24b. MFR CONTROL NO. [redacted]

24c. DATE RECEIVED BY MANUFACTURER 4/ 2/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA	YR.
[redacted]	70	M	03	21	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden, unwitnessed death
This man with history of two myocardial infarcts and coronary bypass surgery about one year ago, had symptomatic premature ventricular contractions for a long time which did not respond well to procainamide or Quinaglute. Started on 100 mg b.i.d. flecainide for one week with subjective improvement. Increased to 150 mg b.i.d., but still felt occasional PVCs. Finally increased to 200 mg b.i.d. After two weeks on this dose, while working on income taxes, he died suddenly, alone.

13. RELEVANT TESTS/LABORATORY DATA

Potassium mid-range a couple of weeks before death and long preceding that. No heart block by history.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

15. DAILY DOSE
400 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHM

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

18. THERAPY DATES *(From/To)*
02/20/86 - 03/21/86

19. THERAPY DURATION
4 WEEKS

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NITROGLYCERIN	YEARS	FUROSEMIDE	YEARS
DIGOXIN	YEARS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 and #13 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
4/10/86	[ ] FOREIGN [ ] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
[X] YES [ ] NO	[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4. REACTION ONSET MO	DA	YR.
[redacted]	45	M	03	28	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden death
Patient with history of anterior myocardial infarct 8-10 years ago and with subsequent bypass surgery experienced a transseptal infarct and developed symptomatic ventricular arrhythmias approximately 1-2 months before death. Lightheadedness and dizziness had led to EKG showing couplets, triplets, and 5-6 beat runs of ventricular tachycardia described as, "ominous". Patient was given 100 mg flecainide acetate b.i.d. for 1 week followed by 150 mg b.i.d. for 2 weeks. Pt felt "great." An office EKG done 3 days before death looked the same as before treatment. About midnight, patient's roommate found him gasping for breath and he died beffore medical assistance could be obtained.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
03/07/86 - 03/28/86

19. THERAPY DURATION
3 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

FUROSEMIDE > 2 MONTHS
DIGOXIN > 2 MONTHS

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*
Please see #7 above. Ejection fraction = 40%.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/10/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL

REPORTS

3M

April 29, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are seven Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Report [redacted] is a followup report. The original report is also attached.

Report [redacted] was at first suspected as a proarrhythmic death and therefore a labeled event. The original report is included in the periodic report. Later the investigator indicated that, in his opinion, the death was not drug related, ie, not a proarrhythmic event. It hence becomes a 15-day reportable case. The original report is attached herein.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure - [redacted] (original)
[redacted] (followup)
[redacted] (original)
[redacted] (followup)

Certified Mail P 648 917 211

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	39	M	2	1	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden death.
Patient was found beside his car beyond medical attention.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Unknown.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE
400 mg

16. ROUTE OF ADMINISTRATION
Oral

17. INDICATION(S) FOR USE
Ventricular Arrhythmia

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*
5/28/85 to 2/1/86

19. THERAPY DURATION
9 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

methyldopa/Aldomet	1 year
furosemide/Lasix	1 year
digoxin(lanoxin),Lanoxin	1 year
dipyridamole/	1 year

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Premature ventricular contracts, nonsustained ventricular tachycardia with congestive heart failure (Clas I), diabetes mellitus, arteriosclerotic heart disease.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-15-07, 3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
NDA 18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
/3/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	40	M	2-	-1	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

SUDDEN DEATH (PROBABLE CARDIAC)
PT. WAS FOUND SLUMPED IN FRONT SEAT OF HIS CAR BY A SECURITY GUARD AT ABOUT 8 A.M. THERE WAS NO INDICATION OF TRAUMA OR VIOLENCE. IMMEDIATE CAUSE OF DEATH WAS REPORTED AS SHOWN ABOVE. IT IS THE OPINION OF THE INVESTIGATOR THAT THE DEATH WAS NOT DRUG RELATED.

13. RELEVANT TESTS/LABORATORY DATA
NO AUTOPSY PERFORMED

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
400 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*
28MAY85 - 01FEB86

19. THERAPY DURATION
8 MONTH

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

METHYLDOPA	1 YEAR	FUROSEMIDE	1 YEAR
DIGOXIN(LANOXIN)	1 YEAR	DIPYRIDAMOLE	1 YEARe
CRYSTALLINE ZINC INSULIN	15 YRS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
PREMATURE VENTRICULAR CONTRACTIONS, NONSUSTAINED VENTRICULAR TACHYCARDIA WITH CONGESTIVE HEART FAILURE (CLASS I),DIABETES MELLITUS, ARTERIOSCLEROTIC HEART DISEASE.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/ 8/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [x] STUDY
- [ ] LITERATURE
- [ ] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [x] YES [ ] NO

25a. REPORT TYPE
- [ ] INITIAL [x] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26

27. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION 5600-7001
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE	3. SEX	4-6. REACTION ONSET		
[redacted]	YRS. 70	F	MO. 2	DA. 2	YR. 86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Syncope, ventricular tachycardia, deep vein thrombosis and pulmonary embolism, death

Syncope developed 02 Feb 86 and she was hospitalized showing junctional rhythm in addition to that of pacemaker. Pacemaker replacement attempted but v-tach developed. Later died with suspected pulmonary embolus from pre-existing deep vein thrombosis.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Plasma flecainide acetate level on 04 Feb 86 = 0.96 microgm/ml

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE 200mg

16. ROUTE OF ADMINISTRATION Oral

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE

Ventricular Tachycardia

18. THERAPY DATES *(From/To)* 05 Nov 85 to 11 Feb 86

19. THERAPY DURATION 3 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

procainamide hcl/Pronestyl	3 months
amiodarone/	3 months
sodium warfarin/Coumadin	14 months

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)* Arteriosclerotic heart disease, coronary arterial disease, sustained ventricular tachycardia, ventricular fibrillation while on indecainide, pacemaker, cardiac enlargement, congestive heart failure, left vent. ejection fraction 15%

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, Minnesota 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
NDA 18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
12/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	F	02	02	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

SYNCOPE, VENTRICULAR TACHYCARDIA, DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM, DEATH
(CHANGES IN THIS FOLLOW-UP REPORT FROM ORIGINAL ARE 1) DELETION OF PROCAINAMIDE AS CONCOMITANT MED AND 2) REWRITE OF SECTION 87) PT HAD SYNCOPAL EPISODE ON 2/2/86 AND WAS TAKEN TO ER. JUNCTIONAL AND PACED RHYTHM (AV SEQUENTIAL PACEMAKER) WERE IN EVIDENCE. SHE WAS TRANSFERRED TO [redacted] ON 2/4/86. A PLASMA FLECAINIDE ACETATE LEVEL WAS 0.96 MCG/ML. AFTER MONITORING, IT WAS DECIDED THAT THE PACEMAKER WAS NOT FUNCTIONING. COUMADIN WAS D/C'ED ON 2/7/86 IN PREPARATION FOR PACEMAKER GENERATOR REPLACEMENT ON 2/10/86. ATTEMPTED PACER REPLACEMENT ON 2/10/86 FAILED. SUSTAINED VT ENSUED BUT WAS

13. RELEVANT TESTS LABORATORY DATA

PLASMA FLECAINIDE ACETATE LEVEL ON 04FEB86 = 0.96 MICROGM/ML

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☑ DIED DUE TO REACTION
- ☑ TREATED WITH Rx DRUG
- ☑ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines.biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*: 06NOV85 - 11FEB86

19. THERAPY DURATION: 3 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☑ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☑ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE
SODIUM WARFARIN — 14 WEEKS
AMIODARONE — 3 MONTHS

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

ARTERIOSCLEROTIC HEART DISEASE, CORONARY ARTERIAL DISEASE, SUSTAINED VENTRICULAR TACHYCARDIA, VENTRICULAR FIBRILLATION WHILE ON INDECAINIDE, PACEMAKER, CARDIAC ENLARGEMENT, CONGESTIVE HEART FAILURE, LEFT VENT. EJECTION FRACTION 15%,

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/24/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☑ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☑ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☑ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID. INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

SUCCESSFULLY CARDIOVERTED. SHE WAS TRANSFERRED TO THE CCU WHERE SHE WAS INTUBATED AND 10 EPISODES OF PACEMAKER-INDUCED VT/VF OCCURRED. EMERGENCY REMOVAL OF PACER GENERATOR RESULTED. RECURRENT VT OCCURRED WITH SUBSEQUENT HYPOTENSION AND BRADYCARDIA UNTIL MORNING OF 2/11/86 WHEN A TEMPORARY PACER WAS PLACED. SHE WAS SOB, CYANOTIC AND HYPOTENSIVE. QRS COMPLEX WIDENED, ATERIAL PO2 DROPPED TO 48MM HG AND LOSS OF PACEMAKER CAPTURE OCCURRED. DESPITE EXTENSIVE RESUSCITATIVE ATTEMPTS SHE DIED AT 20:27. NO AUTOPSY WAS PERFORMED. SUSPECTED CAUSE OF DEATH WAS A PULMONARY EMBOLUS. IT WAS THE INVESTIGATOR'S OPINION THAT DEATH WAS NOT RELATED TO FLECAINIDE.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From-To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

3M

May 1, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure - [redacted]
- [redacted]

Certified Mail P 648 917 212

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	21	F	04	16	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death from overdose
A 21-year-old female patient with mitral valve prolapse and catecholamine dependent ventricular tachycardia ingested approximately 2 Gm of Inderal and 12-16 Gm of Tambocor. Within one hour had blood pressure of 70/40 and pulse 70. Within 2 hours was in asystole with complete heart block; no response to medication, pacemaker, or internal heart massage.

13. RELEVANT TESTS/LABORATORY DATA
None.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

X OVERDOSE
X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
04/15/86 - 04/16/86

19. THERAPY DURATION
1 DAY

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
PROPRANOLOL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
None.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/16/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

HFN-110

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL

3M

April 11, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong/am

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure - [redacted]

Certified Mail P 648 917 193

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	80	M	03	21	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
MYOCARDIAL INFARCTION & *VENTRICULAR FIBRILLATION* LEADING TO CARDIAC ARREST & *DEATH*. RESUSCITATION EFFORTS INCLUDED MULTIPLE ELECTRO-CONVERSION ATTEMPTS & FINALLY ADMINISTRATION OF BRETYLIUM, ALL TO NO AVAIL.

13. RELEVANT TESTS LABORATORY DATA
NONE

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
PAROX VENTRIC TACHYCARD

18. THERAPY DATES *(From/To)*
3/19/86 - 3/21/86

19. THERAPY DURATION
2 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
LIDOCAINE 2 DAYS

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
ADMITTED TO HOSPITAL 3/19/86 BECAUSE OF GASTROINTESTINAL HEMORRHAGE, COMPLICATED BY EPISODES OF SUSTAINED VENTRICULAR TACHYCARDIA. TAMBOCOR 100MG BID & LOW-DOSE LIDOCAINE IV ADMINISTERED, WITH APPARENT ABOLITION OF VENTRICULAR TACHYCARDIA. TERMINAL EVENT WAS SUDDEN IN ONSET, & FINAL VENTRICULAR FIBRILLATION PROVED TO BE REFRACTORY; CARDIAC ARREST FOLLOWED, & WAS NOT RESPONSIVE TO FURTHER REMEDIAL EFFORTS. PRIOR TO HOSPITALIZATION, QUINIDINE & PRONESTYL HAD BEEN USED WITHOUT ADEQUATE CONTROL OF V-TACH; THESE WERE DISCONTINUED ON ADMISSION.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
3/21/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 733-0633

ORIGINAL

3M

April 22, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are four Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product in clinical studies.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure -[redacted]

Certified Mail P 648 917 206

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	58	M	03	06	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

SUDDEN DEATH
PARAMEDICS SUMMONDED TO PATIENT'S HOME TO FIND HIM IN ASYSTOLE.
INVESTIGATOR FELT THAT DEATH WAS PROBABLY NOT CAUSALLY RELATED TO
FLECAINIDE ADMINISTRATION.

c

13. RELEVANT TESTS/LABORATORY DATA

AUTOPSY WAS NOT PERFORMED.

9.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO ☒ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
300 MG	ORAL

17. INDICATION(S) FOR USE

VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
28JAN86 - 04MAR86	35 DAYS

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIPYRIDAMOLE	6YRS 7MOS	NITROGLYCERIN	9 WKS
NIFEDIPINE	8 MOS	FUROSEMIDE	3 WKS
ASPIRIN	6YRS 7MOS	DIGOXIN	RECENT

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

HISTORY OF MYOCARDIAL INFARCT, CLASS III ANGINA, HYPERTENSIVE CARDIO-
VASCULAR DISEASE, CLASS II CONGESTIVE HEART FAILURE, ARTERIOSCLEROTIC
HEART DISEASE.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
3/ 5/86	☐ FOREIGN ☒ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
☒ YES ☐ NO	☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?

☐ YES ☐ NO

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL

3M

March 24, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor , flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product in a foreign country (France).

Sincerely,

Florence N. Wong/tlh

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure [redacted]

Certified Mail P 648 917 179

4/28

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION [illegible]
ROCKVILLE, MD [illegible]

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date; May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	52	F	11	??	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden Death
Patient experienced sudden death without premonitory symptoms.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Unknown.

II. SUSPECT DRUG(S) INFORMATION

SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor[R]/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
200mg	Oral	☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE
Ventricular Arrhythmia

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
1/??/85 to 11/??/85	11 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

meprobamate/ -
none/chemotherapy -

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)* Last clinical examination and holter in April 1985; compliance to therapy was considered as doubtful. Mitral insufficiency (hemodynamically moderate); breast carcinoma (Haldstedt, chemotherapy 1984); alcoholism; April 1985: Sinus rhythm:73/.M; QRS=.72 sec; PVC=0 while on flecainide; no cardiac failure at the t[illegible]m.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
Riker Laboratories, Inc.
225-1S-07, 3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
NDA 18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
2/7/86	☒ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
☒ YES ☐ NO	☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

REPORTS

ORIGINAL

3M

April 9, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure - [redacted]

Certified Mail P 648 917 190

4/21

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	72	M	03	03	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

THROMBOCYTOPENIA, LEUKOPENIA, DEATH

72 YEAR OLD MALE WITH VENTRICULAR TACHYCARDIA DEVELOPED THROMBOCYTOPENIA. WAS HOSPITALIZED FOR TREATMENT. PRIOR TO HOSPITAL ADMISSION THE PATIENT WAS TAKING CIMETIDINE, LASIX, LOPRESSOR, VERAPAMIL, FLECAINIDE AND GENTAMICIN. DURING HOSPITALIZATION LEUKOPENIA DEVELOPED AND CIMETIDINE WAS DISCONTINUED. BONE MARROW EXAMINATION SHOWED EARLY FORMS OF GRANULOCYTIC AND PLATLET SERIES AFFECTED. PATIENT DIED ON ON 15MAR86, 12 DAYS AFTER ADMISSION TO HOSPITAL.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: 24FEB86 - 13MAR86

19. THERAPY DURATION: 2 3/7 WKS

20. DID REACTION ABATE AFTER STOPPING DRUG?

[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

CIMETIDINE
FUROSEMIDE
VERAPAMIL HCL
GENTAMICIN SULFATE
METOPROLOL TARTRATE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

PREVIOUS ANTIARRHYTHMIC THERAPY INCLUDED PROCAINAMIDE AND TONACARD. PATIENT WAS REFRACTORY TO BOTH.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 3/21/86

24d. REPORT SOURCE *(Check one)*

[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT

[X] YES [ ] NO

25a. REPORT TYPE

[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5-85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	54	M	2	18	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Aplastic anemia, death

Onset about two weeks after initiation of Tambocor® therapy for ventricular ectopic arrhythmia, with rapid downhill course, death @ 3/11/86. (NB. Prior to flecainide treatment, pt known to have leukemia and bone marrow ablation secondary to antileukemic drugs.)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Peripheral anemia and leukopenia.
Bone marrow showed progressive loss of cellular elements during last four weeks of life.

C

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☒ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
300 mg	Oral	☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE

Ventricular premature beats

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
@2/4/86 to @3/4/86	1 month

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

disopyramide/Norpace -

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)* Patient had acute myelogenous leukemia; prior therapy included courses of 6 mercaptopurine, Cytosar, and other cytotoxic agents. Developed symptomatic ventricular ectopic beats, inadequately controlled on Norpace alone; addition of Tambocor 100 mg bid improved condition, but complete control of arrhythmia

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
NDA 18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
3/24/86	☐ FOREIGN ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
☒ YES ☐ NO	☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

23. (cont.)

achieved when Tambocor dose was raised to 150 mg bid after four days at 100 mg bid. Sepsis supervened when bone marrow failed, and antibiotic therapy was unavailing.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL REPORTS

3M

March 26, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product in clinical studies.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/he

Enclosure - [redacted]

Certified Mail P 058 016 895

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	73	M	3	11	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death

Pt. experienced angina and collapsed. The death occurred in Arizona out of hospital. No other details are available.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Unknown

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor® /flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE
200 mg

16. ROUTE OF ADMINISTRATION
Oral

17. INDICATION(S) FOR USE
Ventricular arrhythmia

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*
Dec. 85 to 11 Mar. 86

19. THERAPY DURATION
3 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

sodium warfarin/Coumadin	1 month	digoxin/ -	-
prednisone/ -	7 months	diocytl sodium sulfosuccinate/Colace	3 months
furosemide/Lasix	7 months	isosorbide dinitrate/Isordil	months
potassium/ -	3 months		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Ventricular tachycardia, congestive heart failure, inferior myocardial infarct in [redacted], coronary artery disease, pulmonary fibrosis due to Amiodarone, Hickman in place before flecainide for intractable VT.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
3/17/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

5 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 733-0633

ORIGINAL

3M

March 24, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: Follow-up to 15-Day Adverse Reaction Report
NDA 18-830, Tambocor®, (flecainide acetate)

Dear Sir/Madam:

Enclosed is a follow-up to an Adverse Reaction Report pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject product. Also enclosed is a copy of the initial ADR which was submitted to the FDA on January 31, 1986.

Sincerely,

Florence N. Wong/tlh

Florence N. Wong

FNW/tlh

Enclosures [redacted] (follow-up)
[redacted] (initial)

Certified Mail P 646 017 180

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	80	F	11	??	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death Pt with atrial fibrillation was started on flecainide 1 month prior to death at a dose of 100mg/day. One week later the daily dose was increased to 150mg. Patient died three weeks later as a result of a sudden death event. There was no evidence of AV block or an increase in QRS interval. Pt was also taking digoxin and Lasix. 3/17/86...new information reveals pt was also taking theophylline and aspirin.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Unknown

C.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor[R]/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE 150mg

16. ROUTE OF ADMINISTRATION Oral

17. INDICATION(S) FOR USE Atrial Fibrillation

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)* 10/??/85 to 11/??/85

19. THERAPY DURATION 1 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

digoxin/Acetyldigitoxine	2 years
furosemide/Lasix	-
aspirin/	-
theophylline/	-

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

History of chronic bronchitis, mitral valve stenosis with dilated left atrium atrial fibrillation (for two years)

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1N-01, 3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG NDA 18-830

24b. MFR CONTROL NO. [redacted]

24c. DATE RECEIVED BY MANUFACTURER 3/11/86

24d. REPORT SOURCE *(Check one)* ☒ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25 DAY REPORT ☒ YES ☐ NO

25a. REPORT TYPE ☐ INITIAL ☒ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE	3. SEX	4.-6. REACTION ONSET		
[redacted]	YRS. 80	F	MO. 11	DA. ?	YR. 85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)* *Death*

Patient with atrial fibrillation was started on flecainide 1 month prior to death at a dose of 100 mg/day. One week later the daily dose was increased to 150 mg. Patient died three weeks later as a result of a sudden death event. There was no evidence of AV block or an increase in QRS interval. Patient was also taking Digoxin and Lasix.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Unknown

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE: 150 mg

16. ROUTE OF ADMINISTRATION: Oral

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE: Atrial fibrillation

18. THERAPY DATES *(From/To)*: 10/?/85 to 11/?/85

19. THERAPY DURATION: 1 month

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

digoxin/Acetyldigitoxine	2 yrs.
furosemide/Lasilix	-

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

History of chronic bronchitis, mitral valve stenosis with dilated left atrium, atrial fibrillation (for two years).

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: NDA 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 1/13/86

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.- 26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL REPORT

3M

March 19, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure - [redacted]

Certified Mail P 648 917 177

3/31

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date; May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	51	M	1	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden death. Pt with symptomatic atrial fibrillation started on flecainide September 1985, cardioverted to normal sinus rhythm and remained symptom free. Good reviews in Oct 1985 and Dec 1985. On Jan. 13, 1986 collapsed while undertaking mild exercise and was pronounced dead 5 minutes later. Physician said causal relationship to drug "most unklikely". Case also reported to Norwegian Board of Health

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Flecainide blood levels expected.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor[R]/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE
Unknown

16. ROUTE OF ADMINISTRATION
Oral

17. INDICATION(S) FOR USE
Atrial Fibrillation

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*
9/85 to 1/13/86

19. THERAPY DURATION
4 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

None Known.

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Combined aortic valve incompetence and stenosis with 70MM HG pressure gradient across valve. Had atrial fibrillation with some symptoms. Known to have severe left ventricular hypertrophy.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07, 3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
NDA 18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
[illegible]/28/86

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☒ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	?	M	12	23	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden death Patient being treated for sub-acute myocardial infarct was on flecainide for 5 days when he suddenly became breathless and died.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Normal chest x-ray.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate.

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE Unknown

16. ROUTE OF ADMINISTRATION Oral

17. INDICATION(S) FOR USE
Acute Myocardial Infarct

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*
12/18/85 to 12/23/85

19. THERAPY DURATION
5 Days

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

None Known.

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Patient had large myocardia infarct, significant arrhythmia frequency and left ventricular failure (with normal chest x-ray).

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07, 3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
NDA 18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
/25/86

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25.. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

Regulatory Affairs
Riker Laboratories, Inc.

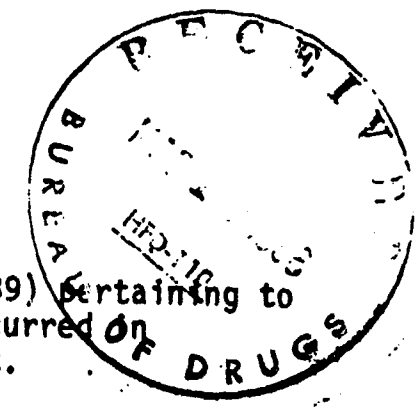
270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL

3M

March 4, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857



Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred on [redacted] association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure [redacted]

Certified Mail P 648 917 165

3/5

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFR-7)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	63	M	1	14	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death secondary to lung cancer.

Patient was diagnosed as having lung cancer 3 weeks following start of flecainide acetate treatment. Entered hospital, became moribund and died 2 weeks after entry.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

CT scan, sputum samples.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

15. DAILY DOSE
200 mg

16. ROUTE OF ADMINISTRATION
Oral

17. INDICATION(S) FOR USE
Ventricular arrhythmia

18. THERAPY DATES *(From/To)*
12/5/85 to 1/14/86

19. THERAPY DURATION
40 Days

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

albuterol/
furosemide/Lasix 5 wks
terbutaline sulphate/
theophylline/Theo-Dur
ranitidine/Zantac
potassium chloride/Klotrix
prednisone/
nitroglycerin/Nitropaste
sulfamethoxazole,
trimethoprim/Septra 5 wks
milk of magnesia-cascara

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Premature ventricular complexes, non-sustained vent. tachycardia, vent. fibrillation, history of myocardial infarction, severe chronic obstructive pulmonary disease, arteriosclerotic heart disease.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories
225-1S-07 3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
NDA 18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
?/6/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 5 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

2

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL

3M

March 6, 1986

MAR 18 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are four Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product in clinical studies.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure - [redacted]

Certified Mail P 648 917 169

3/19

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date; May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID/INITIALS *(In Confidence)* [redacted]

2. AGE	3. SEX	4.-6. REACTION ONSET		
YRS.		MO.	DA.	YR.
70	F	2	2	86

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☒ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Syncope, ventricular tachycardia, deep vein thrombosis and pulmonary embolism, death

Syncope developed 02 Feb 86 and she was hospitalized showing junctional rhythm in addition to that of pacemaker. Pacemaker replacement attempted but v-tach developed. Later died with suspected pulmonary embolus from pre-existing deep vein thrombosis.

13. RELEVANT TESTS/LABORATORY DATA

Plasma flecainide acetate level on 04 Feb 86 = 0.96 microgm/ml

C

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE: 200mg

16. ROUTE OF ADMINISTRATION: Oral

17. INDICATION(S) FOR USE: Ventricular Tachycardia

18. THERAPY DATES *(From/To)*: 06 Nov 85 to 11 Feb 86

19. THERAPY DURATION: 3 months

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

procainamide hcl/Pronestyl	3 months
amiodarone/	3 months
sodium warfarin/Coumadin	14 months

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)* Arteriosclerotic heart disease, coronary arterial disease, sustained ventricular tachycardia, ventricular fibrillation while on indecainide, pacemaker, cardiac enlargement, congestive heart failure, left vent. ejection fraction 15%

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, Minnesota 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: NDA 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 2/12/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date; May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	64	M	2	9	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Worsened congestive heart failure, death

Death possibly due to worsening congestive heart failure. (More information expected).

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Autopsy results pending.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor® / flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

DAILY DOSE: Unknown

16. ROUTE OF ADMINISTRATION: Oral

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE: Ventricular arrhythmia

18. THERAPY DATES *(From/To)*: From unknown to unknown

19. THERAPY DURATION: Unknown

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

None known

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Case forms with history awaited.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1N-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: NDA 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 2/21/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☑ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

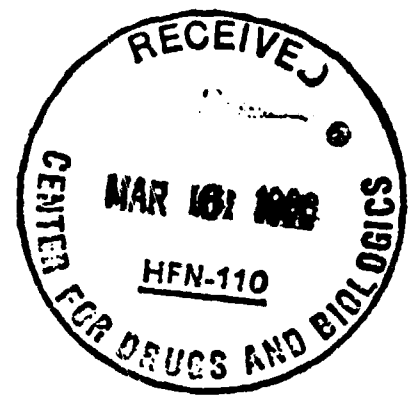
Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 733-0633

ORIGINAL REPORTS

3M

February 25, 1986



Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15 day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product in clinical studies.

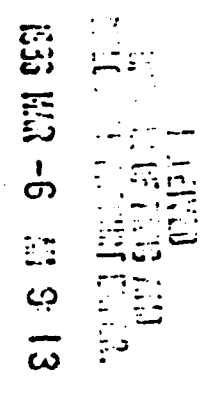
Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/he

Enclosure [redacted]

Certified Mail P648 917 158



DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE	3. SEX	4.-6. REACTION ONSET		
[redacted]	60 YRS.	M	1 MO.	24 DA.	86 YR.

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Congestive heart failure, cardiac arrest, death
Pt. with history of symptomatic congestive heart failure failed other antiarrhythmics and put on flecainide acetate while in hospital. After two days ventricular arrhythmia was being being well controlled. Pt. went home and two or three days later awakened at night in CHF. Paramedics called but patient died about time of arrival at hospital.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

No autopsy. No other laboratory.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE
200 mg

16. ROUTE OF ADMINISTRATION
Oral

17. INDICATION(S) FOR USE
Ventricular tachycardia

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*
18 Jan. 86 to 24 Jan. 86

19. THERAPY DURATION
6 days

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

furosemide/Lasix -
digoxin/ - -
isosorbide dinitrate/Isorbide -

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)* 3-4 coronary bypass operations over past 8 years. Occasional angina in past. 4-5 years ago taken off Pronestyl due to arthritis development. Quinidex caused diarrhea and discontinued a year ago. Tonocard gave no adequate response. Long history symptomatic congestive failure with decreased function fairly well controlled.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
NDA 18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
1/28/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	77	M	1	24	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Myocardial infarction, heart block, cardiac arrest
Pt. is believed to have suffered a myocardial infarction on 24 Jan. 86 when he was admitted with recurrent ventricular tachycardia. The latter converted spontaneously following attempts at cardioversion. During hospitalization he was said to have developed episodes of non-specified heart block. Death was due to cardiac arrest.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

No autopsy performed.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE: 100 mg

16. ROUTE OF ADMINISTRATION: Oral

17. INDICATION(S) FOR USE: Ventricular tachycardia, atrial flutter

18. THERAPY DATES *(From/To)*: 12 Apr. 85 to 25 Jan. 86

19. THERAPY DURATION: 9 months

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

allopurinol/ -	10 months	psyllium hydrophilic mucilloid/Metamucil	9 months
digoxin/ -	9 months	furosemide/Lasix	6 months
nitroglycerin/Nitrobid	9 months	diocytl sodium sulfosuccinate/Colace	9 months
prednisone/ -	9 months	potassium/ -	6 months

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Arteriosclerotic heart disease, coronary artery disease, atrial flutter, nonsustained ventricular tachycardia.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: NDA 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 1/27/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

15 DAY REPORT
— YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers — 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

[redacted]

22. (Cont.)

iron/ -	9 months
nitroclycerin/ -	-

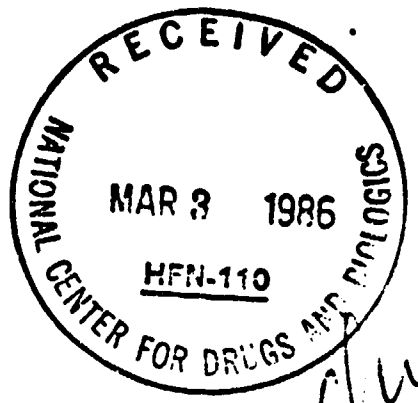
6.1

REPORTS
ORIGINAL

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

3M



3/4

February 21, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report - follow-up report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product in a foreign study. This is a follow-up report. A copy of the original report is also attached.

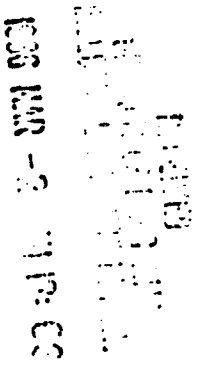
Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jgm
D2/3n

Enclosure - [redacted]

Certified Mail



DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	56	M	12	28	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Patient had been snowmobiling and was found cold, without pulse or respiration. Date of death uncertain. Had history of 3 myocardial infarctions, non-sustained ventricular tachycardia, hypokalemia, ejection fraction of 16%, congestive heart failure, cardiomegaly and left bundle branch block.
Unattended death

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☑ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

flecainide level 30 Oct. 85 was 0.43 microgm/ml. No autopsy.

II. SUSPECT DRUG(S) INFORMATION

* SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
300 mg	Oral	☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE: Ventricular tachycardia

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
15 Feb. 85 to 28 Dec. 85	10 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

digoxin/ - 10 months
potassium chloride/ - 10 months
furosemide/ - 10 months

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Arteriosclerotic heart disease, coronary atherosclerosis, duod. ulcer
(See also #7 above)

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
NDA 18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
1/24/86	☒ FOREIGN ☒ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25b. 15 DAY REPORT	25a. REPORT TYPE
☒ YES ☐ NO	☐ INITIAL ☒ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	56	M	12	28	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term.)*

Unattended death
Patient had been snowmobiling and was found cold, without pulse or respiration. Date of death uncertain. Has history of 3 myocardial infarctions, sustained ventricular tachycardia, sudden death, hypokalemia, ejection fraction of 16%, congestive heart failure, cardiomegaly and left bundle branch block.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

flecainide level 30 Oct. 85 was 0.43 microgm/ml. No autopsy.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor® / flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE
300 mg

16. ROUTE OF ADMINISTRATION
Oral

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE
Ventricular tachycardia

18. THERAPY DATES *(From/To)*
15 Feb. 85 to 28 Dec. 85

19. THERAPY DURATION
10 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

digoxin/ - 10 months
potassium chloride/ - 10 months
furosemide/ - 10 months

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Arteriosclerotic heart disease, coronary atherosclerosis, duod. ulcer.

(See also #7 above)

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
NDA 18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
1/24/86

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 5-DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL

3M

February 14, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product in a foreign country (Canada).

Sincerely,

Florence N Wong/Amm

Florence N. Wong
Regulatory Specialist

FNW/jgm
D2/3n

Enclosure - [redacted]

Certified Mail

2/21

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	56	M	12	28	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Unattended death
Patient had been snowmobiling and was found cold, without pulse or respiration. Date of death uncertain. Has history of 3 myocardial infarctions, sustained ventricular tachycardia, sudden death, hypokalemia, ejection fraction of 16%, congestive heart failure, cardiomegaly and left bundle branch block.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

flecainide level 30 Oct. 85 was 0.43 microgm/ml. No autopsy.

II. SUSPECT DRUG(S) INFORMATION

SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
300 mg	Oral	☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE
Ventricular tachycardia

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
15 Feb. 85 to 28 Dec. 85	10 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

digoxin/ - 10 months
potassium chloride/ - 10 months
furosemide/ - 10 months

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Arteriosclerotic heart disease, coronary atherosclerosis, duod. ulcer.

(See also #7 above)

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
NDA 18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
1/24/86	☒ FOREIGN ☒ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
☒ YES ☐ NO	☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL

3M

February 12, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong / AVB

Florence N. Wong
Regulatory Specialist

FNW/jgm
D2/3n

Enclosures - [redacted]

Certified Mail

Ann 2/24

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE	3. SEX	4.-6. REACTION ONSET		
[redacted]	YRS. 74	F	MO. 12	DA. 27	YR. 85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Ventricular flutter *Ventricular fibrillation* *Cardiac arrest* *Death*

Patient had syncopal episode and was brought to hospital in respiratory arrest. She was intubated and found to be in ventricular flutter which degenerated into ventricular fibrillation and cardiac arrest.

(See additional history in #23 below.)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

No autopsy was performed.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

amboco[R]/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
200 mg	Oral	☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE
Ventricular arrhythmia

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
19 Dec. 85 to 27 Dec. 85	8 days

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

furosemide/Lasix -
potassium/Slow K -
digoxin/ - -
allopurinol/ - -
hydralazine/hydrochlorothiazide/Apresazide -

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)* History of multifocal PVC's, couplets, non-sustained vent-tach, cardiomyopathy, Class I CHF, mild renal failure, PAV block, complete left bu.. le branch block, diabetes mellitus, hypertension, gout.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
NDA 18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
1/22/86	☐ FOREIGN ☒ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25.. 15 DAY REPORT	25a. REPORT TYPE
☒ YES ☐ NO	☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.- 26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

21

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL

3M

February 10, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong /AMM

Florence N. Wong
Regulatory Specialist

FNW/jgm
D2/3n

Enclosures - [redacted]

Certified Mail

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	63	M	1	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death
Patient died 1/13/86. Details of death are not yet known. Personal physician indicates that patient had recently been experiencing respiratory problems.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Unknown

II. SUSPECT DRUG(S) INFORMATION

SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

15. DAILY DOSE: 100 mg

16. ROUTE OF ADMINISTRATION: Oral

17. INDICATION(S) FOR USE: Ventricular tachycardia

21. DID REACTION RE-APPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*: 6/25/85 to 1/13/86

19. THERAPY DURATION: 6.5 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

sodium warfarin/Coumadin	6.5 months	sodium levothyroxine/Synthroid	6.5 months
digoxin/ -	6.5 months	prednisone/ -	-
bumetanide/Bumex	6.5 months	potassium chloride/Klotrix	6.5 months
		heparin sodium/ -	6.5 months

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)* Began taking flecainide 100 mg bid on 6/25/85. Within the first 2 months the dose was reduced to 50 mg bid. (Reason unknown). Patient had chronic obstructive pulmonary disease, Class III-IV, congestive heart failure, and massive cardiomegaly.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: NDA 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 1/20/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144

(612)733-0633

ORIGINAL

3M

February 4, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/he

enclosure

818

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-729)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date; May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted]

2. AGE YRS. 62

3. SEX M

4.-6. REACTION ONSET MO. 1 DA. 21 YR. 86

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)* *Heart failure*

Pt. had diffuse, ischemic cardiomyopathy diagnosed July, 85, marked runs of sustained ventricular tachycardia not responding to other drugs. Pronestyl led to lupus with elevated ANA, joint, pericardial, etc. for which pt. hospitalized. Steroids given, had peptic ulcer. Sustained V-tach recurred, one tablet flecainide given. Controlled V-tach, but 18 hours later pt. went into profound heart failure (History of 20% ejection fraction).

13. RELEVANT TESTS/LABORATORY DATA

Unknown

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE 100 mg

16. ROUTE OF ADMINISTRATION Oral

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE Ventricular tachycardia

18. THERAPY DATES *(From/To)* 20 Jan. 86 to 20 Jan. 86

19. THERAPY DURATION 1 dose

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

prednisone/Prednisone -
digoxin (Lanoxin)/Lanoxin -
furosemide/Lasix -
captopril/Capoten -
ranitidine hydrochloride/Zantac -

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See # 7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG NDA 18-830

24b. MFR CONTROL NO. [redacted]

24c. DATE RECEIVED BY MANUFACTURER 1/23/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

2

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

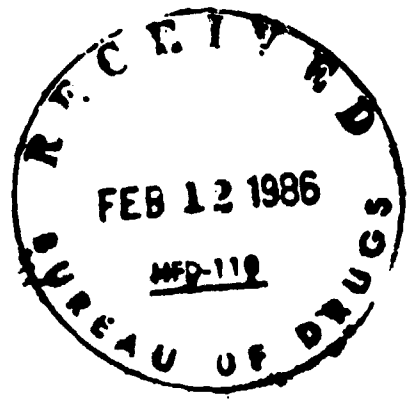
270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

REPORTS

3M

orig.

January 31, 1986



Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

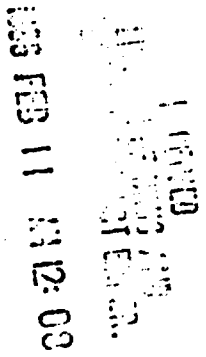
Enclosed are four Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product in a foreign country (France).

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jgm

Enclosures - [redacted]



2/14

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	33	F	10	15	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Patient died after ingesting 20 100 mg flecainide acetate tablets. No autopsy. Possibly the patient also took a benzodiazepine during this episode.

Death

13. RELEVANT TESTS/LABORATORY DATA

No autopsy done.

e

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE
- ☒ OVERDOSE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE
-

16. ROUTE OF ADMINISTRATION
Oral

DICATION(S) FOR USE
Suicide

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*
10/15/85 to 10/15/85

19. THERAPY DURATION
-

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

None known

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

?

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
NDA 18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
1/13/86

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	80	F	11	?	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death

Patient with atrial fibrillation was started on flecainide 1 month prior to death at a dose of 100 mg/day. One week later the daily dose was increased to 150 mg. Patient died three weeks later as a result of a sudden death event. There was no evidence of AV block or an increase in QRS interval. Patient was also taking Digoxin and Lasix.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Unknown

C

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
150 mg	Oral	☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE Atrial fibrillation

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
10/?/85 to 11/?/85	1 month

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

digoxin/Acetyldigitoxine	2 yrs.
furosemide/Lasilix	-

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

History of chronic bronchitis, mitral valve stenosis with dilated left atrium, atrial fibrillation (for two years).

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
NDA 18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
1/13/86	☒ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

5-DAY REPORT	25a. REPORT TYPE
☒ YES ☐ NO	☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE. Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	58	M	12	?	85

7. DESCRISE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden death
Patient had been on flecainide for 15 days. He was being treated for premature ventricular complexes. Patient died in December, 1985 from sudden death.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Unknown

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
200 mg	Oral	☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE
Ventricular arrhythmia

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
?/?/85 to 12/?/85	15 days

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

None/unknown

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Patient had cardiomyopathy with good ejection fraction of the left ventricle. Flecainide was well tolerated for 15 days.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
NDA 18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*	25a. REPORT TYPE
1/13/86	☒ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER	☒ INITIAL ☐ FOLLOWUP

5-DAY REPORT
☒ YES ☐ NO

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

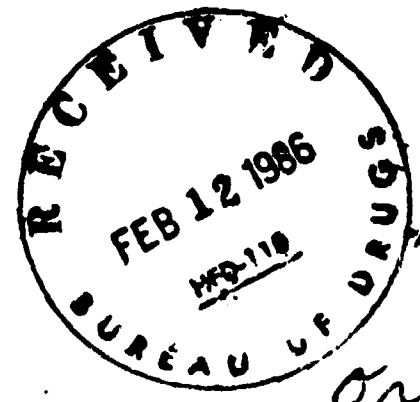
Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

REPORT

3M

January 30, 1986



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Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product in clinical studies.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jgm

enclosure

CL-214

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.
FDA CONTROL NO.
ACCESSION NO.

I. REACTION INFORMATION

PT ID/INITIALS *(In Confidence)* [redacted]

2. AGE	3. SEX	4.-6. REACTION ONSET		
		MO.	DA.	YR.
59 YRS.	M	12	13	85

1. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
Death
Longstanding serious cardiomyopathy, widespread arteriosclerosis, renal failure, Class III CHF, ventricular tachycardia, etc., went downhill and died of multiple system failures 17 days post OP from amputation of leg. (Subject also of report TT-86-006.)

8.-12. CHECK ALL APPROPRIATE TO REACTION
- ☑ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

3. RELEVANT TESTS/LABORATORY DATA
Elevated hepatic enzymes

C

II. SUSPECT DRUG(S) INFORMATION

4. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
Tambocor®/flecainide acetate

5. DOSE: 200 mg

16. ROUTE OF ADMINISTRATION: Oral

7. INDICATION(S) FOR USE: Ventricular tachycardia

8. THERAPY DATES *(From/To)*: 16 Nov. 85 to 12 Dec. 85

19. THERAPY DURATION: 27 days, 17 doses

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
nifedipine/ - -
furosemide/Lasix -
ranitidine hydrochloride/Zantac -
potassium chloride/K-Lor -
heparin sodium/Heparin -
sodium warfarin/Coumadin -
diocytl sodium sulfosuccinate/Colace -
psyllium hydrophilic mucilloid/Metamucil -
bisacodyl/Ducolax supp. - ; aspirin/ - -

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Strep, pneumonia, nephrosclerotic disease, carotid stenosis, cardiomegaly, confusion, peptic ulcer, poor potassium control, adenomatous small bowel polyps, malnutrition, coagulopathy, anemia, hyperglycemia, coronary artery bypass graft, left bundle branch block.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: NDA 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: /86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. ...AY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85)

PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

ENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	68	M	12	11	85

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Unwitnessed sudden death

Patient had an unwitnessed collapse at home while engaged in light physical activity and was found without pulse or respiration.

e

13. RELEVANT TESTS/LABORATORY DATA

No autopsy performed. Holter recording on 9 Dec. 85, 2 days before death, showed marked reduction in PVC's and complex forms compared to one made on 19 Nov. 85 before flecainide was started.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE: 300 mg

16. ROUTE OF ADMINISTRATION: Oral

17. INDICATION(S) FOR USE: Ventricular arrhythmia

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*: 01 Dec. 85 to 11 Dec. 85

19. THERAPY DURATION: 10 days

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

captopril/ - -
digoxin/ - -
prednisone/ - -
furosemide/Lasix -
theophylline/Theo-Dur -
potassium/ - -

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

History of multifocal PVC's, couplets and non-sustained vent-tach, severe CHF, ischemic cardiomyopathy, ASHD, COPD, IVCD, adult-onset diabetes mellitus and history of myocardial infarction.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
NDA 18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
1/22/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

DAY REPORT
ES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. 1

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

REPORTS'

3M

January 29, 1986

orig

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are five Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product in clinical studies.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/he

enclosure

2/10

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFR-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1 PAT ID/INITIALS *(In Confidence)*	2. AGE	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	62 YRS.	M	1	9	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term.)*

Cardiac arrest
Cardiac arrest secondary to previous myocardial infarction (11/27/85).
Previous MI is subject of [redacted]

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Unknown

C

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE: 200 mg

16. ROUTE OF ADMINISTRATION: Oral

17. INDICATION(S) FOR USE: Ventricular arrhythmia

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*: 4/6/84 to 1/9/86

19. THERAPY DURATION: 21 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

furosemide/Lasix	20 months	potassium chloride/ -	7.5 years
aspirin/ -	1 month	triamterene, chrochlorothiazide/Maxzide -	
nitroglycerin/Nitropaste	12 years	dipyridamole/Persantine	7.5 years

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

History of ASHD, myocardial infarction 1979 and 1980, sustained ventricular tachycardia, coronary artery disease, atrial fibrillation.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: NDA 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 1/10/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 10-DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	75	M	12	21	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Myocardial infarction
Patient suffered a myocardial infarction at home on 12/21/85. He was transported to the hospital but never regained consciousness and was found to be "brain-dead". On 12/23/85 he was removed from the respirator and pronounced dead.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Unknown

c

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor[R]/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

15. DAILY DOSE: 100 mg

16. ROUTE OF ADMINISTRATION: Oral

17. INDICATION(S) FOR USE: Ventricular tachycardia

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*: 9/3/85 to 12/21/85

19. THERAPY DURATION: 109 days

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

amiodarone/ -
furosemide/Lasix -
potassium chloride/ -
nitroglycerin/Nitrobid -
nifedipine/ -

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)* History: MI, CHF (Class II), angina (Class II), peripheral vascular disease, ASHD, first degree AV block, RBBB, PVC's, sustained ventricular tachycardia, nonsustained ventricular tachycardia, ventricular fibrillation and syncope. Diagnosis: Myocardial infarction.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: NDA 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 1/17/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

DAY REPORT
ES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

REPORTS!

3M

January 17, 1986

orig

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are four Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product in clinical studies.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/he

enclosure

RECEIVED
BUREAU OF DRUGS
JAN 31 1986
HFD-110

RECEIVED
OFFICE OF DRUG ABUSE
EXPOSURE PROTECT EVAL.
1986 JAN 31 AM 2:23

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	87	M	01	04	86

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Acute myocardial infarction
Patient entered hospital 01 Jan. 86 with myocardial infarction associated with many PVC's. Treatment with Xylocaine controlled PVC's but led to aggressive psychotic behavior on 03 Jan. 86. Flecainide started (Xylocaine discontinued then); after two tablets flecainide PVC's were less frequent, but after third tablet patient suffered another infarct and died.

13. RELEVANT TESTS/LABORATORY DATA

Unknown

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE 200 mg

16. ROUTE OF ADMINISTRATION Oral

17. INDICATION(S) FOR USE Ventricular arrhythmia

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)* 03 Jan. 86 to 04 Jan. 86

19. THERAPY DURATION 1 day

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

digoxin (Lanoxin)/Lanoxin

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Previous history of myocardial infarct with congestive heart failure controlled with digoxin.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG NDA 18-830

24b. MFR CONTROL NO. [redacted]

24c. DATE RECEIVED BY MANUFACTURER 1/8/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25c. 5-DAY REPORT ☐ YES ☐ NO

25a. REPORT TYPE ☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 733-0633

ORIGINAL

3M

January 10, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15 day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product in clinical studies.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jgm

Enclosure

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID./INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	65	M	12	08	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden death

Shortly after breakfast, while visiting relatives, patient collapsed without prior symptoms. Taken to the hospital, his family was told, "He had had a massive heart attack and could not be resuscitated." Flecainide had reduced PVC's from 27,000/22 hrs. before treatment to total elimination of ventricular ectopy on 30 Sept. 85. No autopsy done.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

None available. No autopsy.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
400 mg	Oral	☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE Ventricular arrhythmia

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
17 Sept. 85 to 08 Dec. 85	3 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

nifedipine/ - 3 months
tolbutamide/ - unknown
triamterene/ - unknown
methyldopa/ - unknown
nitroglycerin transdermal/ - 3 months

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Before treatment with flecainide, history of arteriosclerotic heart disease, hypertensive heart disease, first degree heart block, cardiomegaly, old INF/septal infarct, diabetes mel., calcified aortic valve.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
NDA 18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
2/27/85	☐ FOREIGN ☒ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
☒ YES ☐ NO	☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)733-0633

REPORTS
ORIGINAL

3M

January 7, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product in a clinical study.

Sincerely,

Florence N Wong/AVM

Florence N. Wong
Regulatory Specialist

FNW/he

enclosure

1/22

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE	3. SEX	4.-6. REACTION ONSET		
[redacted]	62 YRS.	M	12 MO.	09 DA.	85 YR.

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden death

Death following dizziness and syncope. CPR unsuccessful.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☒ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Not available.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE 400 mg

16. ROUTE OF ADMINISTRATION Oral

17. INDICATION(S) FOR USE Ventricular arrrhythmia

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)* 15 Feb. 85 to 09 Dec. 85

19. THERAPY DURATION 297 days

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

diltiazem HCL/ - 1 yr. 250 days
digoxin/Lanoxin >10 mos.
triamterene, hydrochlorothiazi/Dyaz'de >10 mos.
aspirin/ - 300 days

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Arteriosclerotic heart disease, history of myocardial infarction, left and right ventricle enlargement, coronary artery disease, post coronary bypass graft, history of congestive heart failure.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
IND 18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
12/12/85

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144

(612)733-0633

ORIGINAL

REPORTS

3M

January 7, 1985

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong

Florence N. Wong
Regulatory Specialist

FNW/he

enclosure

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	73	M	12	14	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death *Left ventricular failure*

Endstage multisystem failure resulting from decreased left ventricular function. No attempt was made to resuscitate patient.

13. RELEVANT TESTS/LABORATORY DATA

No autopsy performed.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
50 mg	Oral	☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE
Ventricular arrhythmia

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
28 Sept. 85 to 14 Dec. 85	2 ½ months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

nifedipine/Procardia --
procainamide HCL/Procan SR --
digoxin/Digoxin --
temazepam/Restoril --

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)* History of renal failure, endstage congestive heart failure, coronary bypass surgery (4 vessel), myocardial infarction, transient cerebral ischemic attacks, left carotid endarterectomy, severe coronary artery disease..

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
12/26/85	☐ FOREIGN ☒ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
☒ YES ☐ NO	☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

2

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144

(612)733-0633

REPORTS

ORIGINAL

3M

January 3, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong

Florence N. Wong
Regulatory Specialist

FNW/he

enclosure

1/2~

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

VERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	65	M	12	14	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Unwitnessed Sudden Death

Death: Pt. suffered an unwitnessed sudden death and was dead on arrival at the hospital. It is not known whether the death was due to lack of arrhythmic control, or was an aggravation of the arrhythmia.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Trough plasma levels: 0.40 microgram/ml at 100 mg bid on 11-30-85;
0.29 Microgram/ml at 150 mg bid on 12-6-85;
0.34 microgram/ml at 150 mg bid on 12-11-85

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
300 mg	Oral	☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE: Paroxysmal ventricular tachycardia

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
11-27-85 to 12-14-85	18 days

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

Dilantin/phenytoin	about 10+ years
Lanoxin/digoxin	2 months

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Pt. had a history of sustained ventricular fibrillation, sustained VT and out of hospital sudden death prior to Tambocor therapy. Three other antiarrhythmic drugs had proved ineffective in controlling his arrhythmia.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: NDA #18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 12-17-85

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

2

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

Regulatory Affairs
Riker Laboratories Inc.

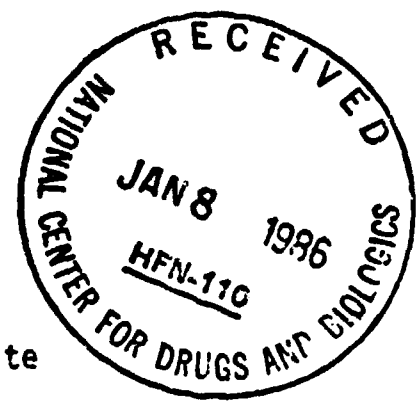
270-3A 3M Center
St. Paul, Minnesota 55144

(612)733-0633

ORIGINAL

3M

January 2, 1986



Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product.

VF

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/he

enclosure

1/13/86

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	72 YRS.	M	12	10	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death
Ventricular fibrillation
Death -- "Coarse ventricular fibrillation" reported by paramedic.

13. RELEVANT TESTS/LABORATORY DATA

"Coarse ventricular fibrillation" noted by paramedic.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

DAILY DOSE: 200 mg

16. ROUTE OF ADMINISTRATION: Oral

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☒ NO ☐ NA

17. INDICATION(S) FOR USE: Ventricular arrhythmia

18. THERAPY DATES *(From/To)*: 5-17-85 to 12-10-85

19. THERAPY DURATION: 7 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

Persantine/dipyridamole 7 months

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Before starting flecainide patient had history of hypertensive cardiovascular disease, first-degree A-V block, cerebrovascular accident sick sinus syndrome and permanent pacemaker installation.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144

24a. IND/NDA. NO. FOR SUSPECT DRUG: NDA 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 12-12-85

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

MEMO OF TELECON

Between:

FDA

Director
Office of Drug Research and Review
Center for Drugs and Biologics

and

Riker Labs

Dr. Jerry Sentzkow
Director, Medical Affairs

Mr. Roland Catherall
Manager, Regulatory Affairs

Mr. David Ward
Associate Director, Clinical Research

Florence Wong, Pharm.D.
Regulatory Specialist

Date: September 13, 1985

The telephone call was initiated to help Riker prepare for an October meeting to discuss the recent approvable letter for their drug flecainide, NDA 18-830. That letter proposed indications for use that were far more restrictive than the Company had proposed and they wished to discuss various ways in which they believe these indications should be broadened. I briefly recapitulated the reasons behind the restrictive labeling, noting that there was both a general problem of how best to use anti-arrhythmics and specific questions raised by the pro-arrhythmogenicity of flecainide in certain patient populations. I emphasized that while this property could be managed in the hospital and was an acceptable risk in patients with serious ventricular arrhythmias, I did not think, on the basis of what I had reviewed to date, that it was an acceptable risk in patients with non-life threatening disease or in patients who could not be hospitalized while the drug was administered to them. I noted that while the labeling specifically recommends flecainide for people with life-threatening arrhythmias, such as sustained ventricular tachycardia, and specifically says that flecainide cannot be recommended for people with lesser arrhythmia such as frequent ventricular premature beats, the labeling was deliberately ambiguous as to whether patients with non-sustained ventricular tachycardia were candidates for flecainide therapy.

I thought the determination of whether non-sustained ventricular tachycardia is a life-threatening ventricular arrhythmia had to be left to the physician.

The Riker representatives, particularly Dr. Jentzkow, thought that there was room for some expansion of the claims. They thought that some non-sustained ventricular tachycardia was clearly debilitating to the patient and that it would not be unreasonable to include a claim for people in that situation. They also thought that some patients with frequent VPBs were so debilitated by the condition that they could not hold jobs etc. and that some of those people might be candidates also. Riker has a considerably increased experience to present to us in October, including several hundred more patients in the 057 protocol which uses the new slow titration regimen; included among those patients are both additional patients with serious ventricular arrhythmias and also patients with less serious arrhythmias, some of whom were started on drug outside the hospital. They also have the results of a monitored release study carried out in Great Britain involving some 300 patients with relatively mild ventricular arrhythmias. Dr. Jentzkow appeared to agree that for both serious and mild arrhythmias the more conservative dosing recommendations that we proposed would be appropriate.

They plan to submit written material by the end of September in preparation for the October meeting. I indicated that there seemed room for some modifications in the labeling, especially with respect to the ambiguous status of non-sustained ventricular tachycardia, and we all appeared to agree that this was not a drug for people with frequent VPBs alone; that is, it is not a drug to "treat the Holter".

I took the occasion also to compliment Riker for the excellent document they had put together in preparation for the advisory committee meeting. I said that I had found it useful, candid, and an outstanding example of that kind of submission. They seemed pleased.

Robert Temple

Robert Temple, M.D.

cc:
Orig. NDA 18-830
HFN-110 Dr. Lipicky
HFN-110 Dr. Chun
HFN-110 CSO
HFN-110 Division File
HFN-101 Dr. Botstein

ODRR/RTemple/md
9-18-85 0124d
F/T: md/9/19/85

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

Date SEP 6 1985

From Director
Office of Drug Research and Review/HFN-100

Subject: NDA 18-830, Flecainide

To Acting Director
Division of Cardio-Renal Drug Products/HFN-110

I noticed in going over the summary basis of approval (SBA) and my notes that three potentially important adverse reactions included in the medical officer's review, and which I wrote into the summary basis of approval are not in the revised labeling we sent the Company. These are exfoliative dermatitis, anorexia, and an episode of swollen lips, tongue and mouth, possibly signifying an allergic reaction. The first and third of these are potentially important and certainly ought to be included in the list of adverse reactions occurring under 1%. Dr. Chun could perhaps call the Company to mention this.

Robert Temple, M.D.

cc:
Orig. NDA 18-830 ✓
HFN-110 Dr. Chun
HFN-110 Division File
HFN-110 CSO

DDRR/RTemple/md
S-3-85 .0103d
F/T: 9/5/85

NOV 13 1986

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA # 18-830

NOV 13 1986

Name of Drug Tombocor (flecainide)

Sponsor: Riker

Type of Submission: ADR

Date of Submission: 9/3/86

Date of Review: 9/12/86

Reviewer: Sughok K. Chun, M.D. HFN-110

A. Resume:

[redacted]

PROFOUND HYPOTENSIVE SHOCK
This is a 65-year-old man with history of hypertension and angina of recert onset was treated satisfactorily with nitroglycerin and nifedipine. He had runs of nonsustained ventricular tachycardia. For this latter condition while in the hospital, he was administered 100mg b.i.d. of flecainide. After three days of this regimen, his arrhythmia was we controlled with a 90% reduction of VPCs. About five days into his treatment course, the patient was found unconscious and unresponsive lying on the floor beside his bed in the intensive care unit. Although monitored, nothing had appeared in terms of abnormal EKG nor was it found in his present condition. His BP was 40/0 and HR of 50. Serum lactate was 23 (this was repeated and confirmed at 23). Cardiac output was determined to have fallen to 2 L/min, internal cardiac chamber pressures incuding PW pressure were normal. Two echocardiograms were WNL. This patient was treated with dobutamine, and 24 hours after the incident his cardiac output was > 4L/min although he remains unresponsive. Flecainide level was drawn shortly after onset of hypotension but results are not yet back.

Concomitant Rx: Nifidipine, NTG.

S K. Chun 10/20/86

Sughok K. Chun, M.D.

cc:
ORIG:
HFN-110
HFN-110/CSO
HFN-110/SChun/10/16/86
cb/10/16/86/1057v

7.1

NOV 13 1986

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA# 18-830

Name of Drug: TOMBOCOR (flecainide) Tablets

Sponsor: Riker Lab

Type of Submission: ADR

Date of Submission: 8/28/86

Date of Review: 9/9/86

Reviewer: Sughok K. Chun, M.D. HFN-110

A. Resume:

A case report of "OVERDOSE, GIANT INVERTED T-WAVES, MARKED PROLONGATION OF JT-INTERVAL" by H.J.G.M. Crijns, J.H. Kingma, J.W. Viersma, and K.I. Lie. Accepted for publication about 8/86 in American Heart Journal.

[redacted] A 61-year-old woman with a longstanding history of hypertension was treated with flecainide 300 mg t.i.d. at the outpatient department because of Lown IV A arrhytmias causing palpitations. Treatment of hypertension with prazosin 1 mg t.i.d. was left unchanged. The palpitations disappeared rapidly. Two weeks after institution of F the patient was admitted to the hospital with complaints of headaches, blurred vision, photophobia, paraesthesias and general weakness. On admission PE revealed HR 89 beats/min., BP 190/125 mmHg and a fourth heart sound. Full neurologic physical examination was unremarkable. Chest X-ray showed a slight enlargement of the left ventricle and no signs of pulmonary congestion. ECG showed broadening of P-waves, prolongation of PR-interval (0.26 s) and widening of QRS-complexes (0.14 s) with left axis deviation indicating conduction delay in the left anterior fascicle. JTc interval (0.37 s). At that moment the flecainide plasma levels was 2500 ng/ml. Flecainide was discontinued. Hypertension was treated succesfully with captopril. Throughout the whole course of admission serum electrolytes were normal. There was a moderate disturbance of renal function (creat. clearance 40 ml per min) which undoubtfully contributed to the excessively high plasma levels of F. The elimination half life of F appeared to be approximately 80 hours. The most remarkable ECG feature was lengthening of JT-interval to 0.56 s (JTc: 0.60 s), with development of giant inverted T-waves on the third hospital day. These changes persisted from day 3 to day 6, at F plasma levels declining from 1860 to 1125 ng/ml, although at the lower plasma levels the changes were less pronounced. During this period there was a reduction in QRS-width.

No arrhythmia was observed during this period.

At a plasma level of 490 ng/ml the JT-interval normalized and giant inverted T-waves had disappeared, while there was still left axis deviation at a QRS-width of 0.09 s. After complete washout of F ECG normalized completely, however, episodes of VT of probably focal origin appeared. F was resumed at a lower dose of 50 mg b.i.d. resulting in plasma levels around 500 mg/ml. At these plasma levels no ECG-abnormalities were seen apart from the usual QRS-widening.

CONCLUSION:

This patient apart from the known therapeutic effects of F on the surface-ECG also an extreme prolongation of JT-interval with giant inverted T-waves, only occurring in a discrete window of plasma levels between 1860 and 1125 ng/ml. Ideda et.al. reported a modest increase of action potential duration of canine ventricular muscle cells by F. This could explain the increase in JT-interval, expecially at toxic plasma levels in this patient. However, this dose not explain the occurrence of giant negative T-waves. Apart from F intoxication, other possible causes of the reported changes and their transient nature could be concomitant cerebral disorder, or AV-block with a slow escape rhythm, for wnich no clinical evidence was present.

Primary inhomogeneous depolarization patterns could have provoked these changes in repolarization. Indeed in this patient during washout of F there was a reduction of QRS-width, indicating improvement of intraventricular conduction. However, this was not parallelled by a proportional decrease in the JT-interval, indicating that the observed repolarization disturbances cannot be explained on the basis of slowed intraventricular conduction only.

In view of these considerations the authers concluded that the JT-prolongation with giant inverted T-waves seems to be characteristic of severe F intoxication.

S K Chun 10/20/86

Sughok K. Chun, M.D.

cc:
ORIG
HFN-110
HFN-110/CSO
HFN-110/SChun/10/16/86
cb/10/16/86/1059v

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

ORIGINAL

3M

August 28, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW:br

Enclosure - [redacted]

Certified Mail P 648 917 304

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	61	F	??	??	??

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
#OVERDOSE, GIANT INVERTED T-WAVES, MARKED PROLONGATION OF JT-INTERVAL#
Material obtained is reflected in the attached manuscript by [redacted] Accepted for publication about 8/86 in American Heart Journal.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X OVERDOSE

13. RELEVANT TESTS LABORATORY DATA
Blood levels peaked at 2.5 ng/ml (normal .2-1.0 ng/ml).

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
900 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

18. THERAPY DATES *(From To)*
??/??/?? - ??/??/??

19. THERAPY DURATION
2 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[X] YES [ ] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [X] NO [ ] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
7/ 3/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [X] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

[redacted]

TRANSIENT GIANT INVERTED T WAVES DURING FLECAINIDE INTOXICATION.

[redacted]

From the Division of Cardiology, [redacted]

Reprint requests: [redacted]
Department of Cardiology, [redacted]

Clinical studies have shown that flecainide used at therapeutic plasma levels neither prolongs JT-interval significantly, nor gives T-wave abnormalities on the surface ECG (1,2). Reports on flecainide causing JT-prolongation are rare (3). Moreover, to our knowledge there are no reports on JT-prolongation with the development of giant inverted T-waves associated with the administration of flecainide.

Here we report a case of an unexpected flecainide-intoxication in which giant inverted T-waves with marked prolongation of the JT-interval appeared during the washout period of flecainide in an intoxicated patient. Because of Lown IV A arrhythmias causing palpitations a 61-year-old woman with a longstanding history of hypertension was treated with flecainide 300 mg t.i.d. at the outpatient department. Treatment of hypertension with prazosin 1 mg t.i.d. was left unchanged. The palpitations disappeared rapidly. Two weeks after institution of flecainide therapy the patient was admitted to the hospital with complaints of headaches, blurred vision, photophobia, paraesthesias and general weakness. On admission physical examination revealed a pulse rate of 89 beats/min., a blood pressure of 190/125 mmHg and a fourth heart sound. Full neurologic physical examination was unremarkable. Chest X-ray showed a slight enlargement of the left ventricle and no signs of pulmonary congestion. The electrocardiogram showed broadening of P-waves (approximately 0.16 s), prolongation of PR-interval (0.26 s) and widening of QRS-complexes (0.14 s) with left axis deviation indicating conduction delay in the left anterior fascicle. The JT-interval was 0.32 s (JTc according to Bazett's formula: 0.37 s). At that moment the flecainide plasma levels was 2500 ng/ml. Flecainide was discontinued and the patient was continuously monitored for ventricular arrhythmias. Hypertension was treated succesfully with captopril. Throughout the whole course of admission serum electrolytes were normal. There was a moderate disturbance of renal function (creat.clearance 40 ml per min) which undoubtfully contributed to the excessively high plasma levels of flecainide. The elimination half life of flecainide appeared to be approximately 80 hours (fig.1). Figure 2 shows typical changes of the electrocardiogram with matching flecainide plasma levels. The most remarkable feature was lengthening of JT-interval to 0.56 s (JTc: 0.60 s), with development of giant inverted T-waves on the third hospital day. These changes persisted from day three untill day six, at flecainide plasma levels declining from 1860 to 1125 ng/ml, although at the lower plasma levels the changes were less pronounced. During this period there was a reduction in QRS-width.

— 900 n. !

Although prolonged JT-interval with giant inverted T-waves are reported to be highly arrhythmogenic (5,6) since they might reflect temporal dispersion of refractoriness and non-uniform recovery of cardiac fibres, we did not observe any arrhythmias. At a plasma level of 490 ng/ml the JT-interval normalized and giant inverted T-waves had disappeared, while there was still left axis deviation at a QRS-width of 0.09 s. After complete washout of flecainide the electrocardiogram normalized completely, however episodes of ventricular tachycardia of probably focal origin appeared. Flecainide therapy was resumed at a lower dose of 50 mg b.i.d. resulting in plasma levels around 500 ng/ml. At these plasma levels no ECG-abnormalities were seen apart from the usual QRS-widening.

In conclusion we observed in this patient apart from the known therapeutic effects of flecainide on the surface-ECG also an extreme prolongation of JT-interval with giant inverted T-waves, only occurring in a discrete window of plasma levels between 1860 and 1125 ng/ml. Ikeda et.al.reported a modest increase of action potential duration of canine ventricular muscle cells by flecainide (7). This could explain the increase in JT-interval in our patient, especially at toxic plasma levels. However this does not explain the occurrence of giant negative T-waves. Apart from flecainide intoxication, other possible causes of the reported changes and their transient nature could be concomitant cerebral disorder, or AV-block with a slow escape rhythm, for which no clinical evidence was present.

Finally primary inhomogeneous depolarization patterns could have provoked these changes in repolarization. Indeed in our patient during washout of flecainide there was a reduction of QRS-width, indicating improvement of intraventricular conduction (fig.2). However, this was not parallelled by a proportional decrease in the JT-interval, indicating that the observed repolarization disturbances cannot be explained on the basis of slowed intraventricular conduction only.

In view of these considerations we conclude that the JT-prolongation with giant inverted T-waves seems to be characteristic of severe flecainide intoxication.

Legend fig. 1 : Washout curve of flecainide, determined by once daily determination of the flecainide plasma level.

Legend fig. 2 : Leads II and V3 showing typical changes of the electrocardiogram during washout of flecainide. Left panel pre-drug state, showing one normal QRS-complex and a ventricular extrasystole.
Paper speed 25 mm/sec.

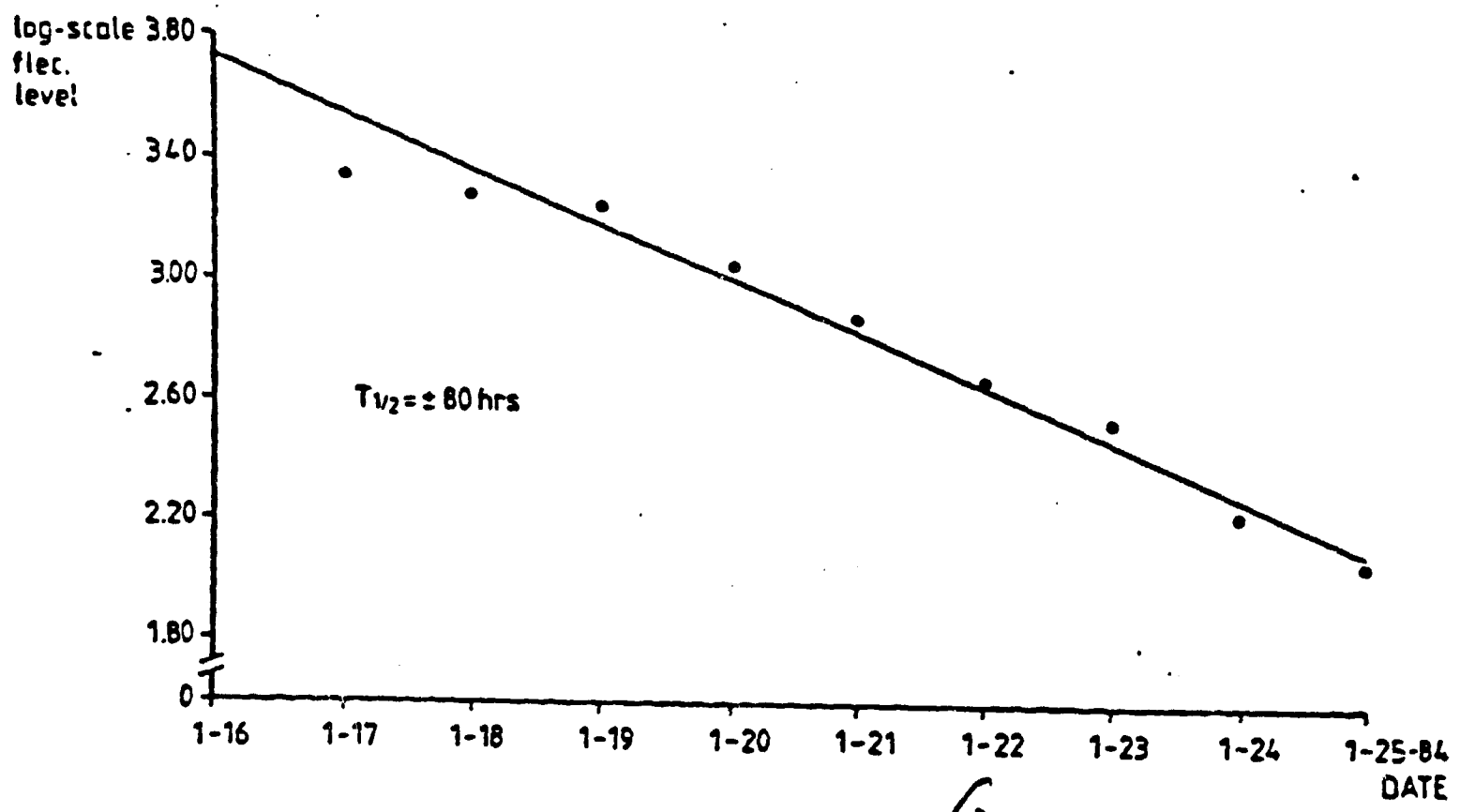

log-scale 3.80
flec.
level
3.40
3.00
2.60
2.20
1.80
0
$T_{1/2}$ = ± 80 hrs
1-16
1-17
1-18
1-19
1-20
1-21
1-22
1-23
1-24
1-25-84
DATE

fig 1

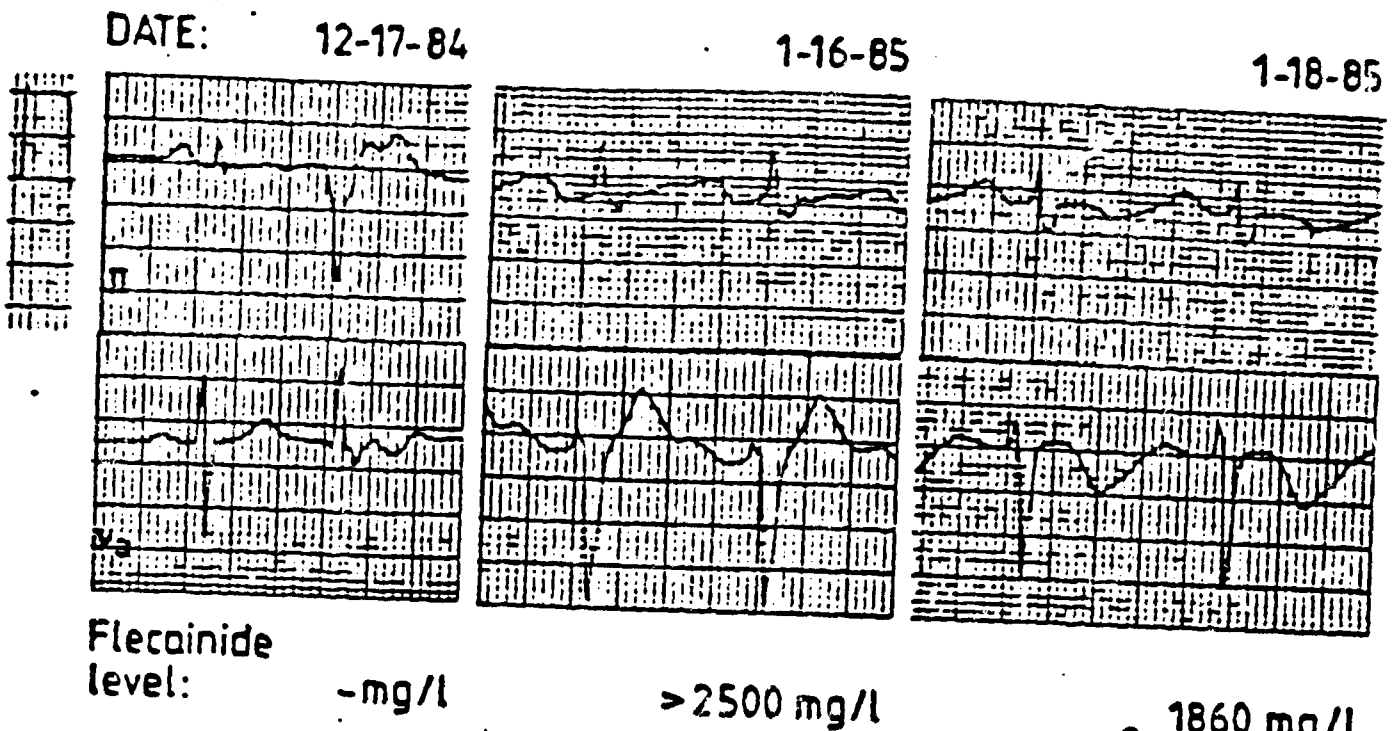

DATE:
12-17-84
1-16-85
1-18-85
Flecainide level:
-mg/l
>2500 mg/l
1860 mg/l

fig 2

REFERENCES.

1. Anderson JL, Stewart JR, Perry BA, Pitt B. et al. Oral flecainide acetate for the treatment of ventricular arhytmias. N Engl J Med 305:473, 1981.
2. Duff HJ, Roden DM, Matucci RJ. et. al. Suppression of resistant ventricular arrhythmias by twice daily dosing with flecainide. Am J Card 48:1133, 1981.
3. Lui HK, Lee G, Dietrich P, Low RI, Mason DT. Flecainide induced QT prolongation and ventricular tachycardia. Am Heart Journal 103:567, 1982.
4. Lown B, Wolf M. Approaches to sudden death from coronary heart disease. Circulation 44:130,1971.
5. Selzer A, Wray HW. Quinidine syncope: paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. Circulation 30:17, 1964.
6. Denes P, Gabster A, Huang SK. Clinical electrocardiographic and follow-up observations in patients having ventricular fibrillation during Holter monitoring. Am J Card 48:9, 1981.
7. Ikeda N, Singh B, Davis L, Hauswirth O. Effects of flecainide on the electrophysiologic properties of isolated canine and rabbit myocardial fibres. J Am Coll Card 5:303, 1985.

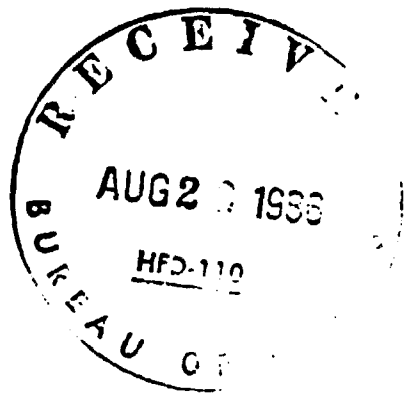
Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

ORIGINAL

3M

August 20, 1986



Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialis.

FNW/jlg

Enclosure - [redacted]
- [redacted]

Certified Mail P 648 917 293

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	75	M	07	30	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

FULMINANT PNEUMONIA (? VIRAL)
This 75-year-old man was first seen on 7/25/86 for angina at which time it was determined from an EKG that he had an infarct probably in the order of a few weeks old. Although not specifically known, it is presumed that he had premature ventricular contractions as flecainide was started at that time. It is noteworthy that at that time chest x-ray was clear. He was next seen at the emergency admission early on 7/31/86 with shortness of breath. Chest x-ray showed developing pneumonia bilaterally. White count and differential were normal and the patient was afebrile. Flecainide as well as Cardizem were discontinued. Cultures were taken and the patient deteriorated clinically. Catheter-

13. RELEVANT TESTS LABORATORY DATA

Autopsy refused.

not F-related.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From To)*: 07/25/86 - 07/30/86

19. THERAPY DURATION: 5 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DILTIAZEM HCL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

One month history of angina with suggestion of resolving myocardial infarct.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 8/ 5/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-738)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ization showed normal pressures and no evidence of heart failure. Pre-mature ventricular contractions had increased. A variety of antibiotics were started on an empirical basis, but the patient continued to deteriorate and died on 8/3/86. Autopsy was refused. The physician thinks that the drug was unrelated to the death which was caused by a pulmonary infection.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

INDICATION(S) FOR USE

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

Riker Laboratories, Inc.

270-3A-01 3M Center
St. Paul, Minnesota 55144
(612)733-0633

1.1

REPORTS

3M

August 7, 1986

ORIGINAL

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jlg

Enclosure - [redacted]
- [redacted]

RECEIVED
AUG 14 1986
HFD-110
BUREAU OF DRUGS

Certified Mail P 648 917 292

8/22

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	64	M	02	09	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

WORSENED CONGESTIVE HEART FAILURE, PLEURAL EFFUSION, DEATH
DEATH POSSIBLY DUE TO WORSENING CONGESTIVE HEART FAILURE. (MORE INFORMATION EXPECTED)
07/24/86..PATIENT WAS A 64 YEAR OLD MALE ADMITTED ON 2/7/86 FOR A PERSISTENT RIGHT SIDED PLEURAL EFFUSION. HIS CARDAIC HISTORY BEGAN IN 1977 WHEN HE UNDERWENT QUADRUPLE ACBP. HE DID WELL UNTIL 12/85 WHEN HE DEVELLOPED ATRIAL FLUTTER, MANIFESTING AS CONGESTIVE HEART FAILURE. HE DID NOT CONVERT TO NSR WITH DIGOXIN AND QUINAGLUTE. SHORT RUNS OF V. TACH WERE ALSO NOTED. HE WAS ELECTRICALLY CARDIOVERTED ON 12/24/85 WITH SIGNIFICANT SYMPTOMATIC IMPROVEMENT. PROCAN SR WAS BEGUN FOR V. TACH. A CARDIAC CATH REVEALED PATENT GRAFTS, AN AKINETIC INFERIOR WALL,

13. RELEVANT TESTS LABORATORY DATA

ANATOMICAL DIAGNOSIS:
1. Ichemic heart disease, manifested by:
(a) Coronary artery atherosclerosis, Grade IV--RCA: 100% occlusion; LAD: 80% occlusion; LCX: 100% occlusion.
i) Status-post aorto-coronary bypass graft X 4 (1977) all

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*
12/31/85 - 02/18/86

19. THERAPY DURATION
39 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

CAPTOPRIL
FUROSEMIDE
POTASSIUM CHLORIDE
DIGOXIN
CHLORPROPAMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

CASE FORMS WITH HISTORY AWAITED

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
7-24-86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

5 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

RV 71/4 PA 56/10 PCWP 25. EF WAS COMPUTED TO BE 37%
PERSISTENT VENTRICULAR ARRHYTHMIAS NECESSITATED THE INITIATION OF
FLECAINIDE ON 12/31/85, WITH SOME INPROVEMENT. A MUGA ON 1/6/86
REVEALED A LVEF OF 25%. HE DID WELL AFTER DISCHARGE, EXCEPT FOR A BRIEF
ADMISSION IN 1/86 FOR EXACERBATION OF CHF. VIGOROUS DIURESIS WAS CONTIN
UED AFTER DISCHARGE. ON 2/7/86 HE WAS ADMITTED FOR A PERSISTENT RIGHT
PLEURAL EFFUSION AND COUGH. THE IMPRESSION ON ADMISSION WAS THAT OF A
64 Y/O MALE WITH CHF, VENTRICULAR ARRHYTHMIAS, AND A RIGHT SIDED PLEURAL
EFFUSION PERSISTING DESPITE VIGOROUS DIURESIS. FURTHER INVESTIGATIVE
STUDIES REGARDING THE ETIOLOGY OF THIS EFFUSION WERE PLANNED. THE META-
BOLIC ABNORMALITIES WERE FELT TO BE SECONDARY TO DEHYDRATION, AND

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

grafts patent and arterialized; right graft with 50% narrowing.
ii) Vessels distal to bypass graft with Grade IV atherosclerosis:
RCA: 90% occlusion; LAD-A: 9% occlusion; LAD-B: 100% occlusion;
LCX: 95% occlusion.
(b) Old transmural myocardia infarction, left ventricle.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
17. INDICATION(S) FOR USE	
18. THERAPY DATES *(From/To)*	19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)* ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER
5 DAY REPORT ☐ YES ☐ NO	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 3)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

CAUTIOUS FLUID REPLACEMENT WAS BEGUN. K WAS REPLACED ALSO. A SWAN-GANZ CATHETER REVEALED RV 80/3, PA 78/30, PCWP 32. FLECAINIDE WAS THOUGHT TO PLAY A ROLE IN THIS EXACERBATION OF CHF SO IT WAS DISCONTINUED ON 2/8/86 AT 23:15 ON 2/8/86 THE PATIENT BECAME UNRESPONSIVE. V TACH AND APNEA WERE NOTED. RESUSCITATIVE MEASURES WERE UNSUCCESSFUL.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

(c) Congestive cardiac failure (clinical).
2. Cardiomegaly (800 gm):
(a) Biventricular hypertrophy
(b) Hypertension (clinical)
(c) Fibrocalcific mitral valve disease (mild)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
17. INDICATION(S) FOR USE	
THERAPY DATES *(From/To)*	19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)* ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER
7 DAY REPORT ☐ YES ☐ NO	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 4)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

3. Pulmonary atelectasis, bilateral: Pulmonary hypertension (secondary to 1. (c). Right pleural effusion (800 ml).
NOTE: Post-mortem blood and pleural cultures are negative.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

5 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

25b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

Riker Laboratories, Inc.

270-3A-01 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL

3M

August 15, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jlg

Enclosure - [redacted]

Certified Mail P 648 917 294

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-720)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved. OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	59	M	06	07	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

RESPIRATORY ARREST, VENTRICULAR FIBRILLATION
This 59-year-old man was admitted to emergency room with ventricular fibrillation and respiratory arrest on 6/7/86. He was maintained on a ventilator and treated with Bretyllium, Lidocaine, IV Cedilanid, epinephrine, and bicarbonate. The next morning (6/8/86), he apparently aspirated bloody vomitus and was started on IV Keflin and hydrocortisone and IV Zantac. Several hours later, his condition further deteriorated with multiple PVCs, hypotensin, grand mal seizure, and asystole. He failed to respond to IV Lidocane and Dopamine and died that day (6/8/86).

C

13. RELEVANT TESTS LABORATORY DATA

6/7/86: Digoxin level 0.62 ng/ml; flecainide level 0.55 mcg/ml. A chest x-ray revealed no acute infiltrates and no overt failure. An initial EKG revealed atrial fibrillation with nonspecific ST depression, suspicious of a subendocardial injury.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: ATRIAL FIBRILLATION

18. THERAPY DATES *(From To)*: 05/30/86 - 06/07/86

19. THERAPY DURATION: 9 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

MECLIZINE
METOCLOPRAMIDE HYDROCHLORIDE
DESIPRAMINE HCL
DIAZEPAM
RANITIDINE
ACETYLSALICYLIC ACID
DIGOXIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Prior to flecainide: peptic ulcer, hiatal hernia, carotid endarterectomy, appendectomy, inner ear disorder, angina.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 7/17/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

Riker Laboratories, Inc.

270-3A-01 3M Center
St. Paul, Minnesota 55144

P-2 ORIGINAL

3M

August 14, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir or Madam:

Pursuant to 21 CRF 314.80, enclosed is the Periodic ADR Report for Tambocor (flecainide acetate) NDA 18-830. There are 60 FDA-1639 forms in this submission, all of which are initial reports.

The time period covered by this report is March 11, 1986 to June 11, 1986.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jg

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	76	M	02	21	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Unresuscitable ventricular tachycardia, death
Patient with many years history of intermittent ventricular tachycardia and history of cardiac arrest 8 years before, stopped Norpace the day before event and started flecainide. Collapsed in cardiologist's office in V-tach which proceeded to V. fibrillation. Treatment with lidocaine, bretylium and shock did not avail. Underlying cardiac status said to be generally good.

13. RELEVANT TESTS LABORATORY DATA
ECG

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [x] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

THERAPY DATES *(From/To)*
02/20/86 - 02/21/86

19. THERAPY DURATION
2 DOSES

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [x] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
FUROSEMIDE YEARS

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
SEE #7 ABOVE.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
2/21/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [x] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [x] NO

25a. REPORT TYPE
- [x] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO	DA.	YR.
[redacted]	72	M	03	08	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

****THROMBOCYTOPENIA, LEUKOPENIA****

72 y.o. man with history of hypertension, arthritis, pemphigous resected abdominal aneurysm and ventricular tachycardia (latter attempted to be treated with procainamide and Norpace but intolerant to them) was admitted to hospital on 19FEB86 for right chest pain. He was on multiple medications. Ventricular fibrillation and cardiac arrest occurred 21FEB86 resuscitated with lidocaine after which TONOCARD was begun. He also had chronic obstructive pulmonary disease which now became prominent requiring addition of aminophylline and SoluMedrol. He now had multifocal atrial?tachycardia for which verapamil was begun. On 22FEB86 respiratory arrest ensued and i.v. LOPRESSOR was added for multifocal

13. RELEVANT TESTS LABORATORY DATA

See #7, above for hematolotical and bacteriological information.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: 28FEB86 - 11MAR86

19. THERAPY DURATION: 11 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

CIMETIDINE
FUROSEMIDE
VERAPAMIL HCL
ISOSORBIDE DINITRATE
POTASSIUM CHLORIDE
PREDNISONE
GENTAMICIN SULFATE
METOPROLOL TARTRATE
METHYLDOPA
DIGOXIN(LANOXIN)
FLUOCINONIDE
TOCAINIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

PREVIOUS ANTIARRHYTHMIC THERAPY INCLUDED PROCAINAMIDE AND TONACARD. PATIENT WAS REFRACTORY TO BOTH. CHRONIC OBSTRUCTIVE PULMONARY DISEASE. SEE ALSO #7, ABC E, FOR ADDITIONAL HISTORY

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/14/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

FORM FDA 1639 (5'85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

atrial?tachycardia. On 27FEB ZINACEF was added for Citrobacter pulmonary infection. Flecainide (100mg tid) was begun on 28FEB86 which yielded complete control of ventricular ectopy. On 04MAR86 a second respiratory arrest developed (without ventricular arrhythmias). 06MAR84 Staph. conjunctivitis developed. That day a third respiratory arrest occurred. On 08MAR86 thrombocytopenia of 60,000 was noted. TAGAMET and heparin were discontinued. On 11MAR86 a decrease in white count was noticed. On 11MAR86 sputum smear suggested herpetic pneumonia, flecainide D/C'ed acyclovir was begun. A bone marrow on 13MAR86 showed left sided granulocytic maturation with toxic change with differential etiology of infectious vs drug-related basis. NORPACE was begun despite earlier

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NC ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
17. INDICATION(S) FOR USE	
THERAPY DATES *(From/To)*	19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NC ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

AMINOPHYLLINE
CEFAZOLIN SODIUM
ALPRAZOLAM
NIFEDIPINE
METHYLPREDNISOLONE
BITOLTEROL MESYLATE
TICARCILLIN DISODIUM
HEPARIN SODIUM

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)* ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER
25 15 DAY REPORT ☐ YES ☐ NO	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFA-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 3)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

intolerance and i.v. acyclovir was added to the oral regimen. on 15MAR Pseudomonas was grown from sputum and i.v. AMIKACIN was added to treatment. The patient died on 17MAR86. The multiple medications the patient was taking before thrombocytopenia was noted are listed in Section 22, below.
ORIGINALLY SUBMITTED AS 15-DAY,ADDITIONAL INFORMATION RECEIVED SHOWED IT TO BE A NON-15 DAY REPORT.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

25.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

25b. TELEPHONE NO. *(Include area code)*

25c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

25d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	??	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

PROARRHYTHMIA
PT SAID TO HAVE DEVELOPED RECURRENT SUDDEN DEATH OR CARDIAC ARREST ON FLECAINIDE. NOT CLEAR WHETHER DUE TO DRUG.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- [X] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

THERAPY DATES *(From To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 3/14/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

UNKNOWN

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	68	F	03	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Ventricular fibrillation, death

Patient (68-year-old female) with recurrent ventricular tachycardia went into ventricular fibrillation and died. Had been refractory to various antiarrhythmics and was started on flecainide 3 days prior to this event.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

THERAPY DATES *(From/To)*: 03/??/86 - UNKNOWN

19. THERAPY DURATION: 3 DAYS

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

None.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/ 1/86

24d. REPORT SOURCE *(Check one)*

[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT

[ ] YES [X] NO

25a. REPORT TYPE

[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA	YR.
[redacted]	59	M	03	19	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#VENTRICULAR TACHYCARDIA#, NON-RESUSCITATABLE. ONSET OF VENTRICULAR TACHYCARDIA LATE IN THE 3RD DAY OF TAMBOCOR TREATMENT, AT DOSE OF 100 MG Q12H. PATIENT ARRIVED AT THE HOSPITAL IN VENTRICULAR FIBRILLATION, ELECTRO-CONVERTED TO VENTRICULAR TACHYCARDIA, BUT ALL ATTEMPTS AT ELECTRO-CONVERSION OF THE VENTRICULAR TACHYCARDIA WERE UNAVAILING, AND DEATH ENSUED AT 1AM 3/20/86.
PATIENT WAS ALSO TAKING PROCAN SR 750 MG QID, WHICH HAD BEEN INSTITUTED SOMETIME PRIOR TO INITIATION OF TAMBOCOR THERAPY.

13. RELEVANT TESTS/LABORATORY DATA
NONE

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
PAROX VENTRIC TACHYCARD

THERAPY DATES *(From To)*
03/17/86 - 03/19/86

19. THERAPY DURATION
3 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
PROCAINAMIDE HCL
POTASSIUM CHLORIDE
FUROSEMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
VENTRICULAR TACHYCARDIA HAD SHOWN RESISTANCE TO PROCAINAMIDE PLUS TOCAINIDE. TOCAINIDE HAD BEEN DISCONTINUED FOR A FEW DAYS BEFORE FLECAINIDE WAS STARTED; HIGH-DOSE PROCAINAMIDE WAS CONTINUED WITH FLECAINIDE 100MG Q12H.
PATIENT HAD END-STAGE CARDIOMYOPATHYWITH CARDIAC ANEURYSM.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/ 3/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	??	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Unresuscitatable ventricular arrhythmia, sudden death
Minutes following exercise in a gynmasium, patient developed ventricular fibrillation that could not be controlled and died.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTIO
- ☐ TREATED WITH Rx DRU
- ☐ RESULTED IN, OR PROLONGED, INPATIE*. HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: 5 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Generally good cardiac status and general health except for ventricular arrhythmias.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/27/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	M	04	30	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

"Ventricular tachycardia, ventricular fibrillation, death"
As an outpatient, this patient who had a long history of refractory atrial fibrillation and, more recently, premature ventricular contractions and couplets, was started on flecainide (having failed earlier therapy with quinidine). Flecainide was begun at 100 mg b.i.d. and increased after several days to 300 mg per day. Feeling well while wearing a Holter monitor, he took out the garbage and collapsed. The Holter showed that he had gone from atrial fibrillation to sustained ventricular tachycardia and then ventricular fibrillation. Admitted to hospital. Treatment with Lidocaine brought him out of his arrhythmia several times, but he was brain dead and expired.

13. RELEVANT TESTS/LABORATORY DATA

See notes on Holter recording in #7 above.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: 04/20/86 - 04/30/86

19. THERAPY DURATION: 10 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

History of myocardial infarction 2 or more years previously. Long history of refractory atrial fibrillation. He had failed therapy with quinidine before flecainide treatment. No prominent heart failure history.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/ 5/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	M	03	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, ventricular tachycardia (during PES)
Patient (70-year-old male) with severe recurrent ventricular tachycardia, congestive heart failure, and a history of myocardial infarction, was placed on flecainide (50 mg b.i.d.) to treat ventricular tachycardia. Patient had been on a variety of antiarrhythmics before flecainide including quinidine, procainimide, and tocainide. After four days of flecainide therapy, the patient was undergoing programmed electrical stimulation during which time he developed a ventricular tachycardia which could not be terminated. After 15 minutes of resuscitative efforts, the patient died from a hemodynamic collapse.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
100 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
03/??/86 - 03/??/86

19. THERAPY DURATION
4 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
DIGOXIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
None.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
5/ 9/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [x] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [x] NO

25a. REPORT TYPE
- [x] INITIAL [ ] FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TE

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	M	03	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden death, ventricular fibrillation, ventricular tachycardia
Patient (70-year-old male) experienced sudden cardiac death 3 weeks after begining flecainide therapy (100 mg b.i.d.) for the treatment of ventricular arrhythmia. Immediately prior to death, patient developed ventricular fibrillation and ventricular tachycardia. Prior medical history contains two previous such experiences where the patient was revived.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTIO
- [ ] TREATED WITH Rx DRU
- [ ] RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: 03/??/86 - 03/??/86

19. THERAPY DURATION: 3 WEEKS

20. DID R ACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Patient had been tried on many antiarrhythmics prior to beginning flecainide. Patient had done poorly on all of these and was switched to flecainide. For three weeks the arrhythmia was well controlled. Physi- does not feel that death was due to flecainide.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/29/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPO R *(Include Zip Code)*

26b. TI

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	M	05	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Ventricular tachycardia, ventricular fibrillation, death
Patient (70-year-old male) was started on flecainide (100 mg b.i.d.) for the treatment of frequent premature ventricular contractions. 36 hours after beginning therapy, the patient went into ventricular tachycardia and eventuallly ventricular fibrillation. Was treated with bretylium and lidocaine unsuccessfully. Patient was also unresponsive to cardio version.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines, biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

18. THERAPY DATES *(From To)*
05/??/86 - 05/??/86

19. THERAPY DURATION
36 HOURS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NITROGLYCERIN
FUROSEMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
12/84 Myocardial infarction, congestive heart failure, cardiomegaly.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
6/ 6/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

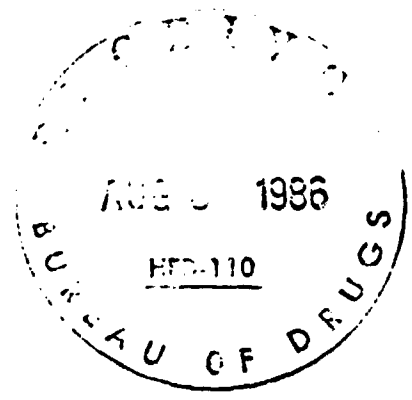
26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Riker Laboratories, Inc.

270-3A-01 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL REPORTS

3M



July 30, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jlg

Enclosure - [redacted]
- [redacted]

Certified Mail P 648 917 281

8/12

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO.	DA	YR.
[redacted]	21	F	04	16	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death from overdose
A 21-year-old female patient with mitral valve prolapse and catecholamine dependent ventricular tachycardia ingested approximately 2 Gm of Inderal and 12-16 Gm of Tambocor. Within one hour had blood pressure of 70/40 and pulse 70. Within 2 hours was in asystole with complete heart block; no response to medication, pacemaker, or internal heart massage.

C

8-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

X OVERDOSE
X LIFE THREATENING

13. RELEVANT TESTS LABORATORY DATA

07/21/86..AUTOPSY RESULTS: FLECAINIDE LEVELS (ALL UNITS IN MICROGRAMS/ML) SERUM 3.24;BLOOD 10.9;URINE 27.2;LIVER 256;BILE - PRESENT;VITREOUS HUMOR 7.4;GASTRIC 190MCG/KG. PROPRANOLOL LEVELS (ALL UNITS IN MICROGRAMS/ML.) BLOOD 1.1;URINE 1.7; LIVER 9.2;BILE - PRESENT;GASTRIC 190MG/KG.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

17. THERAPY DATES *(From To)*
04/15/86 - 04/16/86

18. THERAPY DURATION
1 DAY

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
PROPRANOLOL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
None.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
7-21-86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b.

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Pancytopenia, death
Report from [redacted] indicates patient, while on flecainide, developed pancytopenia and subsequently died. No further details are known.
07JUL86 New information indicates patient was treated with flecainide with good results for several months with no side effects. On his own volition, patient discontinued flecainide and the arrhythmia recurred. flecainide was reintroduced with success 3 weeks prior to death. During this period was also taking valproic acid 1500mg/day for a seizure disorder. Patient died 14JAN86 (cause of death: septicemia)

C

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

HEMOGLOBIN = 6.3 GM/L; PLATELETS = 37000/MM3; PROTHROMBIN = 57%
FIBRINOGEN = NORMAL; BONE MARROW COUNT = BONE MARROW HYPOPLASIA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*: 12/17/86 - 01/07/86

19. THERAPY DURATION: 3 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

VALPROIC ACID

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

INGUINAL HERNIA; SMOKER; EPILEPSY

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/23/86

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Riker Laboratories, Inc.

225-1S-07 3M Center
St. Paul, Minnesota 55144-1000
612/736 5747
(612)733-0633

1.1

REPORTS 3M

June 25, 1986

Orig

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor©, flecainide acetate

Dear Sir/Madam,

Enclosed are four Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jlg

Enclosure - [redacted]

RECEIVED
JUL 1 4 1986
HFD-110
BUREAU OF DRUGS

Certified Mail P 917 256

CC-714

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)* [redacted]

2. AGE YRS. ---

3. SEX -

4-6. REACTION ONSET: MO. -- DA -- YR. --

8-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, myocardial infarction
Attached article notes three deaths due to myocardial infarctions (serious, unlabeled) and six sudden deaths (serious of unknown cause). Five out of six sudden deaths had had previous myocardial infarctions and symptomatic congestive heart failure was present at baseline.

Flecainide Ventricular Tachycardia Study Group: Treatment of resistant ventricular tachycardia with flecainide acetate. American Journal of Cardiology 1986, 57:1299-1304.
NB: THESE CASES WILL HAVE BEEN REPORTED THROUGH IND AND NDA APPLICATION.

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO. [redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/ 1/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [X] LITERATURE
- [ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 10 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

Treatment of Resistant Ventricular Tachycardia with Flecainide Acetate

FLECAINIDE VENTRICULAR TACHYCARDIA STUDY GROUP

Ninety-four patients with ventricular tachycardia (VT), 49 with sustained and 45 with nonsustained VT, who had been refractory to or intolerant of other antiarrhythmic agents were treated in a multicenter, open-label study with flecainide acetate. Most had serious cardiac disorders associated with their arrhythmia: 49 patients (52%) had 1 or more conduction disorders on electrocardiography; 43 (46%) had congestive heart failure; 30 (33%) had left ventricular ejection fractions of 30% or less. Patients were initially treated orally in the hospital with 100 mg twice daily; dosage was titrated upward as needed at 4-day intervals to a maximal dose of 200 mg twice daily. Flecainide plasma level monitoring was performed to ensure plasma levels remained in the therapeutic range of 0.2 to 1.0 μg/ml. Patients were discharged with flecainide therapy if investigators judged it to be safe and effective. Minimum efficacy requirements included elimination of sustained VT and reduction of other ventricular arrhythmias as determined by 1 or more of the following: 24-hour electrocardiographic monitoring, programmed electrical stimulation, exercise testing and in-hospital monitoring. Sixty-eight patients (72%) were discharged with flecainide therapy. After a mean follow-up of 8 months, 45 patients (48%) were still taking flecainide, including 22 of 49 (45%) with sustained and 23 of 45 (51%) with nonsustained VT. Nine patients with sustained VT and 1 patient with nonsustained VT had aggravation of arrhythmia. Two patients had third-degree heart block. Nine patients died after discharge from the hospital: 6 from out-of-hospital sudden death and 3 from acute myocardial infarctions. Flecainide is an effective antiarrhythmic agent when used for the short- and long-term control of resistant VT.

(Am J Cardiol 1986;57:1299–1304)

Approximately 400,000 persons die suddenly each year in the United States,[1] principally from ventricular tachyarrhythmias.[2] The mortality rate in patients with recurrent sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) ranges from 30 to 50% per year[3–6]; in patients with nonsustained VT and left ventricular dysfunction the mortality rate ranges from 15 to 30% per year.[7–9] Therapy in these patient groups has been based on the assumption that suppression of the underlying ventricular arrhythmia, as assessed by continuous electrocardiographic (ECG) monitoring or programmed electrical stimulation, will improve expected survival rates.

Members of the Flecainide Ventricular Tachycardia Study Group are listed in the Appendix. This study was supported by a grant from Riker Laboratories, Inc., St. Paul, Minnesota. Manuscript received August 15, 1985; revised manuscript received January 8, 1986, accepted January 9, 1986.

Address for reprints: Leonard N. Horowitz, MD, Division of Clinical Cardiac Electrophysiology, Likoff Cardiovascular Institute, Hahnemann University Hospital, Broad & Vine Streets, Philadelphia, Pennsylvania 19102-1192.

Flecainide acetate has been shown to markedly suppress ventricular arrhythmias in patients with chronic stable ventricular ectopy[10–12]; however, its use has been limited in more high-risk patients. In this multicenter, open-label study the efficacy and safety of flecainide was assessed in patients with drug-resistant recurrent VT.

Methods

Study design: The primary purpose of this study was to evaluate the efficacy and safety of oral flecainide acetate in patients with drug resistant VT (VT in patients who were intolerant of or refractory to all previous antiarrhythmic therapy). Sustained VT was defined as consecutive ventricular complexes occurring at a rate of more than 100 beats/min lasting at least 30 seconds or requiring cardioversion. Investigators could enroll patients who had ECG findings such as bundle branch block, first-degree atrioventricular (AV) block with a PR interval shorter than 0.28 second, intraventricular conduction delay with a QRS interval of 0.15 second or less, or who had congestive heart failure, including New York Heart Association class

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(Am J Cardiol 1986;57:1299–1304)

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Address for reprints: Leonard N. Horowitz, MD, Division of Clinical Cardiac Electrophysiology, Likoff Cardiovascular Institute, Hahnemann University Hospital, Broad & Vine Streets, Philadelphia, Pennsylvania 19102-1192.

TABLE I Clinical Characteristics

Characteristic	Sustained VT (n = 49)	Nonsustained VT (n = 45)	All Patients (n = 94)
Mean age (yr)	60	62	61
Men	35 (71%)	32 (71%)	67 (71%)
White	46 (94%)	38 (84%)	84 (87%)
Origin			
Coronary artery disease	38 (78%)	31 (69%)	69 (73%)
Valvular heart disease	3 (6%)	5 (11%)	8 (9%)
Cardiomyopathy	4 (8%)	4 (9%)	8 (9%)
Systemic hypertension	1 (2%)	0	1 (1%)
Primary rhythm disorder	2 (4%)	4 (9%)	6 (6%)
Other	1 (2%)	1 (2%)	2 (2%)
Associated disorders			
Remote MI	33 (67%)	22 (49%)	55 (59%)
CHF	23 (47%)	20 (44%)	43 (46%)
EF <30%	20/46 (43%)	10/44 (23%)*	30/90 (33%)
AV conduction disorder	31 (63%)	18 (40%)*	49 (52%)
Previous antiarrhythmic drugs (n)	4.9 ± 2.2	3.9 ± 2.1*	4.4 ± 2.2

* Differences between sustained and nonsustained VT were significant ($p < 0.05$).

In 4 patients baseline ejection fraction was not determined.

AV = atrioventricular; CHF = congestive heart failure; EF = ejection fraction; MI = myocardial infarction; VT = ventricular tachycardia.

III or IV. Patients were excluded from the study if they had digitalis intoxication arrhythmias, second- or third-degree heart block, recent unstable myocardial infarction or pacemaker-dependent rhythm. Patients with diminished renal function (creatinine clearance of less than 20 ml/min/m^2) or with noncardiac disease that might interfere with absorption, metabolism or excretion of flecainide could not participate. Consenting male and nonpregnant female patients, 21 years of age or older, could participate if they met these criteria and agreed to be hospitalized for a minimum of 7 days while flecainide therapy was initiated.

Prestudy evaluation: Before flecainide therapy was begun, all patients gave a history and underwent physical examination, baseline hematologic and blood chemistry studies, urinalysis and chest radiography. Arrhythmias were documented by a rhythm strip, 12-lead electrocardiogram, 24-hour ECG recording or electrophysiologic study. After patients discontinued all previous antiarrhythmic therapy for at least 4 drug half-lives, baseline 12-lead and 24-hour electrocardiograms were recorded and baseline radionuclide ejection fraction was determined. Patients could have electrophysiologic testing at the discretion of the investigator to determine inducibility of VT. If desired, lidocaine was allowed as a maintenance antiarrhythmic drug during the transition period or while awaiting the therapeutic effect of flecainide.

Dosage: The starting dose of flecainide in all patients was 100 mg twice daily. Based on efficacy evaluations and adverse experiences, dose increases to 150 mg twice daily followed by 200 mg twice daily were allowed at 4-day intervals. Predose plasma flecainide levels obtained on the fourth day of each dosage regimen were also used to guide dosage changes. Investigators sought to maintain predose plasma levels within the therapeutic range of 0.2 to 1.0 μg/ml.[13,14] The maximal dose prescribed in the study was 200 mg twice daily; if this did not produce the desired therapeutic result, the patient was withdrawn from the study and therapy was considered to have failed.

Efficacy was judged by each investigator, but criteria always included the elimination of sustained or symptomatic VT when present at baseline. No strict criterion was established for efficacy judged by noninvasive (Holter or telemetric) monitoring techniques. For patients known to have inducible VT, efficacy was substantiated with programmed electrical stimulation and was defined as the elimination of inducible VT. Partial efficacy was noted if inducible VT was slowed and hemodynamically better tolerated or if sustained VT became nonsustained with the drug.

Follow-up: Investigators performed interval evaluations for safety and efficacy on patients at the time of hospital discharge, 1 and 3 months after initiating flecainide therapy, and at quarterly intervals thereafter. Interval follow-up studies included performing 12-lead ECG recording, 24-hour ECG recording, routine biochemical laboratory testing and plasma flecainide trough level determination. Repeat radionuclide ejection fractions were determined at week 1 and months 3 and 6 in patients who had baseline ejection fractions of 30% or less.

Patients continued to receive flecainide as long as, in the opinion of the investigators, it remained safe and effective within the recommended dose range. Alterations in dosage regimen were allowed to improve efficacy or to eliminate adverse effects.

Determination of plasma flecainide levels: The concentration of unchanged flecainide in plasma was determined by gas-liquid chromatography[15] or high-performance liquid chromatography.[16]

Results

Enrollment in the study began in January 1983; this report presents the results of the initial 94 patients with a history of VT who were entered in the study. The number of patients studied in each of the centers ranged from 1 to 22 (median 5 per center).

Demographics: The mean age, sex distribution, race, etiologic diagnosis and other characteristics of the 94 patients in the study are presented in Table I. Most of the patients had coronary artery disease (73%) and approximately half had sustained VT. Twenty-two of the 49 patients with a history of sustained VT were known to have experienced VF or VT requiring resuscitation.

Mean baseline radionuclide ejection fraction for the 90 patients who completed the procedure was 39 ± 16% (range 15 to 79%).

The most common conduction disturbances were first-degree AV block (16%), intraventricular conduction delay (16%) and bundle branch block (12%). Fascicular block (6%), prolonged QT interval (6%) or sinus node dysfunction (3%) were also present in some patients. Six patients had ventricular demand pacemakers.

All patients entered in the study had been treated with at least 1 antiarrhythmic agent before receiving

flecainide (range 1 to 14 per patient). The mean number of antiarrhythmic drugs prescribed before flecainide was 4.4 for all patients, 4.9 for patients with sustained VT and 3.9 for those with nonsustained VT. Previously prescribed antiarrhythmic drugs were discontinued in 58% because of inadequate therapeutic effect, 31% for adverse experiences and 11% for other reasons. The 2 most frequently prescribed agents were procainamide and quinidine, tested in 96 and 94% of patients, respectively.

Efficacy results: During in-hospital evaluation, 68 of 94 patients were judged to be effectively treated (see Methods) and discharged with flecainide therapy. During a follow-up period of 4.5 to 12 months (mean 8), 9 patients died and 14 patients discontinued flecainide treatment, 1 patient because of loss of therapeutic effect, 6 patients because of adverse effects and the others for personal or other reasons unrelated to drug effect. Forty-five patients (48%) continued to take flecainide. Of the 49 patients with sustained VT, 59% (29 of 49) were discharged with flecainide therapy and 45% (22 of 49) continued with long-term therapy. Of the 45 patients with nonsustained VT, 87% (39 of 45) were discharged with flecainide therapy and 51% (23 of 45) continued with long-term treatment. Forty-four of the 45 ongoing patients have had no recorded episodes of sustained or symptomatic VT. One patient experienced dizziness during nonsustained VT, but continued therapy because the frequency of attacks was reduced compared with baseline.

Analyzable 24-hour ECG recordings were available at baseline and before hospital discharge for 48 patients. Patients who discontinued flecainide during the hospitalization because of adverse reactions, obvious lack of efficacy by in-hospital telemetry, or because of results of programmed electrical stimulation often did not undergo repeat 24-hour ECG recordings. Thus, the results of 24-hour ECG monitoring primarily represent data from patients who tolerated flecainide and appeared to be responding. VT was documented on baseline 24-hour ECG recordings in 43 of 48 patients: 77% of these (33 of 43) had complete suppression of VT at the time of discharge, leaving 23% (10 of 43) who still had nonsustained VT on their recordings. All patients free of VT on baseline 24-hour ECG recordings remained free of VT on their recordings at the time of discharge.

Programmed electrical stimulation during flecainide therapy was performed in 23 patients: 30% (7 of 23) had complete suppression of VT, 30% (7 of 23) had partial suppression (VT inducible, but was nonsustained or slower and hemodynamically better tolerated) and 39% (9 of 23) had no suppression of inducible VT. All 14 patients with complete or partial suppression of inducible VT were discharged with flecainide therapy. Five of the 7 patients who demonstrated complete suppression and 3 of 17 with partial suppression continued to take flecainide. One patient discharged with flecainide therapy after complete suppression died suddenly out of hospital; another discontinued the drug because of noncardiac adverse experiences. Four patients discharged with flecainide treatment after partial suppression discontinued therapy, 1 patient because of loss of therapeutic effect, 1 because of noncardiac adverse effects and 1 because of increased ventricular premature complexes (VPCs) during stress testing; 1 patient died from acute myocardial infarction. One of the 9 patients who showed no suppression during programmed electrical stimulation was discharged from the hospital with flecainide therapy because of the reduction of spontaneous VT. This patient remained ongoing after 9 months of flecainide therapy.

Flecainide dosage/plasma levels: At the time of discharge, only 7 of 68 successfully treated patients (10%) required the maximal dose of 400 mg/day of flecainide to control their VT. Thirty-one patients (46%) required 300 mg/day. The minimal dose of 200 mg/day was effective in 27 of 68 successfully treated patients (40%). Two additional patients were discharged with 150 mg/day and 1 patient was discharged with 250 mg/day. Doses were similar whether patients were treated for sustained or nonsustained VT (mean 268 and 272 mg/day, respectively).

Predose plasma levels were available for 30 of 68 successfully treated patients (30 of 68) at the time of hospital discharge. Mean plasma levels for these patients (mean dose 260 mg/day) was 0.54 μg/ml (range 0.26 to 0.93). The mean predose plasma levels at the time of discharge for patients with sustained VT (0.56 μg/ml) and nonsustained VT (0.53 μg/ml) were similar.

Ejection fractions: Radionuclide ejection fractions in 15 patients whose baseline ejection fractions were 30% or less and who had follow-up ejection fraction determinations while taking flecainide are shown in Figure 1. Mean ejection fractions for these patients were 22 ± 5% at baseline, 24 ± 7% at 1 week and 22 ± 7% at 3 months.

Discontinued therapy: Flecainide therapy was discontinued in 40 patients (43%). Twenty-six patients discontinued during the in-hospital evaluation and 14 discontinued after discharge with flecainide therapy.

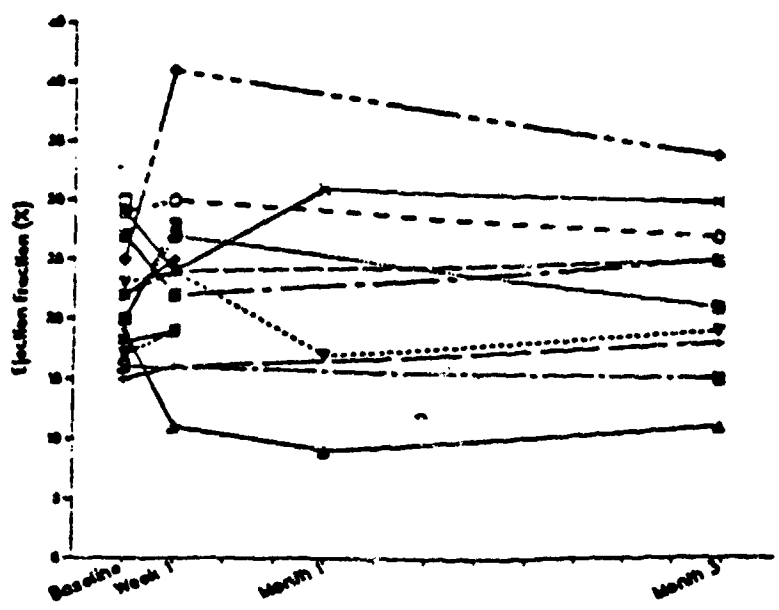

FIGURE 1. Changes in radionuclide ejection fraction over time in patients with ejection fractions of 30% or less at baseline.

TABLE II Reasons for Discontinuing Therapy

Reason	Total (n = 94)	In Hospital (n = 34)	Out of Hospital (n = 68)
Inadequate response	12	11	1
Worsened arrhythmia	10	9	1
Noncardiac adverse experiences	5	1	4
Conduction disturbances	4	3	1
Congestive heart failure	1	1	0
Other (personal, noncompliance, intercurrent disease)	8	1	7
Total discontinuations	40	26	14

The reasons for discontinuing therapy are listed in Table II.

Deaths: Nine patients (10%) died after discharge from the hospital with flecainide therapy. No patient died during the initial hospital evaluation. Three patients died from an acute myocardial infarction. Two infarctions were documented by autopsy and 1 by typical ECG and enzyme changes. Six patients died suddenly out of hospital 3 weeks to 8 months after starting flecainide therapy; of these 6, 5 had previous myocardial infarctions; symptomatic congestive heart failure was present at baseline in 4 of the patients; ejection fractions were 20 to 26% in 4 of the patients, 35% in 1 patient and 57% in 1. Three of the 6 patients were being treated for sustained VT, all of whom had previous cardiac arrests. The other patients were being treated for nonsustained VT. Two of the 6 had symptomatic ischemic events immediately before death. Therapy in 1 patient who died suddenly was guided primarily by programmed electrical stimulation. In this patient, sustained VT was induced before flecainide was administered, and VT was not inducible while the patient was taking flecainide. Therapy in the other 5 patients was based on results of 24-hour ECG monitoring. Two of these 5 patients showed greater than 80% suppression of VPCs and 100% suppression of VT complexes. One showed no suppression of VPCs but 98% suppression of VT complexes. One patient's recordings showed an increase of VPCs (from 100 to 175 complexes in 24 hours) but 100% suppression of VT complexes. The remaining patient lacked evaluable baseline Holter data; follow-up recordings showed 3 complex runs of VT.

Adverse effects: *Proarrhythmic events:* While receiving flecainide, 10 patients showed aggravation of arrhythmias as defined by the investigator. Treatment was discontinued in all 10, 7 during the initial phase of hospitalization. Nine of these 10 patients were receiving treatment for sustained VT. In 4 patients the proarrhythmic events were characterized by increased VPCs and an increase in the number of nonsustained VT events. Two patients had inducible VT during programmed electrical stimulation that was more easily induced (required fewer extrastimuli) than at baseline. One patient had spontaneous VT while taking flecainide that was of a different morphologic pattern than that produced during baseline programmed electrical stimulation.

Three patients had clinically significant proarrhythmic events, all of which occurred during the in-hospital dose-titration phase: One patient had sustained VT initially resistant to cardioversion. Although the VT rate was slower during flecainide therapy compared with baseline (cycle length of 333 and 230 ms, respectively), vasopressors were required during 7 hours of sustained VT after which the patient underwent successful cardioversion. The second patient had VT with a slower rate (cycle length of 530 ms compared with 400 ms at baseline) that degenerated into VF. Cardioversion was successful only after bretylium was administered. The third patient had VT with a shorter cycle length during flecainide therapy (from 333 to 300 ms), requiring repeated cardioversions to achieve sinus rhythm. In this last patient ejection fraction was not determined because of persistent (many days), sustained VT at baseline. The other 9 patients with proarrhythmic events had ejection fractions of 24 to 53% (median 29%).

Conduction disorders: Therapy was discontinued in 4 patients because of conduction disorders; in 2 asymptomatic third-degree AV block developed, which resolved after discontinuing therapy. Baseline PR intervals in the 2 patients were 0.20 and 0.24 second. QRS intervals were 0.08 and 0.12 second at baseline. However, 29 other patients entered the study with PR intervals of 0.20 second or greater and 24 entered with QRS intervals of 0.12 second or greater without having second-degree AV block or complete heart block. Five patients had right bundle branch block while taking flecainide. Three patients continued to take flecainide after having bundle branch block and 2 discontinued flecainide because of this.

Congestive heart failure: New or worsened congestive heart failure occurred in 6 patients (6%), 4 of whom had a history of congestive heart failure. Flecainide therapy was discontinued in only 1 of the 6 patients. Congestive failure was successfully treated by adding or increasing the dose of diuretic drugs to the flecainide regimen in the other 5 patients. Ejection fractions at baseline in these 6 patients ranged from 18 to 33% (mean 26%).

Noncardiac adverse effects: Dizziness and visual disturbances such as transient blurred vision and difficulty focusing were the most common adverse effects. These occurred in 7 and 6%, respectively, in this study. There were no biochemical or hematologic laboratory results indicative of organ toxicity.

Outcome as a function of type of heart disease, severity of arrhythmia and myocardial function: The outcome of patients was not significantly affected by the presence of coronary artery disease, sustained VT or myocardial dysfunction. Although there were no statistically significant differences in the rate of favorable outcome (percent of ongoing patients) between any of the groups using chi-square analysis, worsened arrhythmia and inadequate response tended to be more common in patients treated for sustained VT.

Discussion

The results of this study demonstrate that administration of flecainide using a low initial dose, upward

titration at 4-day intervals and plasma level monitoring can achieve efficacy and safety in the short- and long-term treatment of those patients with drug-resistant sustained and nonsustained VT, including patients with myocardial dysfunction and conduction disorders.

Although the differences were not statistically significant, there was a trend toward lower efficacy in patients with myocardial dysfunction. Whether this was related to the greater difficulty in treating arrhythmias in such patients, the negative inotropic effect[17] of flecainide, or both, cannot be answered with this study. However, 5 of 6 patients in whom congestive heart failure developed during flecainide therapy continued therapy with adjustment in diuretic dosage. The incidence of congestive heart failure during flecainide therapy in this study was less than that reported by Podrid et al[18] for disopyramide.

Proarrhythmic events with various antiarrhythmic drugs may take the form of increased frequency of VPCs, increases in repetitive complexes (pairs, runs), facilitation of spontaneous or induced VT, development of new arrhythmias, or difficulty in conversion of ventricular arrhythmia.[13,19,20] Antiarrhythmic drugs have been reported to produce proarrhythmic events in about 5 to 20% of patients. The incidence of proarrhythmic events with all antiarrhythmic drugs may vary[19–21] according to the types of patients treated. Higher rates are expected in patients whose myocardial function is severely compromised and those who have a history of serious arrhythmias, such as sustained VT.[13] In previous studies, flecainide has been associated with proarrhythmic events in 4.2% of patients treated for chronic VPCs and nonsustained VT and 12% of patients in compassionate use studies in which patients with more severe heart disease were treated for recurrent VT.[13] In this study 10 patients (10.6%) developed proarrhythmic events. Since 9 of 10 proarrhythmic events occurred in patients with sustained VT and all but 1 proarrhythmic event occurred during in-hospital initiation of therapy, we believe in-hospital monitoring is advisable during initiation of antiarrhythmic therapy with flecainide in patients with sustained VT.

The typical form of significant proarrhythmic effect observed in patients treated with flecainide and other class IC agents is incessant, monomorphic, sustained VT. This can occur in patients with previously documented sustained VT or in patients with only previously documented nonsustained VT. Although this VT is typically slower than previous episodes in an individual patient, difficulty with resuscitation and death can occur.

In most patients, flecainide slows cardiac conduction sufficiently to produce measurable increases in the duration of the PR and QRS intervals on the electrocardiogram.[13] QT intervals are increased primarily because of QRS widening.[13] Conduction disturbances such as sinus pause, second- or third-degree AV block and bundle branch block occur occasionally, and therefore, patients should be monitored during initiation of therapy and managed on the smallest effective dose in order to minimize these effects.

This study showed a marked reduction compared with previous studies[8,10] in noncardiac adverse effects, particularly dizziness and visual disturbances. This is most likely related to the lower doses used in this study. Early dose-ranging studies[15] suggested that therapeutic responses generally occurred with doses of 400 mg/day or less. This study found that 90% of successfully treated patients were controlled with 300 mg/day or less. This study also shows that trough plasma flecainide levels can be a useful guide to therapy. It is likely that the lower maintenance doses used in this study (and the lower incidence of adverse effects) were partially the result of the investigators' efforts to maintain the trough plasma levels in the presumed therapeutic range of 0.2 to 1.0 μg/ml.

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Riker Laboratories, Inc.

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3M

June 30, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 2852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and u[illegible]led adverse experience which occurred in association wit[illegible] use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/br

Enclosure -[redacted]

Certified Mail P 648-917-258

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)* [redacted]

2. AGE YRS. ---

3. SEX -

4-6. REACTION ONSET: MO -- DA. -- YR. --

8-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, Congestive heart failure, Cerebrovascular accident
Manuscript: "Classification by Type of Ventricular Arrhythmia Predicts Frequency of Adverse Cardiac Events from Flecainide," by [redacted]
Reports: One death due to inceased congestive failure, one death possibly due to cerebral vascular accident, and 87 sudden deaths (cause not determined) but not due to proarrhythmia so far as known.
Note - The above-mentioned patients were previously re[illegible] through the flecainide NDA submission. These are not new data.

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
UNKNOWN

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYT[illegible]A

18. THERAPY DATES *(From To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO. [redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/ 1/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [X] LITERATURE
- [ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)* [redacted]

26b. TELEPHONE NO. *(Include area code)* [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted]

2. AGE YRS. ---

3. SEX -

4-6. REACTION ONSET: MO. -- DA. -- YR. --

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, Congestive heart failure, Cerebrovascular accident
Manuscript: "Classification by Type of Ventricular Arrhythmia Predicts Frequency of Adverse Cardiac Events from Flecainide," by [redacted]
Reports: One death due to inceased congestive failure, one death possibly due to cerebral vascular accident, and 37 sudden deaths (cause not determined) but not due to proarrhythmia so far as known.
Note - The above-mentioned patients were previously reported through the flecainide NDA submission. These are not new data.

8-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: UNKNOWN

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/ 1/86

24d. REPORT SOURCE *(Check one)*: ☐ FOREIGN ☐ STUDY ☒ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT: ☒ YES ☐ NO

25a. REPORT TYPE: ☐ INITIAL ☒ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

CLASSIFICATION BY TYPE OF VENTRICULAR ARRHYTHMIA PREDICTS FREQUENCY OF ADVERSE CARDIAC EVENTS FROM FLECAINIDE

[redacted]

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***Riker Laboratories, Inc., 3M Company, St. Paul, Minnesota. 55144

Running Title: Classification of Arrhythmia

Address Reprint Requests To:

[redacted]

ABSTRACT

Antiarrhythmic therapy is known to be associated with a significant risk of adverse cardiac reactions, including a proarrhythmic response. The predictive value for cardiovascular safety of a patient classification system by entry ventricular arrhythmias, presence or absence of organic heart disease, and drug dose for flecainide acetate, in 1330 patients, followed for 292 ± 393 days was evaluated. Baseline arrhythmia subgroups included patients with premature ventricular complexes only, non-sustained ventricular tachycardia and sustained ventricular tachycardia. Proarrhythmic events occurred in 6.8% of patients overall, were serious in 2.3%, and lethal in 1.0%. However, proarrhythmia was highly dependent on entry arrhythmia class: serious non-lethal proarrhythmia occurred in 6.6% of patients with sustained ventricular tachycardia, only 0.9% with non-sustained ventricular tachycardia and 0% with premature ventricular complexes ($p<0.01$). Proarrhythmic deaths occurred in 3.1% with sustained ventricular tachycardia, 0.2% with non-sustained ventricular tachycardia, and 0% with premature ventricular complexes only ($p<0.01$). Proarrhythmia was also influenced by the presence of structural heart disease: serious non-lethal proarrhythmia occurred in 2.6% with, versus 0.4% without, organic heart disease, and death occurred in 1.2% versus 0%, respectively. These adverse events were also dependent on dosing regimen. Flecainide caused new or worsened heart failure in 1.4%, all in patients with underlying organic heart disease. Heart failure was not clearly related to dose or arrhythmia-type,

however. Symptomatic conduction disturbances occurred in 2.2%, and were predicted by pre-existent sinus node disease, but not by other baseline features.

The safety of flecainide was markedly enhanced by a slow, incremental approach to dosing, especially in high risk patients. Because most proarrhythmia occurred early during dose-finding, hospitalization for drug initiation would appear to improve safety in patients with sustained ventricular tachycardia, heart failure, and sinus node dysfunction. These data confirm the usefulness of a clinical classification system, based on severity of arrhythmia disorder and presence of structural heart disease, in predicting serious adverse proarrhythmic events with flecainide.

Key Words: Ventricular arrhythmia
Flecainide acetate
Proarrhythmia
Congestive heart failure

INTRODUCTION

Over the past few years, intense study of new antiarrhythmic agents has shown that this class of drugs has the potential for life threatening side effects[1]. A reassessment of the risk/benefit ratio of using antiarrhythmic agents is thus necessary. The physician must now consider not only the electrocardiogram diagnosis of the ventricular arrhythmia type in assessing this risk/benefit relationship but also must determine whether the arrhythmia is likely to be benign, potentially lethal or lethal to the patient[2]. Criteria for such a classification based on clinical experience have been suggested, including consideration of the degree of structural heart disease and the hemodynamic consequences of the ventricular arrhythmia. New potent antiarrhythmic agents which belong to the modified Vaughn-Williams Classification IC have recently been made available[3]. Such agents need to be assessed to determine their potential to cause proarrhythmic or other cardiac adverse events.

The objective of this manuscript is to evaluate the incidence of life threatening or serious cardiac adverse reactions from the use of the newly available Class IC antiarrhythmic agent flecainide when given to patients at varying risk: those with or without structural heart disease, those with arrhythmias of different severities and those treated with high versus lower initial doses. Such an evaluation may serve as the basis for developing a clinical approach to the use of flecainide which will optimize its benefit and minimize its risk.

METHODS

The flecainide clinical efficacy and safety data base collected from February 1980 to July 1985 was reviewed retrospectively to define the relative risks of death and serious cardiac adverse experiences in a patient population stratified for severity of underlying ventricular arrhythmia, presence or absence of structural heart disease, dose of flecainide administered, and whether flecainide was administered as part of outpatient or inpatient therapy. This data base comprised 1,330 patients derived from the United States data base plus two European trials, as follows:

1. An early in-hospital dose ranging study[4,5,6] and its long term follow up (Riker flecainide studies numbered 030,031). N=37

2. An outpatient double blind parallel designed comparative study of flecainide versus quinidine and its chronic follow up study (032,033)[7]. N=260

3. A prematurely discontinued attempt at studying flecainide in the early post myocardial infarction period (037). N=10

4. A study evaluating the safety and efficacy of chronic oral flecainide from Rotterdam, The Netherlands (035). N=76

5. A compassionate use experience[8] using a 400 mg/day initial dose with upward titration at investigator discretion and primarily comprised of patients with lethal ventricular arrhythmias (028,057). This study will be called the "high initial dose compassionate study". N=277

6. A study[9] in patients with ventricular tachycardia treated in-hospital under monitored conditions with a 200 mg/day initial dose and slow upward titration (057 amended). This study will be called the "low initial dose ventricular tachycardia study". N=429

7. An open label safety and efficacy study in patients with various forms of ventricular arrhythmias (067). N=86

8. A post marketing surveillance study conducted in the United Kingdom. N=155

STRATIFICATION VARIABLES

Clinical strata of interest in assessing risk/benefit ratio were defined in advance prior to retrospective data-base analysis. Patients from this database were stratified according to the severity of their underlying ventricular arrhythmia, divided into those with 1) premature ventricular complexes only, 2) those with nonsustained ventricular tachycardia and 3) those with sustained ventricular tachycardia and/or ventricular fibrillation. Sustained ventricular tachycardia was defined as

ventricular tachycardia lasting 30 seconds or longer, requiring cardioversion, or associated with hemodynamic consequences such as syncope or hypotension. Nonsustained ventricular tachycardia was defined as 3 or more ventricular complexes in a row lasting less than 30 seconds and not associated with hemodynamic consequences.

The data base was further classified according to the presence or absence of "structural heart disease". Structural heart disease was considered to be present when a patient had atherosclerotic coronary artery disease, significant valvular heart disease, congenital heart disease, cardiomyopathy, or the presence of a ventricular aneurysm or previous cardiac surgery. Patients with cardiomegaly by chest x-ray, echocardiography or cardiac catheterization were also considered to have structural heart disease. Patients categorized by investigators as having primary electrical heart disease or no apparent etiology for the ventricular arrhythmia were considered to have "no structural heart disease".

Patients were further classified as having received orally either 200, 300, 400, or 600 mg per day of flecainide. Patients who received doses lower than 200 mg per day were included in the 200 mg per day classification. No patient received more than 600 mg per day. Intermediate doses were rounded upward. The sample size for each total daily dose level was based on the number of patients who at any time while receiving flecainide were exposed to that particular total daily dose of the drug. Patients were counted more than once in the denominator if they were exposed to

multiple flecainide doses. They were counted in the numerator at the dose they were receiving when the adverse event occurred. An adverse event was attributed only to the dose of flecainide on which it occurred.

Patients were also categorized into those who received out-of-hospital or in-hospital initiation of flecainide. Out-of-hospital initiation occurred in all patients in the flecainide-quinidine comparison study and its follow up. Approximately 25% of patients in the open label safety and efficacy study (067) and approximately 60% of the post marketing surveillance study conducted in the United Kingdom were started as outpatients. All other patients had inpatient initiation of flecainide.

CARDIAC ADVERSE EVENTS

The cardiac adverse events reviewed in this popuiation included occurrence of proarrhythmia, congestive heart failure, and conduction disturbances.

Proarrhythmic events were identified by a direct, retrospective questionnaire from each investigator concerning each patient entered into the above cited studies prior to March of 1983, or after that time (prospectively) by case report forms designed t specifically define proarrhythmic events. Proarrhythmic events were classified into 1 of 3 categories:

1. Those arrhythmic events that resulted in death.

2. Those events that were considered serious but non-lethal, defined as worsened ventricular arrhythmias that required immediate termination with drugs, overdrive pacing, or cardioversion. If the proarrhythmic event was associated with hypotensive symptoms, it was also considered serious but non-lethal.

3. Other proarrhythmic events as judged by the investigator included those with an increase in premature ventricular complexes (using previously published criteria)[8], new or increased frequency of nonsustained ventricular tachycardia or new ventricular arrhythmias characterized by a change in morphology or rate (of ventricular tachycardia) but which did not result in worsening of symptoms as compared to baseline.

Congestive heart failure resulting in death or discontinuation of flecainide was also reviewed. This information was obtained from prospective data; investigators were specifically asked to assess patients for congestive heart failure whether it was new or an exacerbation of a prior state, and what impact its occurrence had on the patient's care.

All patients with documented conduction disturbances were reviewed. Those considered to be important were defined as new advanced atrio-ventricular block (greater than first degree) or sinus node dysfunction with sinus pauses or arrest, junctional escape rhythms, or new, symptomatic sinus bradycardia as defined

by the individual investigators.

All deaths in the data base were reviewed and the cause of death, whether drug related or not, was categorized into the following:

1. Noncardiac deaths.
2. Deaths due to acute myocardial infarction documented by typical electrocardiogram and enzyme changes and/or autopsy.
3. Deaths due to congestive heart failure or low output states.
4. In-hospital sudden arrhythmic deaths,
5. Out-of-hospital sudden deaths.

Data from the 277 patients in the high initial dose compassionate study and data from the 429 patients in the low initial dose ventricular tachycardia study were displayed separately to define the effects of a different dosing regimen on the incidence of various cardiac events. Analysis of patient demographics, cardiac disease status, and arrhythmia diagnoses confirmed that these two study populations were identical. They differed only in the dosing regimens employed. The initial dose of flecainide used in the compassionate initial high dose study was 400 mg/day orally with a maximum of 600 mg/day and no specific requirement was made as to dose escalation intervals, the need for cardiac monitoring, or the use of flecainide plasma levels in guiding therapy. Conversely, patients enrolled in the low initial dose ventricular tachycardia study were required to be initially treated in-hospital under monitored conditions with

the dose regimen starting at 200 mg/day, increasing, only if needed, by 50 mg bid at intervals no more frequently than every 4 days, to a maximum of 400 mg/day. Plasma monitoring was used with the purpose of avoiding plasma levels >1.0 micrograms per ml. Because of this difference in dose recommendations there was a tendency for patients in the low initial dose ventricular tachycardia study to be treated chronically at lower doses. Half of the patients in the high initial dose compassionate study were treated chronically with doses greater than 300 mg/day, whereas 80% of the patients in the ventricular tachycardia study were treated with 300 mg/day or less.

The time of occurrence of these events was segregated into those occurring within 14 days and at those more than 14 days after initiation of flecainide therapy. Events occurring within the 14 day time frame were of interest, since hospitalization during initiation of therapy might reduce the risk to the patient of any serious cardiac events which occurred. Full dose-ranging, beginning at 100 mg every 12 hours with increments every 4 days to 150 and 200 mg doses may require up to 12 or more days of observation until the effective dose is achieved. This analysis was intended to identify groups of patients at risk of serious cardiac events early in therapy, so that appropriate recommendations could be made concerning who ought to be hospitalized during therapy initiation. Tentative recommendations were that patients should be hospitalized if they had a history of sustained ventricular tachycardia, evidence of

symptomatic congestive heart failure, or a history of sinus node dysfunction.

A logit approach was used to evaluate adverse cardiac events in terms of potential predictors for their association with the incidence of adverse cardiac events. For this analysis, the predictors considered were presence/absence of structural heart disease and arrhythmia type. For the compassionate use and ventricular tachycardia study data, High or low initial starting dose was also considered as a potential predictor. The significance of each of these variables as a predictor of outcome, as well as the independence of these predictors, was assessed. It is evident that there may be other potential predictors that are not evaluated in this analysis. However, due to the relative infrequent occurrence of some of these cardiac adverse events, a model to assess numerous predictors was not feasible.

RESULTS

The 1330 patients in this data base have been followed for a mean of 292 (range 1-1843) 393 days with a median of 104 days. Of these patients 573 (43%) are still on flecainide with a mean follow up of 506 (range 4-1843) 464 days. Of the rest, 157 (12%) discontinued due to inadequate efficacy, (145 (11%) died, 77 (9%) due to aggravation of arrhythmia, 19 (1.5%) because of CHF, 20 (1.5%) because of conduction changes, and 216 (16%) due to other reasons such as the study ending, non-qualifier, poor compliance, intercurrent illness, personal decision, and lost to followup, and

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Table 1 details the number of patients in each baseline subgroup , defined by type of ventricular arrhythmia as it related to structural heart disease, total daily dose, and outpatient-inpatient initiation of therapy. The population was approximately equally divided into those who were treated with premature ventricular complexes alone (n=470) for nonsustained ventricular tachycardia (n=469) and for sustained ventricular tachycardia (n=391). Approximately 80% of patients had structural heart disease, and approximately 75% had therapy initiated while in-patients. Almost 90% of patients in the data base received ≤ 400 mg per day of flecainide.

PROARRHYTHMIA

Proarrhythmic events were recorded in 90 (6.8%) of the 1330 patients in the data base. Table 2 shows that patients with sustained ventricular tachycardia had a much greater incidence (16.4%) of proarrhythmic events than PVC patients (1.7%) or non-sustained ventricular tachycardia patients (3.8%). The sustained ventricular tachycardia patients in the high initial dose compassionate study had twice the incidence of proarrhythmic events (26%) compared to the patients in the low initial dose study of ventricular tachycardia (13.1%). Analyses indicated that type of ventricular arrhythmia ($p \leq .01$) and initial flecainide dose ($p \leq .05$) were both significant independent predictors of proarrhythmic events. Table 3 shows the incidence of possible or probable proarrhythmic induced deaths which occurred in 13 patients (1.0%) in the entire population of 1330

people. This table shows that 22 deaths occurred from proarrhythmia in patients treated for premature ventricular complexes. Only one (0.2%) death occurred among the 469 patients treated for nonsustained ventricular tachycardia. That death occurred in the high initial dose compassionate study (057) (1 of 118 patients), whereas no deaths have occurred in the 204 patients treated with nonsustained ventricular tachycardia in the low initial dose ventricular tachycardia study. The patient who died was an 80 year old man with severe coronary artery disease and Class III congestive heart failure who was treated with flecainide after having had a recent subendocardial myocardial infarction with pulmonary edema. Prior to starting flecainide he had several episodes of nonsustained ventricular tachycardia. Flecainide was begun at 200 mg per day and increased to 400 mg per day with good control of ventricular ectopy. He was discharged home 9 days after starting flecainide and after 2 days on 400 mg per day. He returned to the emergency room on the evening of discharge with a wide irregular tachycardia without P-waves that deteriorated into cardiogenic shock and death. The relation of flecainide (versus deteriorating ischemic heart disease) to the terminal arrhythmia was not clear.

In patients treated for sustained ventricular tachycardia, a 10% incidence (10 of 100 patients) of death from proarrhythmia was noted in the high initial dose compassionate study and this rate dropped to 0.5% (1 of 198 patients) in the low initial dose ventricular tachycardia study, a twenty-fold decrease ($p<.01$). In fact, no patient in the latter study died of a proarrhythmic

event in the subsequent 2 1/2 years prior to this data analysis. In the compassionate use and ventricular tachycardia studies, type of arrhythmia ($p<.05$) and initial dose ($p<.01$) were found to be independent predictors for proarrhythmic death.

Table 4 shows the incidence of serious non-lethal proarrhythmic events. These occurred in 30 patients (2.3%), 29 of whom had structural heart disease. None of the patients treated for premature ventricular complexes developed a serious non-lethal proarrhythmic event. Of the four patients with nonsustained ventricular tachycardia who had a serious non-lethal proarrhythmic event, all had structural heart disease, three had congestive heart failure and two had depressed left ventricular ejection fractions (29% and 36%). In three of the patients, the proarrhythmic event resulted in syncope and in the other resulted in a wide complex tachycardia that required cardioversion. Patients with sustained ventricular tachycardia had the highest incidence of serious non-lethal proarrhythmic events (6.6%).

Table 5 details "other proarrhythmic events". The incidence of this form of proarrhythmia did not appear to be related to the presence or absence of structural heart disease but did correlate with the severity of the baseline arrhythmia. Patients with sustained ventricular tachycardia had the highest risk for this type of proarrhythmia.

Table 6 shows the relationship of flecainide dose to types of proarrhythmic events that occurred in patients with sustained ventricular tachycardia. There was no consistent relationship

between dose and the incidence of proarrhythmic events of any type in patients treated for premature ventricular complexes only or for nonsustained ventricular tachycardia. These data demonstrate that there is a dose relationship to "all proarrhythmic events", to those "resulting in death", and to those "of the serious non-lethal type" in patients with sustained ventricular tachycardia over the range of 200 to 400 mg/day. The number of patients exposed to 600 mg/day is too small to draw meaningful conclusions about a relationship.

CONGESTIVE HEART FAILURE

Out of 1330 patients, 6 patients (0.5%) died from congestive heart failure that might be attributed to flecainide and 19 were discontinued from flecainide therapy after developing new or worsening congestive heart failure. All 6 patients who died had significant myocardial dysfunction prior to receiving flecainide. There was no relationship between congestive heart failure and the dose of flecainide received. Four of the patients who died had a history of sustained ventricular tachycardia and 2 had a history of nonsustained ventricular tachycardia. Of the 2 patients with nonsustained ventricular tachycardia, 1 had a history of myocardial infarction with recent exacerbation of angina and an exacerbation of congestive heart failure 3 weeks prior to receiving flecainide. After 3 days on flecainide, he developed increasingly severe congestive heart failure and died. The investigator felt that the sudden onset may have been caused by new ischemia and therefore a definite relationship with flecainide could not be established. The second patient who had

non-sustained ventricular tachycardia had coronary artery disease and an ejection fraction of 22%. He had done well on flecainide for 3 months when signs of worsened congestive heart failure developed. Despite decreasing dosage of flecainide, he was admitted for uncompensated congestive heart failure 9 days later and died 1 week afterwards of ventricular tachycardia, felt to be secondary to worsened congestive heart failure. The investigator stated that the death was probably not related to flecainide.

New or worsened congestive heart failure caused discontinuation of flecainide in 19 patients (1.4%). All 19 had structural heart disease and there was no relationship between discontinuation for congestive heart failure and the type of underlying arrhythmia or dose of flecainide. Of the 19 patients, 3/470 (0.6%) were treated for premature ventricular complexes only, 10/469 (2.1%) for nonsustained ventricular tachycardia, and 6/391 (1.5%) for sustained ventricular tachycardia. Ten of the 19 patients (53%) discontinued flecainide within 14 days of initiation of the dose. Two of these 10 had sustained ventricular tachycardia, and 6 had severe congestive heart failure with low ejection fractions and therefore 8 of the 10 patients who had to be discontinued within 14 days would have received in-hospital initiation of flecainide. The other 2 patients who would not have received in-hospital initiation were treated for nonsustained ventricular tachycardia and developed symptoms of congestive heart failure as outpatients 7 and 11 days after initiation of flecainide. Both responded to discontinuation of flecainide without requiring specific therapy

for congestive heart failure.

CONDUCTION DISTURBANCES

Significant conduction disturbances were reported in 29/1330 (2.2%) and none were fatal. The incidence of significant conduction disturbances was not related to the severity of the underlying arrhythmia, presence or absence of structural heart disease, or dose of flecainide. Of these 29 patients, 11 developed symptoms associated with the conduction disturbances consisting of dizziness, weakness, or pre-syncope in 7, and syncope in 4. Table 7 details the symptomatic conduction disturbances by subgroups, and shows that the prevalence of these conduction disturbances was not related to the type of ventricular arrhythmia treated or the total daily dose of drug.

Of the 29 patients who developed conduction disturbances, 20 discontinued flecainide and 9 continued on the drug, 8 of whom received a permanent pacemaker. Prior to initiating flecainide therapy, 19 of the 29 patients had known preexisting conduction disturbances. Of the 4 patients who developed syncope, 2 had known underlying sinus bradycardia due to sick sinus syndrome and the other 2 had sustained ventricular tachycardia and left bundle branch block at baseline. In all four cases the syncope which occurred when the patients were given flecainide was due to prolonged sinus pauses. No patient developed syncope because of the occurrence of AV nodal or His Purkinje system complete heart block.

DEATHS

Of 1330 patients receiving flecainide, 123 (9.7%) died. Both the presence of structural heart disease ($p \leq .01$) and type of ventricular arrhythmia ($p \leq .05$) were found to be independent predictors of the incidence of death. The incidence of death in patients with sustained ventricular tachycardia (16.1%) was greater than that for patients with premature ventricular complexes (3.2%) or nonsustained ventricular tachycardia (9.6%). All but three of these deaths occurred in patients with structural heart disease. Of the 3 patients without structural heart disease, 1 died of metastatic carcinoma, 1 had unobserved sudden death at home after 7 months on flecainide in which the cause of death was possible cerebral vascular accident secondary to hypertensive disease, and the third patient had sudden cardiac death at home 16 days after initiation of flecainide but had a prior history of sudden cardiac death. All 3 of these patients had documented control of their ventricular arrhythmia on flecainide prior to death.

In-hospital arrhythmic death occurred in 42 patients (3.2%) and out-of-hospital sudden deaths in 49 patients (3.7%), which includes those deaths thought to be due to proarrhythmic events, as discussed above. All but 2 of these deaths occurred in patients with structural heart disease ($p<0.05$) and there was a highly significant ($p<0.05$) independent relationship to the type of underlying ventricular arrhythmia (Table 8). There was no clear overall relationship between dose of flecainide and sudden death, but there was a tendency for higher doses to be associated

with sudden death in patients with sustained ventricular tachycardia. Patients treated in the high initial dose compassionate study had twice the death rate compared to those treated in the low initial dose ventricular tachycardia study.

EVENTS WITHIN 14 DAYS OF INITIATION OF THERAPY

The occurrence of adverse cardiac events and death was correlated with whether or not flecainide was initiated as therapy to inpatients or outpatients, and how long after initiation they occurred.

No proarrhythmic deaths have occurred when flecainide was initiated to outpatients with premature ventricular complexes or nonsustained ventricular tachycardia. Fifteen patients in this data base have been exposed to flecainide as outpatients with the diagnosis of sustained ventricular tachycardia, and 1 proarrhythmic death occurred (6.7%).

Twelve of the 13 proarrhythmic deaths occurred within 14 days of initiation of flecainide, 11 with sustained ventricular tachycardia, and 1 with nonsustained ventricular tachycardia plus Class III congestive heart failure with an ejection fraction of <30%. All 12 would have been hospitalized if the recommendations for hospitalization were followed (i.e. hospitalize patients with sustained ventricular tachycardia, evidence of symptomatic congestive heart failure, or history of sinus node dysfunction).

Of the 30 patients with serious non-lethal proarrhythmic events, 23 (77%) occurred within 14 days of initiation of flecainide. All but 1 of these patients would have received in-hospital initiation of flecainide if recommended guidelines for such initiation were used.

Three of the 6 deaths due to congestive heart failure occurred within 14 days of initiating flecainide. All 3 would have been initiated in-hospital using the recommended criteria for in-patient initiation.

Of the 4 patients who developed syncope on flecainide three experienced the event within 14 days of initiating flecainide. One had been treated for sustained ventricular tachycardia and the other 2 had known sinus node dysfunction at baseline. All 3, therefore, would have had in-hospital initiation of flecainide following the recommendation that patients with sinus node dysfunction or sustained ventricular tachycardia be initially dosed as inpatients.

Thirty-seven patients with in- or out-of-hospital sudden death died within 14 days of initiation of flecainide therapy. Twenty-seven of these 37 patients were treated for sustained ventricular tachycardia and the other 10 had evidence of significant myocardial dysfunction. Therefore all of these patients would have received in-hospital initiation of flecainide following the recommendation for inpatient treatment.

DISCUSSION

The data in this manuscript were derived from a carefully recorded prospectively determined set of trials of the new potent Class IC antiarrhythmic agent flecainide acetate. This large data base can therefore serve as a means of defining relationships between classification of ventricular arrhythmias, dose rate of flecainide administration, and the occurrence of serious cardiac adverse events.

CLASSIFICATION OF ARRHYTHMIA VERSUS EFFICACY AND ADVERSE EVENTS

Classification of patients with ventricular arrhythmias into those with premature ventricular complexes only, non-sustained ventricular tachycardia and sustained ventricular tachycardia has previously been demonstrated to correlate well with the efficacy of flecainide[4-9]. In patients with premature ventricular complexes only and non-sustained ventricular tachycardia who were treated in placebo controlled and quinidine comparative randomized trials[4-7], 80-90% of such patients will demonstrate excellent efficacy on flecainide. Conversely, in patients treated for sustained ventricular tachycardia using noninvasive and/or electrophysiologic approaches approximately 20-50% of patients will respond to flecainide[9,10,11]. This is a higher response rate than seen with other Class I antiarrhythmic agents[1,2].

This manuscript defines the relative risk of serious adverse cardiac effects: proarrhythmia, congestive heart failure, conduction disturbances on flecainide therapy and also shows that

their incidence is correlated closely with the classification system used for ventricular arrhythmias[2,3]. However, the development of symptomatic conduction disturbances is related to the electrophysiologic action of flecainide and is better predicted by knowing the baseline sinus node function rather than by the class of ventricular arrhythmia before treatment.

Of the 470 patients treated for premature ventricular complexes only, there were no flecainide related deaths, no serious proarrhythmic events, and a low sudden cardiac death rate (2.3%). Among the 469 patients treated for nonsustained ventricular tachycardia, there was one possible proarrhythmic death, 4 serious non-lethal proarrhythmic events, 2 patients who died due to congestive heart failure, and a combined sudden death incidence in these patients of 6.4%.

INITIATION OF FLECAINIDE TO OUTPATIENTS VERSUS INPATIENTS

The data herein support that flecainide can be safely initiated to selected outpatients since the prevalence of serious cardiac adverse reactions is quite low. Obviously, more data are required to confirm these results with higher confidence. Hospitalization is recommended for all patients with a history of sustained ventricular tachycardia when treated with any antiarrhythmic. For patients with less severe arrhythmias, hospitalization during initiation of flecainide is recommended if they have symptomatic congestive heart failure or sinus node dysfunction. These characteristics were present in all but three of the patients treated for premature ventricular complexes or

nonsustained ventricular tachycardia who had death or serious cardiac adverse experience within 14 days of therapy. Everyone of the 10 patients treated for premature ventricular complexes or nonsustained ventricular tachycardia who had in-hospital or out-of-hospital sudden death within 14 days would have received in-hospital initiation of flecainide. Three of the 4 patients with serious proarrhythmic events would have been hospitalized. The remaining patient was treated for nonsustained ventricular tachycardia reported to the emergency room with light-headedness and was found to be in a wide complex tachycardia requiring cardioversion. Eight of the 10 patients treated for premature ventricular complexes or nonsustained ventricular tachycardia who required early discontinuation of flecainide from congestive heart failure also would have been hospitalized. The 2 who would not had only mild symptoms of congestive heart failure and required no therapy other than discontinuing flecainide. Thus it is clear that all patients who might have benefited from hospitalization would be hospitalized if the recommendations were followed.

RISK VERSUS BENEFIT OF FLECAINIDE

Thus, the concern of benefit versus risk for the use of flecainide in patients with ventricular arrhythmias can be more clearly estimated by the data provided in this report. While it is quite clear that patients receive benefit from eliminating hemodynamic or life-style limiting symptoms by reducing their arrhythmia by the potent agent flecainide, it is still unknown

whether the potential benefit of preventing sudden cardiac death in high risk patients will in fact be confirmed when antiarrhythmic agents are used to eliminate the major risk factor of ventricular arrhythmias. Very little data exist analyzing the serious cardiac adverse reactions using other antiarrhythmic drugs as based on the nature of the patients being treated and characteristics of their ventricular arrhythmias. We do know that, for example, that initiating quinidine in outpatients with benign or potentially lethal ventricular arrhythmias likewise has a very low incidence of proarrhythmia (about 6%) and no deaths as was also seen in this study using flecainide[12]. A much higher prevalence of proarrhythmia and particularly the presence of torsade de pointes is mostly seen in patients treated with quinidine who manifest atrial fibrillation, congestive heart failure or hypokalemia. Thus, it appears that it is more important to understand the clinical conditions associated with the arrhythmia rather than the arrhythmia itself if one wishes to predict the potential for serious cardiac adverse reaction due to antiarrhythmic drug therapy. Thus, we recommend for flecainide, as for other antiarrhythmic agents, that initiation of therapy be done in-hospital for patients with sustained ventricular tachycardia, those with serious compromised left ventricular function particularly with symptomatic congestive heart failure and unstable cardiac states such as unstable ischemia and electrolyte inbalance (particularly hypokalemia). Patients with sick sinus syndrome are at risk of developing higher degrees of block from potent antiarrhythmic drugs as flecainide and therefore all such patients should be initiated with such therapy

in-hospital.

CLINICAL USE OF FLECAINIDE IN SERIOUS CASES

The data comparing the high initial dose compassionate study and the initial low dose ventricular tachycardia study demonstrate clearly the principle that one must treat the seriously ill patient with a sustained ventricular tachycardia not only in-hospital but with a careful dosage regimen, starting with a small total daily dose of the drug and not increasing that dose until steady state has been reached. Initiating therapy with a lower dose of flecainide at 100 mg/bid is a safety precaution that should be followed for all patients to be treated since this agent is so potent and higher doses are often not needed. Thus, a regimen for flecainide using an initial dose of 100 mg bid with incremental increases of 50 mg bid every 4 days under careful monitoring of both the electrocardiogram and blood levels has markedly reduced the prevalence of serious proarrhythmia, congestive heart failure and death. Patients rarely require more than 200 mg bid when lethal ventricular arrhythmias are present where up to 600 mg per day of flecainide has been found to increase somewhat the yield of successfully treated patients in those with benign and potentially lethal ventricular arrhythmias initiated as outpatients[4-7].

In summary, it is not only the form of the ventricular arrhythmia that determines the predictability of serious cardiac adverse reactions from antiarrhythmic drugs but also the accompanying clinical characteristics. The classification of

patients with ventricular arrhythmias into those with premature ventricular complexes, non-sustained ventricular tachycardia and sustained ventricular tachycardia not only has basis in differentiating the predictable efficacy rates from flecainide and other antiarrhythmic agents but also the ability to predict serious adverse cardiac events. The use of this classification system to report antiarrhythmic drug trial efficacy and safety results and defining patients for sudden cardiac death prevention trials seems warranted.

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TABLE 1

PATIENTS IN DATA BASE STRATIFIED FOR VARIOUS BASELINE CHARACTERISTICS AND DOSE(S) RECEIVED

	PVC ONLY		NONSUSTAINED VT		SUSTAINED VT		TOTAL	
STRUCTURAL HEART DISEASE								
NO	132	28.1%	64	13.6%	28	7.2%	224	16.8%
YES	338	71.9%	405	86.4%	363	92.8%	1106	83.2%
TOTAL	470		469		391		1330	100.0%
TOTAL DAILY DOSE*								
200	260	55.3%	347	74.0%	301	77.0%	908	68.3%
300	142	30.2%	250	53.3%	195	49.9%	587	44.1%
400	324	68.9%	218	46.5%	160	40.9%	702	52.8%
600	44	9.4%	50	10.7%	25	6.4%	119	8.9%
STUDY								
High initial dose compassionate use study	59	12.6%	118	25.2%	100	25.6%	227	17.1%
Low initial dose VT study	27	5.7%	204	43.5%	198	50.6%	429	32.3%
OUTPATIENT INITIATION OF THERAPY	273		88		15		376	

*Patients were included more than once if exposed to multiple flecainide dosages.

PVC = Premature Ventricular Complex
VT = Ventricular Tachycardia

TABLE 2

ALL PROARRHYTHMIC EVENTS

	PVC ONLY		NONSUSTAINED VT		SUSTAINED VT		TOTAL	
STRUCTURAL HEART DISEASE								
NO	4/132	3.0%	2/64	3.1%	2/28	7.1%	8/224	3.6%
YES	4/338	1.2%	16/405	4.0%	62/363	17.1%	82/1106	7.4%
TOTAL	8/470	1.7%	18/469	3.8%	64/391	16.4%	90/1330	6.8%
STUDY								
High initial dose compassionate use study	0/59	0.0%	2/118	1.7%	26/100	26.0%	28/277	10.1%
Low initial dose VT study	2/27	7.4%	6/204	2.9%	26/198	13.1%	34/429	7.9%

PVC = Premature Ventricular Complex
VT = Ventricular Tachycardia

TABLE

DEATH FROM PROARRHYTHMIC EVENTS

	PVC ONLY		NONSUSTAINED VT		SUSTAINED VT		TOTAL	
STRUCTURAL HEART DISEASE								
NO	0/132	0.0%	0/64	0.0%	0/28	0.0%	0/224	0.0%
YES	0/338	0.0%	1/405	0.2%	12/363	3.3%	13/1106	1.2%
TOTAL	0/470	0.0%	1/469	0.2%	12/391	3.1%	13/1330	1.0%
STUDY								
High initial dose compassionate use study	0/59	0.0%	1/118	0.8%	10/100	10.0%	11/277	4.0%
Low initial dose VT study	0/27	0.0%	0/204	0.0%	1/198	0.5%	1/429	0.2%

PVC = Premature Ventricular Complex
VT = Ventricular Tachycardia

TABLE 4

SERIOUS NONLETHAL PROARRHYTHMIC EVENTS

	PVC ONLY		NONSUSTAINED VT		SUSTAINED VT		TOTAL	
STRUCTURAL HEART DISEASE								
NO	0/132	0.0%	0/64	0.0%	1/28	3.6%	1/224	0.4%
YES	0/338	0.0%	4/405	1.0%	25/363	6.9%	29/1106	2.6%
TOTAL	0/470	0.0%	4/469	0.9%	26/391	6.6%	30/1330	2.3%
STUDY								
High initial dose compassionate use study	0/59	0.0%	0/118	0.0%	8/100	8.0%	8/277	2.9%
Low initial dose VT study	0/27	0.0%	2/204	1.0%	12/198	6.1%	14/429	3.3%

PVC = Premature Ventricular Complex
VT = Ventricular Tachycardia

TABLE 5

OTHER PROARRHYTHMIC EVENTS

	PVC ONLY		NONSUSTAINED VT		SUSTAINED VT		TOTAL	
STRUCTURAL HEART DISEASE								
NO	4/132	3.0%	2/64	3.1%	1/28	3.6%	7/224	3.1%
YES	4/338	1.2%	11/405	2.7%	25/363	6.9%	40/1106	3.6%
TOTAL	8/470	1.7%	13/469	2.8%	26/391	6.6%	47/1330	3.5%
STUDY								
High initial dose compassionat : use study	0/59	0.0%	1/118	0.8%	8/100	8.0%	9/277	3.2%
Low initial dose VT study	2/27	7.4%	4/204	2.0%	13/198	6.6%	19/429	4.4%

PVC = Premature Ventricular Complex
VT = Ventricular Tachycardia

TABLE 6

RELATIONSHIP OF FLECAINIDE DOSE
TO TYPE OF PROARRHYTHMIA IN PATIENTS
TREATED FOR SUSTAINED VENTRICULAR TACHYCARDIA

	ALL		SERIOUS NON-LETHAL		DEATHS	
TOTAL DAILY DOSE*						
200	14/301	4.7%	7/301	2.3%	0/301	0.0%
300	22/195	11.3%	9/195	4.6%	3/195	1.5%
400	24/160	15.0%	7/160	4.4%	8/160	5.0%
600	4/25	16.0%	3/25	12.0%	1/25	0.5%

*Patients were included more than once if exposed to multiple flecainide dosages.

TABLE 7

SYMPTOMATIC CONDUCTION DISTURBANCES

	PVC ONLY		NONSUSTAINED VT		SUSTAINED VT		TOTAL	
RUCTURAL HEART SEASE								
NO	3/132	2.3%	0/64	0.0%	0/28	0.0%	3/224	1.3%
YES	2/338	0.6%	2/405	0.5%	4/363	1.1%	8/1106	0.7%
TOTAL	5/470	1.1%	2/469	0.4%	4/391	1.0%	11/1330	0.8%
UDY								
High initial dose compassionate use study	0/59	0.0%	1/118	0.8%	4/100	4.0%	5/277	1.8%
Low initial dose VT study	0/27	0.0%	1/204	0.5%	0/198	0.0%	1/429	0.2%

PVC = Premature Ventricular Complex
VT = Ventricular Tachycardia

TABLE 8
IN-HOSPITAL ARRHYTHMIC DEATHS
AND OUT-OF-HOSPITAL SUDDEN DEATHS

	PVC ONLY		NONSUSTAINED VT		SUSTAINED VT		TOTAL	
STRUCTURAL HEART DISEASE								
NO	1/132	0.8%	0/64	0.0%	1/28	3.6%	2/224	0.9%
YES	10/338	3.0%	30/405	7.4%	49/363	13.5%	89/1106	8.0%
TOTAL	11/470	2.3%	30/469	6.4%	50/391	12.8%	91/1330	6.8%
STUDY								
High initial dose compassionate use study	4/59	6.8%	7/118	5.9%	20/100	20.0%	31/277	11.2%
Low initial dose VT study	0/27	0.0%	9/204	4.4%	18/198	9.1%	27/429	6.3%

PVC = Premature Ventricular Complex
VT = Ventricular Tachycardia

TABLE 8
IN-HOSPITAL ARRH' MIC DEATHS
AND OUT-OF-HOSPITAL SUDDEN DEATHS

	PVC ONLY		NONSUSTAINED VT		SUSTAINED VT		TOTAL	
TRUCTURAL HEART ISEASE								
NO	1/132	0.8%	0/64	0.0%	1/28	3.6%	2/224	0.9%
YES	10/338	3.0%	30/405	7.4%	49/363	13.5%	89/1106	8.0%
TOTAL	11/470	2.3%	30/469	6.4%	50/391	12.8%	91/1330	6.8%
TUDY								
High initial dose compassionate use study	4/59	6.8%	7/118	5.9%	20/100	20.0%	31/277	11.2%
Low initial dose VT study	0/27	0.0%	9/204	4.4%	18/198	9.1%	27/429	6.3%

PVC = Premature Ventricular Complex
VT = Ventricular Tachycardia

Riker Laboratories, Inc.
270-3A-1 3M Center
St. Paul, Minnesota 55144
(612)733-0633

7.1 REPORTS

ORIGINAL

3M

June 24, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jlg

Enclosure - [redacted]
- [redacted]
- [redacted]

Certified Mail P 917 255

7/8

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved. OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO	DA.	YR.
[redacted]	63	M	12	23	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

MYOCARDIAL INFARCT, ACUTE LEFT VENTRICULAR FAILURE, SUDDEN DEATH
PT BEING TREATED FOR SUB-ACUTE MYOCARDIAL INFARCT WAS ON FLECAINIDE FOR 4 DAYS WHEN, AFTER A BRIEF WALK, HE SUDDENLY BECAME BREATHLESS AND DIED. DIURETICS HAD BEEN BEGUN 11 DAYS BEFORE DEATH (7 DAYS BEFORE FLECAINIDE)FOR SIGNS OF RECURRENT LEFT HEART FAILURE. HISTORY OF CORONARY ARTERY DISEASE. PREVIOUSLY HAD HAD V. TA[illegible] AND PULMONARY EDEMA ON ON LIGNOCAINE. 19DEC85 HOLTER SHOWED MULTIFOCAL PREMATURE VENTRICULAR COMPLEXES.

13. RELEVANT TESTS LABORATORY DATA

NORMAL CHEST X RAY
SEE #7, ABOVE.

c

8-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

DAILY DOSE	16. ROUTE OF ADMINISTRATION
200 MG	ORAL

17. INDICATION(S) FOR USE

VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
12-19-85 - 12-23-85	4 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?

- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

FUROSEMIDE 11 DAYS AMILORIDE 11 DAYS

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

PATIENT HAD LARGE MYOCARDIAL INFARCT, SIGNIFICANT ARRHYTHMIA FREQUENCY AND LEFT VENTRICULAR FAILURE (WITH NORMAL CHEST X RAY)
FOR ADDITIONAL HISTORY SEE #7 ABOVE.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
3/21/86	[X] FOREIGN [ ] STUDY [ ] LITERATURE [ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
[X] YES [ ] NO	[ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

- [ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	72	M	02	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, purpura
Patient (72-year-old male) developed extensive purpura 12 days after a myocardial infarction. Also had actinoreticulosis and Mycosis fungoides. During this time, patient was started on flecainide (100 mg qd) for the treatment of frequent PVCs and ventricular tachycardia. Patient died on 02/14/86 from intravascular coagulation considered by physician to be a development of the Mycosis fungoides and not the result of concomittant use of flecainide.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [x] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

02/12/86: Fibrin: 5.6G - Blood platelet: 135,000
02/14/86: Fibrin: 2.4g - Blood platelet: 35,000 - V factor: 5g%
Prothrombin time: 43%; cephalin-kaolin time: 85 sec.
= Spreaded intravascular coagulation

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?

- [ ] YES [ ] NO [x] NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
100 MG	ORAL

INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

- [ ] YES [ ] NO [x] NA

18. THERAPY DATES *(From To)*	19. THERAPY DURATION
02/10/86 - 02/13/86	3 DAYS

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

HEPARIN SODIUM
DIGOXIN
THEOPHYLLINE
FUROSEMIDE
DOBUTAMINE HYDROCHLORIDE
NONE
ISOSORBIDE DINITRATE
NONE
DOPAMINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Myocardial infarction, actinoreticulosis, Mycosis fungoides.

IV. FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
5/14/86	[x] FOREIGN [ ] STUDY [ ] LITERATURE [ ] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT	25a. REPORT TYPE
[x] YES [ ] NO	[x] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

- [ ] YES [ ] NO

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4-6. REACTION ONSET — MO. | DA. | YR.

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

8-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

+hepatic function abnormal, SGOT 51gmv/ml; SGPT: 730mv/ml; SGT 311v/l
+renal heart failure (renal function normal previously)
+metabolic acelosis

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 5 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID: INITIALS *(In Confidence)* [redacted]

2. AGE YRS. 55

3. SEX M

4.-6 REACTION ONSET: MO. 01 DA. 06 YR. 86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
Upper respiratory infection treated with ampicillin 1/6/86 to 1/14/86.

8.-12. CHECK ALL APPROPRIATE TO REACTION
- ☐ DIED DUE TO REACTION
- ☒ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 400 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*: 05/21/85 - ONGOING

19. THERAPY DURATION: 7.5 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
POTASSIUM CHLORIDE
DIPYRIDAMOLE
ASA, MAG ALUMINUM HYDROXIDE
FUROSEMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
ASHD, coronary artery bypass graft, myocardial infarct (2)

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO. [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/16/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT ☒ YES ☐ NO

25a. REPORT TYPE ☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)* [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80

JL 30

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA #: 18-830

Name of Drug: Tombocor (flecainide acetate) Tablets

Sponsor: Riker Lab.

Type of Submission: ADRs

Date of Submission: 6/20/86, 6/18, 6/13/86

Date of Review: July 1, 1986

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

6/20/86 14 ADRs are reported
Sudden cardiac death-3, death due to MI-1, pulmonary edema-4, TIA - 1, Sore throat - 1, Parcytopenia, death* - 1, coma - 1, Neuropathy - 2, recurrent simsitis -1, *: port from France - No detail information

6/18/86 unexpected ADRs are:

[redacted] Death, acute renal failure, cholestatic jaundice, elevated liver enzymes, epigastric pain

Patient (72-year-old male) was started on flecainide (100 mg b.i.d.). Patient also had chronic obstructive pulmonary disease and was in CHF. Approximately 4 days after beginning flecainide patient was hospitalized with the chief complaint of epigastric pain and nausea. Lab data revealed an increase bilirubin, serum creatinine, and BUN. Patient showed signs of cholestatic jaundice. A cholesystectomy on 05/04/86 showed no obstruction and was otherwise unremarkable. Patient continued to show evidence of elevated liver enzymes and acute renal failure. Death on 05/09/86.

[redacted] Dyspnea, hemoptysis Patient

90-year-old male had been taking F for about one week. Patient suddenly developed dyspnea and began spitting up blood. He was admitted to the hospital for observation and tests. F was discontinued and the patient recovered.

[redacted] Hiccups

Patient (65-year-ld male) developed intractable hiccups three days after starting F 100 mg b.i.d. After seven days of intractable hiccups F was discontinued. Prior to discontinuing F, patient was treated with chloral hydrate and phenothiazines for the hiccups with no success.

S K Chun 7/28/86
Sughok K. Chun

cc: Orig.
HFN/110
HFN/110/CSO
HFN/110/SChun
keg/7/18/86;7/28/86/0604r

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

3M

June 20, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

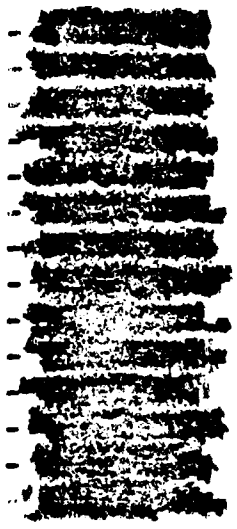
Enclosed are duplicate copies of fourteen Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jlg

Enclosure -



Certified Mail P 648 917 252

6/27

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	73	F	04	27	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death
This 73 y.o. woman was admitted via ER for schizoid personality disorder. Holter recording showed 400 VPC's/hr and 6-7 supraventricular ectopic beats/hr. Cardiac consult concluded dilutional hyponatremia by history, psychiatric illness, ASHD with ventricular arrhythmia. In addition to drugs shown in #22, below, was on cimetidine and tocainide which were discontinued on 5APR86. Flecainide 100mg bid begun 10APR86 and Holter on 11APR showed 2 VPC/hr and no supraventricular ectopics. On 15APR disopyramide cut to 150mg tid and further reduced to 150 bid on 17APR. On 22APR86 she was discharged to a psychiatric hospital where loxapine was added to her regimen. She died 5 days later under

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*: 04/10/86 - 04/26/86

19. THERAPY DURATION: 16 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

LOXAPINE	5 days	DISOPYRAMIDE	LONGTIME
LABETALOL HCL	LONGTIME	FLURAZEPAM HCL	LONGTIME
NONE			

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Dilutional hyponatremia by past history and arteriosclerotic heart disease with ventricular arrhythmias.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/ 6/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE. Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

circumstances not yet determined but under continued investigation. Current information suggests death was rather of sudden, non-CHF cardiac type such as serious ventricular arrhythmia as opposed to convulsion or other non-cardiac event.
(N.B. Initiated under old internal guidelines, case would not today be considered 15-day type. Continued as a 15-day, however, to avoid clerical confusion for FDA and internal record keeping.)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines.biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6 REACTION ONSET MO.	DA.	YR.
[redacted]	50	M	01	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

*VENTRICULAR FIBRILLATION (PROBABLE), SUDDEN DEATH**
PT WITH SYMPTOMATIC ATRIAL FIBRILLATION STARTED ON FLECAINIDE SEP85, CARDIOVERTED TO NORMAL SINUS RHYTHM AND REMAINED SYMPTOM FREE. GOOD REVIEWS IN OCT85 AND DEC85. ON 13JAN86 COLLAPSED WHILE UNDERTAKING MILD EXERCISE AND WAS PRONOUNCED DEAD 5 MIN LATER. PHYSICIAN SAID CAUSAL RELATIONSHIP TO DRUG "MOST UNLIKELY". FEELS DUE TO AORTIC VALVE. CASE ALSO REPORTED TO NORWEGIAN BOARD OF HEALTH.
(N.B.: UNDER CURRENT INTERNAL CRITERIA CASE WOULD NOT TODAY BE REPORTED AS 15-DAY, BUT RETAINED AS SUCH FOR THIS FOLLOW-UP REPORT)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

FLECAINIDE BLOOD LEVELS:
06SEP85 0.385MG/ML
06DEC85 0.247 AND 0.237MG/ML
06DEC85 ECG: PR=0.180SEC, QRS=.10SEC, QT=0.40SEC (ALL CONSISTENT WITH LOW FLECAINIDE EFFECT.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: ATRIAL FIBRILLATION

18. THERAPY DATES *(From To)*: 09-01-85 - 01-13-86

19. THERAPY DURATION: 4 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

COMBINED AORTIC VALVE INCOMPETENCE AND STENOSIS WITH 70MM HG PRESSURE GRADIENT ACROSS VALVE. HAD ATRIAL FIBRILLATION WITH SOME SYMPTOMS. KNOWN TO HAVE SEVERE LEFT VENTRICULAR HYPERTROPHY.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/27/86

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved. OMB No 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO	DA	YR
[redacted]	62	M	02	21	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
Death, myocardial infarction
Acute myocardial infarction resulted in secondary cardiogenic shock and death.

8-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
2/21/86: BUN 19; Glucose 155; pH 7.43; Na 134; CPK 22; PCO2 29; K 4.1; LDH 162; Hgb 17.3; PO2 137; WBC 15,000; CO2 18.
Serial EKGs showed complete left bundle branch block and an idioventricular rhythm. Serial cardiac enzymes didn't show significant elevation.
Chest X-ray showed massive cardiomegaly and changes consistent with CHF.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*
03/21/85 - 02/21/86

19. THERAPY DURATION
11 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN	11 MONTHS	NITROGLYCERIN	11 MONTHS
POTASSIUM CHLORIDE	11 MONTHS	DIOCYTL SODIUM SULFOSUCCINATE	10 MONTHS
AMIODARONE	10 MONTHS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*
Severe ischemic and congestive cardiomyopathy, history of malignant ventricular arrhythmias, severe diffuse multivessel disease.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST. PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
5/ 5/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [X] STUDY
- [ ] LITERATURE
- [ ] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

NOTE. Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6 REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
Pancytopenia, death
Report from France indicates patient, while on flecainide, developed pancytopenia and subsequently died. No further details are known.

8-12 CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS / LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

18. THERAPY DATES *(From To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
5/14/86

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Coo*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

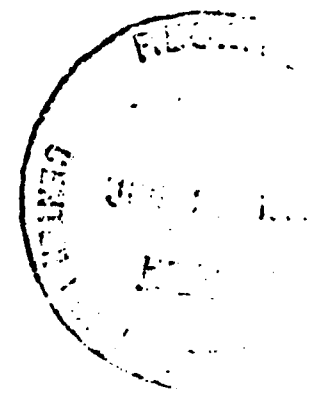
26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

3M

June 18, 1986



Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jlg

Enclosure - [redacted]
- [redacted]

Certified Mail P 648 917 250

6/27

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved OMB No. 0910-0001
Expiration Date May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA	YR
[redacted]	72	M	05	01	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, acute renal failure, cholestatic jaundice, elevated liver enzymes, epigastric pain
Patient (72-year-old male) was started on flecainide (100 mg b.i.d.) for the treatment of ventricular arrhythmias. Patient also had chronic obstructive pulmonary disease and was in congestive heart failure. Approximately four days after beginning flecainide patient was hospitalized with the chief complaint of epigastric pain and nausea. Lab data revealed an increase bilirubin, increase serum creatinine, and increase BUN. Patient showed signs of cholestatic jaundice. A cholesystectomy on 05/04/86 showed no obstruction and was otherwise unremarkable. Patient continued to show evidence of elevated liver enzymes and acute

13. RELEVANT TESTS LABORATORY DATA

Lab values: 1. Increase liver enzymes--SGOT 3X Normal
2. Bilirubin 5/1/86 = 1.8; 8/5/86 = 6.6 Normal (<1.5)
3. Creatinine 5/1/86 = 2.7; 5/8/86 = 7.0
4. Urine Output 5/8/86 less than 600 ml per day
5. Cholesystectomy 5/4/86 Negative findings

8-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics,*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*: 04/25/86 - 05/03/86

19. THERAPY DURATION: 8 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG? [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN(LANOXIN)
POTASSIUM CHLORIDE
PREDNISONE
FUROSEMIDE
PROBENECID

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Patient was allergic to quinidine.
Chronic renal failure.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/ 9/86

24d. REPORT SOURCE *(Check one)*: [ ] FOREIGN [ ] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT: [X] YES [ ] NO

25a. REPORT TYPE: [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? [ ] YES [ ] NO

26d ARE YOU A HEALTH PROFESSIONAL? [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-5. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

renal failure. Death occurred on 05/09/86.

13. RELEVANT TESTS/LABORATORY DATA

Autopsy findings showed severe cardiac disease, acute renal failure, liver necrosis and intrahepatic bile duct obstruction.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION DATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT ☐ YES ☐ NO

25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

7.1 REPORTS ORIGINAL

3M

June 9, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure - [redacted]
- [redacted]

Certified Mail P 648 917 242

6/20

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	75	F	03	11	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

UNRESUSCITATABLE VENTRICULAR FIBRILLATION, SUDDEN DEATH
Patient with new MI admitted to hospital in pulmonary edema. Developed ventricular tachycardia for which flecainide acetate was started 100 mg b.i.d. About a week later, runs of V-tach continued; so patient was being transferred to CCU in preparation for increasing dose of flecainide when patient developed ventricular fibrillation and could not be resuscitated although electrical defibrillation, i.v. lidocaine and bretylium were tried.
[redacted] Although with these further data it is clear event was not a 15-day report, case shall continue in our files as 15-day to avoid confusion.

13. RELEVANT TESTS/LABORATORY DATA
CPK reached 394.
No autopsy.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
03-04-86 - 03-11-86

19. THERAPY DURATION
7 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
DIGOXIN
FUROSEMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
SEE #7 above. It was also noted that patient have severe left ventricular dysfunction.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
6/ 2/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

ORIGINAL

3M

June 2, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor , flecainide acetate

Dear Sir/Madam,

Enclosed are nine Adverse Reaction Reports (Form FDA 1639) plus copy of an initial report previously submitted pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong/RE

Florence N. Wong
Regulatory Specialist

FNW/he

Enclosure - [redacted] followup and initial report

Certified Mail P 648 917 237

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved OMB No. 0910-0001
Expiration Date May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6 REACTION ONSET MO.	DA	YR
[redacted]	---	-	??	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
#DEATH#
SKETCHY DETAILS FROM REPRESENTATIVE INDICATE ONLY DEATH OF PATIENT WHILE TAKING TAMBOCOR (FLECAINIDE ACETATE).

13. RELEVANT TESTS LABORATORY DATA
INITIAL REPORT FROM REPRESENTATIVE SUGGESTED BILIRUBIN AND/OR CREATININE WERE ELEVATED. WHETHER BEFORE OR AFTER TAMBOCOR IS PRESENTLY UNCLEAR.

8-12 CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From-To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
HISTORY OF DIABETES, CONGESTIVE HEART FAILURE, DEHYDRATION.
? HISTORY OF HYPERKALEMIA, ? HISTORY OF ELEVATED BILIRUBIN AND/OR CREATININE.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
3/18/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [X] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO	DA.	YR.
[redacted]	76	M	01	31	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Worsening CHF, Renal Decompensation, Terminal arrhythmias, Death
This 76 y.o. male had history of diabetes, hypertensive cardiovascular disease, arteriosclerotic heart disease and heart failure. These were being treated with a variety of drugs including Procardia, digoxin, Lasix, Captopril and insulin. He had been discharged from nospital only 21JAN86 when he had been treated for congestive failure. He was also taking flecainide at a dose of 100mg bid, but the reason for this is unclear as no history of arrhythmia is noted before hospitalization. While out of hospital, and presumably while taking flecainide, he CHF returned with edema, elevation of BUN and creatinine and hyperk ia. His ECG showed prominent T-waves, QRS widening and small P-wav is

13. RELEVANT TESTS LABORATORY DATA

On admission K-6.9, BUN=82, creatinine 5.6, glucose 238.
Second day: BUN=96, creatinine 5.1, glucose=125.
Day of Death: K=5.0, BUN-81, creatinine=4.7.
Flecainide day before death=2.31 (N=0.2-1.0) microgm/ml.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [X] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
200 MG	ORAL

17. INDICATION(S) FOR USE
UNKNOWN

18. THERAPY DATES *(From To)*	19. THERAPY DURATION
01-??-86 - 02-13-86	? 1-3 WKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN(LANOXIN)
POTASSIUM CHLORIDE
FUROSEMIDE
DIAZEPAM
NIFEDIPINE
ISOPHANE INSULIN
CAPTOPRIL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

SEE #7, ABOVE. IN ADDITION HISTORY OF DEPRESSION WITH SEVERAL HOSPITALIZATIONS FOR THAT CONDITION. PREVIOUS HISTORY OF HOSPITALIZATION FOR MI (8/84) AND SERVERE HYPERTENSION WITH CHF 12/83 AND 1/86. THROMBOPHLEBITIS IN THE PAST.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER
5/23/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

congestive failure was treated with moderate success and the hyperkalemia treated with insulin and glucose. As time went on ECG showed narrowing of QRS, 1st degree block and intraventricular conduction defect. Flecainide level drawn day before death was 2.31 (N=0.2-1.0) microgm/ml. Final events included V-tach proceeding to V-fib and arrest. Physician felt renal failure probably pre-renal in origen -- possibly contributed to by diabetes. The role of flecainide may have been contributory.

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

ORIGINAL

3M

May 30, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are four Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure - [redacted]

Certified Mail P 648 917 240

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved. OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	55	M	02	20	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, Adams-stokes syndrome
Patient (55-year-old male) suffered a postero-lateral myocardial infarction in January 1986, based on an underlying coronary arterial sclerosis already initially complicated by disturbances of rhythm. The long-term holter-monitoring on 02/13/86 to 02/14/86 showed six cuplets, ventricular extrasystoles, and ventricular tachycardia with short duration. The cardiologist then prescribed flecainide (100 mg t.i.d.). The controlling holter-ECG from 02/17/86 to 02/18/86 showed a complete suppression of cuplets and a reduction of PVCs. Up to 02/17/86 no change of QRS-complexes or QT-time could be seen.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300 MG

16. ROUTE OF ADMINISTRATION: ORAL

INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

17. THERAPY DATES *(From To)*: 02/17/86 - 02/20/86

19. THERAPY DURATION: 3 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN
NIFEDIPINE
NONE
ISOSORBIDE DINITRATE
METHYLPREDNISOLONE

23 OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-83u

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/15/86

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	--	--	--

8-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden death
Manuscript submitted 03/05/86 to the International Symposium on Ventricular Tachycardia at Vittel: "Effects of Flecainide in Patients with Sustained Ventricular Tachycardia and Fibrillation," [redacted]
In this study with 22 patients receiving Tambocor from 5 to 19 months, one patient experienced sudden death.

13. RELEVANT TESTS LABORATORY DATA

C.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: UNKNOWN

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/ 8/86

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [X] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

[redacted] : 85-093/Eu.

EFFECTS OF FLECAINIDE IN PATIENTS WITH SUSTAINED VENTRICULAR TACHYCARDIA AND FIBRILLATION

[redacted]

Departments of cardiology, [redacted]

We studied the effect of Flecainide (F) in 18 patients (pts) w: sustained ventricular tachycardia (VT) and 4 pts with ventric.: fibrillation (VF). 10 pts had a healed myocardial infarction, : had other etiologies. 13 pts had failed a mean of 2.2 drugs (r. 1-5), in 9 pts F was the first drug. 15 pts had maximal ex: cise testing (ET) and 16 pts had 24 hour Holter monitoring (HM at control and one week after start of oral F (mean dose 223, r. 100-400 mg). Programmed electrical stimulation (PES) was carried out in 11 pts before and after iv F (2 mg/kg in 20 mi: Therapy was guided by close clinical monitoring of VT symptoms. The median values of the maximal Lown scores (L max) decrease: after oral F from ia to 0 during ET, but remained unaltered :: during HM. At control PES 10/11 pts had inducible VT or VF. Af: iv F 5/11 pts had still inducible VT. The mean cycle length increased from 265 to 328 ms ($p < 0.05$) after iv F.
During clinical follow up (mean 11, r. 5-19 months), 6/22 pts (27%) showed a symptomatic recurrence of VT on F including 1 p: with sudden death (SD). 5 pts stopped F: 1 pt following aggra:: tion of congestive heart failure (this pt died later of SD on Amiodarone), 1 pt due to drug fever and liver function disturbances, 1 pt due to incessant trigemini and 2 pts with pro-arrhythmic effects (1 VT, 1 VF, the latter provoked by ET).
The results of ET, HM and PES related to the clinical symptom: during longterm follow up are shown in the table.

recurrent	PES (n=11)		ET (n=15)		HM (n=16)	
VT	inducible	not ind.	no change*	decrease	no change*	decrea:
+	2	3	4(1)	1	5(1)	:
-	3	3	4(1)	4	6	:

* numbers within parentheses indicate pts with increase of L ma

We conclude that 1) F is a moderately effective agent in the treatment of VT/VF, as 50% (11/22) of pts can be treated adequately using close clinical monitoring. 2) the maximal Lown score of both HM and ET was a poor indicator to predict the clinical outcome of oral F. 3) iv testing of F by PES was of little valu to predict longterm outcome of oral F in our serious of patients.

7.1

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

ORIGINAL

3M

May 22, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor , flecainide acetate

Dear Sir/Madam,

Enclosed are seven Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong/kt

Florence N. Wong
Regulatory Specialist

FNW/tlh

Enclosure - [redacted]

Certified Mail P 648 917 230

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6 REACTION ONSET MO.	DA.	YR.
[redacted]	64	M	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death
Patient (64-year-old male) with premature ventricular contractions [redacted] was treated for about one week with flecainide (100 mg b.i.d. and inbetween for one or two days with 150 mg b.i.d.). Repeated ECGs did not show QRS widening or bradycardia. Sudden emergency situation (details not known) required hospitalization. Patient died after about one week in the hospital.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: 7 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Family doctor never saw a death certificate. He is convinced that flecainide was not involved in the death of the patient. The hospital has, so far, refused to give any information.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 3/31/86

24d. REPORT SOURCE *(Check one)*
- [x] FOREIGN [ ] STUDY [ ] LITERATURE
- [ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [x] YES [ ] NO

25a. REPORT TYPE
- [x] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO.	DA	YR.
[redacted]	75	F	04	27	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

DEATH
PATIENT WAS ADMITTED TO HOSPITAL FOR SCHIZOPHRENIA. AT THAT TIME WAS TAKING DISOPYRAMIDE LABETALOL. IN HOSPITAL FLECAINIDE ACETATE AND LOXAPINE WERE ADDED. PATIENT WAS TRANSFERRED TO PSYCHIATRIC HOSPITAL WHERE SHE DIED. (REPORTER ADVISES IT WILL REQUIRE ABOUT 3 WEEKS TO OBTAIN MORE COMPLETE INFORMATION.)

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot. no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: UNKNOWN

18. THERAPY DATES *(From To)*: ??/??/86 - 04/26/86

19. THERAPY DURATION: UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

LOXAPINE
LABETALOL HCL
DISOPYRAMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/29/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-720)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6 REACTION ONSET MO	DA.	YR.
[redacted]	53	F	03	06	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

INCREASE IN DIZZINESS, SUDDEN DEATH
Patient was a 53 y.o. woman with history of double valve replacement, chronic obstructive pulmonary disease, left bundle branch block and symptomatic recurrent ventricular ectopy with salvos and intermittent supraventricular tachycardia. She also had history of vertiginous-like dizziness. After starting flecainide she was monitored daily via telephonic means which showed no significant changes in QRS or PR intervals. Her dizziness seemed to increase in frequency after start of flecainide, and Holter showed no related dysrrhythmia. She was hospitalized to examine possibility of CNS bleed as cause of dizziness but died suddenly

13. RELEVANT TESTS LABORATORY DATA

Daily telemetry monitoring from home showed no QRS or PR widening beyond acceptable limits. Holter recordings showed no association between dizzy spells and ECG.

8-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: 02-13-86 - 03-06-86

19. THERAPY DURATION: 3 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

METOLAZONE
DIGOXIN(LANOXIN)
POTASSIUM CHLORIDE
FUROSEMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

HISTORY OF LEFT BUNDLE BRANCH BLOCK, DOUBLE VALVE REPLACEMENT, SYMPTOMATIC VENTRICULAR RECURRENT ECTOPY WITH SALVOS AS WELL AS INTERMITTENT SUPRAVENTRICULAR TACHYCARDIA. SHE ALSO HAD EPISODES OF VERTIGINOUS-LIKE DIZZINESS. FOLLOWING HER RECENT VALVE REPLACEMENTS SHE HAD SIGNIFICANT EDEMA AND DYSPNEA.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/19/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6 REACTION ONSET MO.	DA.	YR.
[redacted]	30	M	12	09	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Cardiac arrest, death
An otherwise healthy man, born 1956, had ventricular extrasystoles since 1982. Further examination showed normal conduction system, normal vessels, and an ectopic focus in the left ventricle. He was treated with an antiarrhythmic agent and until spring 1985, when this was changed to flecainide 150 mg. b.i.d.; from June 1985, 200 mg b.i.d.** Further ambulatory controls were satisfactory, but on December 9, 1985, he got a cardiac arrest and during (professional) resuscitation no cardiac function was observed.
**PATHOLOGIST CLAIMS PT WAS STILL ON 150MG BID AT TIME OF DEATH

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

Autopsy was performed 24 hours after death. The heart was normal including the conduction system. There was no evidence of infarction or myocarditis, hardly any athrosclerosis, no signs of cardiomyopathy, and no ectopic focus could be identified. The other organs were normal. Flecainide plasma levels at autopsy revealed 5.2 mcg/ml of flecainide.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
400 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*
04/??/85 - 12/09/85

19. THERAPY DURATION
~ 8 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/10/86

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	??	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

SUDDEN DEATH
PATIENT WITH RECENT MI RETURNED TO HOSPITAL IN PULMONARY EDEMA. DEVELOPED VENTRICULAR TACHYCARDIA FOR WHICH FLECAINIDE ACETATE WAS STARTED 100 MG B.I.D. ABOUT A WEEK LATER, RUNS OF V-TACH CONTINUED; SO PATIENT WAS BEING TRANSFERRED TO CCU IN PREPARATION FOR INCREASING DOSE OF FLECAINIDE WHEN PATIENT DIED SUDDENLY AND COULD NOT BE RESUSCITATED.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*
??/??/86 - ??/??/86

19. THERAPY DURATION
7 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
SEE #7 ABOVE.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/25/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [X] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

7.1

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

REPORTS 3M

May 15, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/he

Enclosure - [redacted]

Certified Mail P 648 917 222

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved. OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)* [redacted]

2. AGE YRS: ---

3. SEX: -

4-6. REACTION ONSET: MO. ?? | DA. ?? | YR 86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
DEATH
"VERY HIGH-RISK PATIENT" "ON AMIODARONE UNTIL DAY BEFORE STARTING FLECAINIDE". HAVE ATTEMPTED CONTACT WITH PHYSICIAN 4 TIMES WITHOUT SUCCESS IN OBTAINING ANY ADDITIONAL INFORMATION.

8-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: UNKNOWN

18. THERAPY DATES *(From/To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: 1 DAY

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
AMIODARONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 2/14/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26. 26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO	DA	YR
[redacted]	---	F	02	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
SUDDEN DEATH
PT. WAS WOMAN OF UNKNOWN AGE WITH HISTORY OF DOUBLE VALVE REPLACEMENT, CHRONIC OBSTRUCTIVE PULMONARY DISEASE, LEFT BUNDLE BRANCH BLOCK AND SYMPTOMATIC RECURRENT VENTRICULAR ECTOPY WITH SALVOS AND INTERMITTENT SUPRAVENTRICULAR TACHYCARDIA. SINCE STARTING FLECAINIDE 100MG BID SHE HAD BEEN MONITORED VIA TELEMETRY FROM HER HOME DAILY WITH NO ABNORMAL WIDENING OF QRS NOTED. SHE WAS PLACED IN HOSPITAL FOR NEUROLOGICAL WORKUP OF INTERMITTENT DIZZY SPELLS AND DISCHARGED. SHE DIED SUDDENLY.

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTIO
- [ ] TREATED WITH Rx DRU
- [ ] RESULTED IN, OR PROLONGED, INPATIEI HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
DAILY TELEMETRY MONITORING FROM HOME SHOWED NO QRS WIDENING BEYOND ACCEPTABLE LIMITS.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines.biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*
??-??-86 - 02-13-86

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
ALLOPURINOL
DIGOXIN(LANOXIN)
POTASSIUM CHLORIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
HISTORY OF LEFT BUNDLE BRANCH BLOCK, DOUBLE VALVE REPLACEMENT, SYMPTOMATIC VENTRICULAR RECURRENT ECTOPY WITH SALVOS AS WELL AS INTERMITTENT SUPRAVENTRICULAR TACHYCARDIA.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
3/11/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000

ORIGINAL

3M

May 15, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam,

Pursuant to 21 CRF 314.80, enclosed is the Periodic ADR Report for Tambocor®(flecainide acetate) NDA 18-830.

The time period covered by this report is December 11, 1985 to March 11, 1986.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/he

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	62	M	01	21	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

HEART FAILURE
PT. HAD DIFFUSE, ISCHEMIC CARDIOMYOPATHY DIAGNOSED JLY85. MARKED RUNS OF SUSTAINED VENTRICULAR TACHYCARDIA NOT RESPONDING TO OTHER DRUGS. PRONESTYL LED TO LUPUS WITH ELEVATED ANA, JOINT, PERICARDIAL, ETC. FOR WHICH PT HOSPITALIZED. STEROIDS GIVEN, HAD PEPTIC ULCER. SUSTAINED V-TACH RECURRED, ONE TABLET FLECAINIDE GIVEN. CONTROLLED V-TACH, BUT 18 HRS LATER PT WENT INTO PROFOUND HEART FAILURE (HX OF 20% EJECTION FRACTION).

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 100 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*: 20JAN86 - 20JAN86

19. THERAPY DURATION: 1 DOSE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

PREDNISONE
FUROSEMIDE
RANITIDINE
DIGOXIN(LANOXIN)
CAPTOPRIL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

SEE # 7 ABOVE.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 1/23/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[x] HEALTH PROFESSIONAL [ ] CONSUMER

25a. 15 DAY REPORT
[ ] YES [x] NO

25a. REPORT TYPE
[x] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT (INITIALS *(In Confidence)*)	2. AGE YRS	3. SEX	4-6 REACTION ONSET MO.	DA.	YR.
[redacted]	62	M	01	15	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

PROARRHYTHMIA, DEATH
PT WITH HISTORY OF CORONARY ARTERIOSCLEROTIC HEART DISEASE AND LEFT VENTRICULAR DYSFUNCTION HAD BEEN ON A NUMBER OF ANTIARRHYTHMICS BEFORE WITHOUT SUCCESS TO TREAT RUNS OF V-TACH -- OCCASIONALLY SUSTAINED VT. ON 100MG FLECAINIDE BID FOR 4 DAYS PT RAISED TO 150 BID WITH GOOD CONTROL, BUT 2 DAYS LATER DEVELOPED EPISODES OF V-TACH UNRESPONSIVE TO LIDOCAINE (EARLIER ONES HAD RESPONDED). V FIB DEVELOPED WITH CARDIO-VERSION IN AND OUT BUT,PATIENT FINALLY EXPIRED.

13. RELEVANT TESTS LABORATORY DATA
NO AUTOPSY.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☒ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*
09JAN86 - 15JAN86

19. THERAPY DURATION
6-7 DAYS

20 DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
CORONRY ARTERIOSCLEROTIC HEART DISEASE, LEFT VENTRICULAR DYSFUNCTION CONTROLLED WITH DIURETICS.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
1/26/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	02	05	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
PROARRHYTHMIA (INTRACTABLE VENTRICULAR FIBRILLATION), DEATH

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTI
- ☐ TREATED WITH Rx OR
- ☐ RESULTED IN, OR PROLONGED, INPATIE HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
FUROSEMIDE
CAPTOPRIL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
2/ 6/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	02	11	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

PROARRHYTHMIA (ELECTROCARDIOGRAPHIC ABNORMALITIES), DEATH
PT ON QUINIDINE AND AMIODARONE WHO CONTINUED TO HAVE VENTRICULAR ARRHYTHYMIAS PUT ON FLECAINIDE AS WELL. DEVELOPED ELECTROMECHANICAL DISSASSOCIATION WITH WIDE QRS AND TACHYCARDIA. REPORTER, A COLLEAGUE OF PT'S PHYSICIAN, CONSIDERED DEFINITELY A DRUG EFFECT, BUT COULD NOT DETERMINE WHICH OF THE THREE DRUGS IT SHOULD BE ASCRIBED TO NOTING THAT THIS PT HAS VERY SICK AND THAT THIS TYPE OF DEATH OCCURS EVEN IN PTS WHO ARE NOT RECEIVING MEDICATION.
NOTE: AMIDARONE DISCONTINUED WHEN FLECAINIDE STARTED, BUT STILL CONSIDERED PRESENT IN VIEW OF ITS LONG HALF-LIFE.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*: ?09FEB86 - 11FEB86

19. THERAPY DURATION: ?1-2 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

QUINIDINE — AMIODARONE — TIL 9FEB86

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

SEE 7 ABOVE. PATIENT HAD RECURRENT VENTRICULAR TACHYCARDIA AND CARDIAC ARREST.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 2/12/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [x] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [x] NO

25a. REPORT TYPE
- [x] INITIAL [ ] FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

NAME WITHHELD AT REQUEST OF INFORMANT.

26b. TELEPHONE NO *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

FORM FDA 1639 (5'85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved OMB No. 0910-0001
Expiration Date May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6 REACTION ONSET MO.	DA	YR.
[redacted]	---	M	12	22	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

UNRESUCITATABLE CARDIAC ARREST, DEATH
PT WITH SUSTAINED VENTRICULAR TACHYCARDIA WHO HAD FAILED OR OBTAINED UNACCEPTABLE SIDE EFFECTS FROM TONOCARD, QUINIDINE, NORPACE AND PRONESTYL RECEIVED FLECAINIDE ACETATE FOR 4 DAYS AT 200MG/DAY THEN 3-4 DAYS AT 300MG/DAY DEVELOPED CARDIAC ARREST WHICH COULD NOT BE RESUCITATED. PATIENT HAD POOR CARDIAC FUNCTION AND WAS ALSO ON BETA BLOCKER.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- [x] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*: 14DEC85 - 22DEC85

19. THERAPY DURATION: 8 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
SEE 7 ABOVE.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 2/ 6/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[x] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [x] NO

25a. REPORT TYPE
[x] INITIAL [ ] FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5-85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-720)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*
[redacted]

2. AGE YRS. ---

3. SEX M

4.-6. REACTION ONSET: MO. 02 | DA. 12 | YR. 86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
VENTRICULAR TACHYCARDIA, DEATH
PT HAD BEEN FOUND AT HOME WITH CARDIAC ARREST 27JAN86 AND HOSPITALIZED. HAD BEEN IN AND OUT OF VENTRICULAR TACHYCARDIA FAILING TREATMENT WITH LIDOCAINE AND BRETYLOL. FLECAINIDE TRIED FOR 2 DOSES, BUT PATIENT AGAIN ENTERED V-TACH AND RESISTED EFFORTS AT RESUCITATION. PROFESSIONALS CARING FOR PATIENT DID NOT BELIEVE FLECAINIDE PLAYED A ROLE IN PATIENT'S DEATH.

8.-12 CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
12FEB86 - 12FEB86

19. THERAPY DURATION
2 DOSES

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
LIDOCAINE
BRETYLIUM

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
PLEASE SEE 7 ABOVE.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
2/13/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

Index of 1639s for Time Period
December 11, 1985 to March 11, 1986

TAMBOCOR (flecainide acetate), NDA# 18-830

I. Initial Reports This Period

A. Serious Labeled

Manufacturing Report No.	Reaction Term
1. [redacted]	Tachycardia
2. [redacted]	Cardiac failure, death
3. [redacted]	Hypotension
4. [redacted]	Arrhythmia, death
5. [redacted]	Arrhythmia, death
6. [redacted]	Arrhythmia, death
7. [redacted]	Chest pain
8. [redacted]	Cardiac arrest, death
9. [redacted]	Tachycardia, death
10. [redacted]	Hepatic function abnormal
11. [redacted]	Convulsions, syncope, ventricular tachycardia
12. [redacted]	Bronchospasm

B. Nonserious

Manufacturing Report No.	Reaction Term
1. [redacted]	Stomatitis ulcerative
2. [redacted]	Acidosis
3. [redacted]	Hepatic function abnormal
4. [redacted]	Urinary retention
5. [redacted]	Anxiety, depression, confusion, halucinations
6. [redacted]	Fever
7. [redacted]	Psychosis, confusion

II. Follow-up Reports this Period

None.

TABULATION OF ALL FDA-1639 REPORTS
December 11, 1986 - March 11, 1986

UNLABELED SERIOUS

BODY SYSTEM	REACTION TERMS	NUMBER OF REPORTS
BODY AS A WHOLE	DEATH	24
CARDIOVASCULAR DISORDERS	CARDIAC FAILURE	3
	CYANOSIS	1
	EDEMA	3
GASTROINTESTINAL SYSTEM DISORDERS	DUODENAL ULCER	1
	ESOPHAGITIS	2
	GASTROENTERITIS	1
HEART RATE AND RHYTHM	ARRHYTHMIA	1
	CARDIAC ARREST	4
	TACHYCARDIA*	1
MYO ENDO PERICARDIAL	MYOCARDIAL INFARCTION	4
PSYCHIATRIC DISORDERS	SUICIDE ATTEMPT	2
RESISTANCE MECHANISM	INFECTION	4
RESPIRATORY SYSTEM DISORDERS	BRONCHITIS	1
	PLEURISY	1
	PNEUMONIA	3
	RESPIRATORY DEPRESSION	1
	SINUSITIS	1
SKIN AND APPENDAGE DISORDERS	RASH PUSTULAR	1
VASCULAR (EXTRACARDIAC) DISORDERS	CEREBROVASCULAR DISORDER	1
	THROMBOSIS	1
	THROMBOSIS ARTERIAL	1

*TT-86-011 was actually a labeled event submitted in error as unlabeled.

LABELED SERIOUS

BODY SYSTEM	REACTION TERMS	NUMBER OF REPORTS
BODY AS A WHOLE GENERAL DISORDERS	DEATH	6
	MALAISE	1
	CHEST PAIN	1
CARDIOVASCULAR DISORDERS	CARDIAC FAILURE	3
	ECG ABNORMAL	4
	HYPOTENSION	1
	SYNCOPE	4
CENTR & PERIPH NERV SYST DISORDERS	CONVULSIONS	2
	DIZZINESS	1
GASTROINTESTINAL SYSTEM DISORDERS	ABDOMINAL PAIN	1
HEART RATE & RHYTHM DISORDERS	ARRHYTHMIA	6
	AV BLOCK	1
	CARDIAC ARREST	1
	HEART BLOCK	1
	TACHYCARDIA	3
	TACHYCARDRIA VENTRICULAR	4
LIVER & BILIARY SYSTEM DISORDERS	HEPATIC FUNCTION ABNORMAL	2
RESPIRATORY SYSTEM DISORDERS	BRONCHOSPASM	1
	DYSPNEA	1

NONSERIOUS

BODY SYSTEM	REACTION TERMS	NUMBER OF REPORTS
BODY AS A WHOLE GENERAL DISORDERS	FEVER	1
GASTROINTESTINAL SYSTEM DISORDERS	STOMATITIS ULCERATIVE	1
LIVER & BILIARY SYSTEM DISORDERS	HEPATIC FUNCTION ABNORMAL	1
METABOLIC & NUTRITIONAL DISORDERS	ACIDOSIS	1
PSYCHIATRIC DISORDERS	ANXIETY	1
	CONFUSION	2
	DEPRESSION	1
	HALLUCINATION	1
	PSYCHOSIS	1
URINARY SYSTEM DISORDERS	URINARY RETENTION	1

INDEX OF 15-DAY REPORTS BY BODY SYSTEM

DECEMBER 11, 1985 - MARCH 11, 1986

Manufacturer's Control Number	Date of Submission	Reaction Term
BODY AS A WHOLE - GENERAL DISORDERS		
[redacted]	01/03/86	DEATH
	01/07/86	DEATH
	01/10/86	DEATH
	01/02/86	DEATH
	01/07/86	DEATH
	01/17/86	DEATH
	01/29/86	DEATH
	02/10/86	DEATH
	01/29/86	DEATH
	01/31/86	DEATH
	01/31/86	DEATH
	02/14/86	DEATH
	02/21/86	Follow-up
[redacted]	01/30/86	DEATH
	02/12/86	DEATH
	01/30/86	DEATH
	02/25/86	DEATH
	02/25/86	DEATH
	03/04/86	DEATH
	03/06/86	DEATH
	03/06/86	DEATH
	03/24/86	DEATH
	03/19/86	DEATH
	03/19/86	DEATH
	03/19/86	DEATH
	04/22/86	DEATH
CARDIOVASCULAR DISORDERS, GENERAL		
[redacted]	01/07/86	CARDIAC FAILURE
	03/05/86	CARDIAC FAILURE
	01/03/86	CIRCULATORY FAILURE
	02/06/86	EDEMA
	02/06/86	EDEMA
	03/06/86	EDEMA
	03/26/86	CYANOSIS
GASTROINTESTINAL SYSTEM DISORDERS		
[redacted]	03/19/86	DUODENAL ULCER
	01/17/86	ESOPHAGITIS
	01/29/86	ESOPHAGITIS
	01/29/86	GASTROENTERITIS

INDEX OF 15-DAY REPORTS BY BODY SYSTEM
12/11/85 - 03/11/86

Manufacturer's Control Number	Date of Submission	Reaction Term
HEART RATE AND RHYTHM DISORDERS		
[redacted]	02/12/86	AV BLOCK
	01/29/86	CARDIAC ARREST
	01/29/86	CARDIAC ARREST
	02/12/86	CARDIAC ARREST
	02/25/86	CARDIAC ARREST
	02/12/86	TACHYCARDIA
MYO ENO PERICARDIAL & VALVE DISORDER		
[redacted]	01/29/86	MYOCARDIAL INFARCTION
	01/17/86	MYOCARDIAL INFARCTION
	01/29/86	MYOCARDIAL INFARCTION
	02/25/86	MYOCARDIAL INFARCTION
PSYCHIATRIC DISORDERS		
[redacted]	01/13/86	SUICIDE ATTEMPT
	03/05/86	SUICIDE ATTEMPT
RESISTANCE MECHANISM DISORDERS		
[redacted]	01/07/86	INFECTION
	01/10/86	INFECTION
	02/25/86	INFECTION
	03/25/86	INFECTION
RESPIRATORY SYSTEM DISORDERS		
[redacted]	02/12/86	BRONCHITIS
	01/17/86	PLEURISY
	01/17/86	PNEUMONIA
	01/17/86	PNEUMONIA
	01/29/86	PNEUMONIA
	01/29/86	RESPIRATORY DEPRESSION
	03/05/86	SINUSITIS
SKIN & APPENDAGES DISORDERS		
[redacted]	04/22/86	RASH PUSTULAR
VASCULAR (EXTRACARDIAC) DISORDERS		
[redacted]	02/17/86	CEREBROVASCULAR DISORDER
	01/10/86	THROMBOSIS
	01/30/86	THROMBOSIS ARTERIAL
	03-05-86 Follow-up	

NARRATIVE SUMMARIES

Distribution of FDA 1639s - First Quarterly Report

	U.S. Spontaneous	Clinical	Foreign Spontaneous	Total
Serious-Unlabeled (15-Day)	3	41	12	56
Serious-Labeled	12	NA	NA	12
Nonserious	7	NA	NA	7
Total	22	41	12	75

NOTE: As a uniform policy, flecainide is always listed in box 14 of the FDA 1639 form as being the sole suspect drug for each report.

NARRATIVE SUMMARY AND ANALYSIS OF 15-DAY REPORTS

NOTE: Fifty-six 15-day 1639 alert reports were submitted during this quarter. The unlabeled ADEs associated with these and their distribution among body systems are displayed in the tabulation entitled, "Unlabeled Serious." The same information, including the corresponding report number and date of submission, is displayed on the "Index of 15-Day Reports by Body System."

BODY AS A WHOLE

Death Analyses

Death was noted as an adverse drug reaction on 30 FDA 1639 forms submitted this quarter. The sources of these reports are identified in the following table:

FDA 1639 Reports Submitted Containing Death as an ADE

	U.S. Spontaneous	Clinical	Foreign Spontaneous	Total
Unlabeled (15-Day)	2	19	3	24
Labeled (Non 15-Day)	6	NA	NA	6
Total	8	19	3	30

NOTE: This section discusses all 15-day reported deaths. The case numbers of these reports are given in the appended index with the six non-15-day death reports ([redacted] the 1639s of which are enclosed with this report.

Current labeling for Tambocor® includes two situations for which we considered death as a labeled event: (1) deaths associated with proarrhythmic effects, and (2) nonresuscitatable ventricular tachycardia or ventricular fibrillation. We have aimed to call a death "labeled" only if there was direct electrocardiographic evidence that one of the above two situations obtained. In this quarter, six deaths were considered "labeled" and 24 "unlabeled." As a the discriminator between labeled and unlabeled deaths is fortuitous, depending chiefly on the presence or absence of terminal ECG data, we have pooled these two groups for purposes of this analysis.

The great majority of reported deaths (19/30) occurred in the course of clinical trials (16 U.S.; 3 foreign). Eleven spontaneous reports were received (8 U.S.; 3 foreign). Ten deaths appeared to be associated in the final stages with dysrhythmias ([redacted]). Five appeared to be associated with heart failure ([redacted]). In 12 cases the nature of events immediately associated with death could not be determined ([redacted]). In three cases, the immediate cause of death was myocardial infarct ([redacted]), lung cancer ([redacted]), and pulmonary embolus following mechanical failure of pacemaker ([redacted]).

Of the 25 cases of death for which ages were reported, 6 were in the 6th decade, 11 in the 7th, 6 in the 8th, and 2 in the 9th. Daily dose of flecainide being employed at the time of death were: 6 patients <200 mg, 10 patients = 200 mg, and 2 patients = 400 mg. Duration of treatment ranged from less than 1 week for 5 patients, 1 to 3 months for 9 patients, 3 to 12 months for 9 patients, and more than 12 months for 1 patient.

Patients for whom death reports were submitted this quarter had history of serious to desparate underlying cardiac disease. Among the 5 dying primarily of heart failure were 2 with multisystem failure, 1 with cardiomyopathy, and 2 with known congestive failure. The 10 patients whose deaths were associated with dysrhythmias and the 12 for whom the immediately associated events were unknown had serious cardiac conditions by history, these frequently included myocardial infarct, sudden death, sustained ventricular tachycardia or ventricular fibrillation, A-V and major bundle blocks, cardiomyopathies, and congestive heart failure.

Patients who died met criteria warned about in current labeling for high risk groups in terms of cardiac dysrhythmias and/or compromised cardiac mechanical function.

Misuse of the drug outside current prescribing information does not appear to be a feature of these cases for the United States. In one case [redacted], addition of Tambocor to high-dose quinidine and amiodarone in a severely ill patient was followed by death felt to be due to drug, but with uncertainty as to which drug it might be ascribed.

Inspection of all cases for concommitant medications revealed no combinations of drugs employed with flecainide which were considered to be suspicious in their frequency among patients who died compared to that among patients who did not.

The following cases concern those deaths reported spontaneously from early U.S. use of Tambocor: [redacted] (* indicates those sent as 15-day reports). Although five cases were treated for less than one day and had serious underlying conditions, it would appear that the drug was being used properly for such patients from the standpoints of starting treatment in hospital and employing recommended dosage regimens.

CARDIOVASCULAR DISORERS

None of these cases was a spontaneous U.S. report.

The three cases of "edema" were in fact pulmonary edema which were received as spontaneous reports from France. Little additional information is available to our French colleagues. One of the cardiac failures was left ventricular failure--part of a multisystem failure case from U.S. clinical studies. The remaining two are also from France. One, a case of circulatory failure in association with marked widening of the QT interval and use of amiodarone. The second, a case of cardiogenic shock associated with use of amiodarone.

The patient with acrocyanosis ("cyanosis") was suspected of shedding microemboli from a thrombus located on the left ventricular wall.

HEART RATE AND RHYTHM

The four cases of cardiac arrest have been discussed in the death analysis above. The case of arrhythmia is the one from France discussed above regarding widening QT in circulatory failure.

MYOCARDIAL INFARCTION

Since close of this quarter's data base, further information indicated that an MI was not associated with case [redacted]. Reports [redacted] and [redacted] were discussed in the death analyses above--the former having followed four days after a previous, pre-flecainide infarct, and the latter after nine months of treatment. Report [redacted] concerned infarct in a patient with pre-flecainide infarct who had taken Tambocor for more than one year and for whom the drug was continued through and after the event.

VASCULAR (EXTRACARDIAC) DISORDERS

Report [redacted] was discussed in the death analyses above and concerned a patient with postsurgical multisystem failure who also had a pre-flecainide history of coagulopathy and similar thrombotic events. The subject of [redacted] had taken flecainide for more than five years when he developed venous thrombosis and pulmonary embolus. Tambocor was continued. Report [redacted] concerns a 38-year-old male who had history of interatrial septal defect (repaired) and atrial fibrillation. He experienced a minor stroke five months into his flecainide course and a more major one at six months.

GASTROINTESTINAL SYSTEM DISORDERS

Both gastroenteritis (minimal hemorrhagic duodenitis) and esophagitis concern the same patient ([redacted]) who had taken Tambocor for 13 months when the conditions were diagnosed. Tambocor treatment continues. Esophageal stricture was diagnosed in patient [redacted] about three years into flecainide treatment and soon after starting erythromycin. Treatment with flecainide continues. Patient [redacted] had longer than a two-year history of duodenal ulcer treated with H-2 antagonists. Six days after starting flecainide, the duodenal ulcer perforated and the defect was repaired. Tambocor was not continued as it had shown no control prior to the event.

PSYCHIATRIC DISORDERS

(Neither of the following cases is from the U.S.)

Report [redacted] concerns a person who died following ingestion of 20 tablets of flecainide and benzodiazapines. It is not known what, if any, resuscitative efforts were employed. The individual was not a Tambocor patient.

The second case ([redacted] concerns a man who took 50 Tambocor tablets and a large quantity of alcohol. He was treated in hospital with isoprenaline, atropine, and installation of pacemaker. After two days of being unconscious, he recovered over the next four to five days. (More details are expected on this case.)

RESPIRATORY SYSTEM DISORDERS

Six items in this category are present by virtue of the requirement to classify as "serious" events for which a prescription drug is administered. Being intercurrent infections, they also qualified as "unlabeled". "Respiratory Depression" is a "fluke" of terminology deriving from the description of a patient who died as being "without pulse or respiration". It is not respiratory depression in the usual sense.

SKIN AND APPENDAGE DISORDERS

The case listed here is one of postoperative infection included by virtue of requirements to report as "serious" those conditions for which prescription drugs are administered.

LABELED SERIOUS AND NONSERIOUS EVENTS

NOTE: Each 1639 form may contain several ADE terms. Current regulations require that the 1639 form, itself, rather than each ADE it bears, be qualified as "serious" or "nonserious". Thus, many of the ADE's listed as "serious labeled" are not intrinsically "serious" but rather have been swept along on a report of which some other aspect was "serious". This introduces an artifactual, fortuitous distinction between "labeled serious" and "labeled nonserious" events which can dilute the impact of their numbers. For this reason, in this section all labeled events are discussed together regardless of whether they were submitted on a 1639 which was labeled "serious" or "nonserious". While all cases have been reviewed, each is not specifically commented upon here.

BODY AS A WHOLE

Deaths have been discussed in conjunction with 15-day reports.

Although "fever" is a labeled event, the instance reported this quarter ([redacted]) is of interest. This 77-year-old hospitalized man was in generally good condition except for hypertension and premature ventricular contractions. Tambocor® 100 mg b.i.d. was prescribed for control of the arrhythmia. Forty-five minutes after the first dose, he spiked a fever of 102° F which returned to normal over the next few hours. Forty-five minutes following the second dose, he developed a fever of 101° F. Aside from feeling slightly weak during the febrile periods, he remained well. No other drugs were being admnistered at the time, although a nadolol-benzoflumethazide combination product had been taken until five days prior to initiation of Tambocor therapy.

CARDIOVASCULAR DISORDERS

All cases of cardiac failure occurred in reports covered in the death analyses above.

Four cases were reported this quarter (3 French, 1 U.S.) citing Torsade de Pointes ([redacted]). The first report concerned a woman with hypokalemia who had been taking amiodarone until one month before the event. QT inerval was widened and ventricular fibrillation developed. Flecainide exposure (dose/duration) were unknown, but the drug was discontinued. Patient recovered.

The second case was one of a 60-year-old man who had taken flecainide for three months at a dose of 300 mg per day--originally prescribed for atrial fibrillation with slow idopathic rhythm as well as premature ventricular contractions. He had also been taking digoxin. The patient was paced and recovered.

The third case was that of a 58-year-old woman with history of aortic insufficiency, mitral valve stenosis and atrial fibrillation. For seven months she had taken amidarone (100 mg/day) and for five months flecainide (150 mg/day). She was taken to hospital upon developing syncope and circulatory failure. There she was found to have prolonged QT interval and hypomagnesemia. She was treated with an IV bolus of magnesium and recovered.

The fourth case in the series is the only one from the United States. This spontaneious report was of a 78-year-old woman with a history of five-vessel coronary bypass surgery, hypertension, congestive heart failure, and ventricular tachycardia. As an inpatient she was taking digoxin, clonidine, dipyridimol, aspirin, and potassium chloride when started on 100 mg flecainide b.i.d. four days before the event. She had just undergone a stress test, which she passed without inciting ventricular tachycardia, when she developed a 12-second run of Torsade followed by syncope and convulsions. She was treated with lidocaine and recovered. Flecainide was discontinued.

The first and second cases had predisposing electrolyte abnormalities, the third was being treated for atrial arrhythmia (not approved indication in the U.S.), and the fourth had multiple drug therapy and severe underlying cardiac disease which obscures the picture with respect to causation.

ECG changes: One event associated with use of flecainide concerned a 70-year-old man with a history of myocardial infarct and ventricular tachycardia for which he had been taking flecainide for more than two years at a dose of 300 mg per day. He developed syncope, was administered CPR and displayed a QT interval of 0.58 seconds. He recovered and continued on flecainide.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS

A 57-year-old male [redacted] with no known history of seizures developed episodes of petit mal diagnosed by a neurologist as partial complex seizures. He had been taking flecainide for 25 months before these events for ventricular tachycardia at a dose of 200 mg per day. He was also taking cefazolin and temazepam at the time. Electrophysiological testing using IV flecainide to determine if ventricular tachycardia might be inducible was negative. Flecainide was continued, and carbamazepine was added for seizure control.

PSYCHIATRIC DISORDERS

Report [redacted] describes a 40-year-old woman with ventricular tachycardia who took Tambocor 200 mg per day for three days. She was taking no other medication. She developed anxiety, depression, disorientation, and hallucinations. A psychiatrist who examined her discontinued Tambocor, and within two days her symptoms had disappeared. She had no previous history of psychiatric disorders.

Similarly, a 62-year-old woman with diabetes, blindness, renal insufficiency (dialysis patient) and history of three myocardial infarcts was prescribed 200 mg flecainide per day for control of ventricular tachycardia. Two days later she developed psychotic behavior and disorientation. Tambocor was discontinued, and 24 hours later her symptoms had disappeared. She was also taking diltiazem and digoxin at the time.

"Hallucinations" and "psychotic behavior" are not in the current labeling for Tambocor.

LIVER AND BILIARY SYSTEM DISORDERS

In a report received from France ([redacted]) a woman (age unknown) with a history of amiodarone-associated hepatic abnormalities before starting Tambocor, developed cardiogenic shock. In the hospital she was observed to have elevated SGOT. Tambocor was discontinued. Subsequent course is unknown.

From the United States came a report ([redacted]) of a 68-year-old man with history of hypertension, idiopathic cardiomyopathy, angina and severe congestive heart failure. He had ventricular tachycardia treated earlier with procainamide, which was discontinued due to marked ANA elevation, and with Tonocard® until six days before the current event. He was also taking digoxin, furosemide and diltiazem. He entered hospital for prostatic surgery. Tonocard was discontinued, and Tambocor® was started at 100 mg b.i.d. Two days later the dose was increased to 150 mg b.i.d. with complete suppression of ventricular tachycardia. Prostatectomy was performed using spinal anesthesia. Following surgery meperidine, a cephalosporin, trimethoprim, and sulfamethoxazole were added. Two days following surgery, jaundice and elevated liver function values developed.

The third case ([redacted]), the second reported spontaneously from the United States, involved a 48-year-old woman with history of two myocardial infarcts and with severe congestive heart failure and ventricular tachycardia. Flecainide, 50 mg b.i.d., was being administered along with captopril, digoxin, furosemide, and bumetanide when she developed (two weeks following the start of flecainide) jaundice and elevated SGOT and SGPT. Tambocor was discontinued, but her cardiac condition continued to deteriorate and she died. Her physician attributed the hepatic features to progressive, marked congestive failure rather than to flecainide.

NARRATIVE OF ACTION TAKEN

Current labeling appears to be covering well such events as have been reported during this first quarter of United States marketing. "Hallucinations" and "psychotic behavior" were specific terms reported which do not appear as such in present labeling although a number of closely related psychiatric conditions are present. It shall be a matter of continuing consideration whether these shall be incorporated in future labeling.

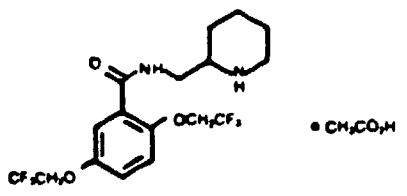
Based upon a careful review of information received this quarter through the drug experience reporting system, it appears to this reviewer that the experiences present no information which could be incorporated into current prescribing material on Tambocor® to improve prescriber understanding or use of this agent.

New TAMBOCOR® (flecainide acetate) B.I.D.

DESCRIPTION:

TAMBOCOR® (flecainide acetate) is an antiarrhythmic drug available in tablets of 100 mg for oral administration.

Flecainide acetate is benzamide, N-(2-piperidinylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)-, monoacetate. The structural formula is given below:



Flecainide acetate is a white crystalline substance with a pK_a of 9.3. It has an aqueous solubility of 48.4 mg/ml at 37°C.

CLINICAL PHARMACOLOGY:

TAMBOCOR has local anesthetic activity and belongs to the membrane stabilizing (Class I) group of antiarrhythmic agents. It has electrophysiologic effects characteristic of the IC class of antiarrhythmics.

Electrophysiology. In man, TAMBOCOR produces a dose-related decrease in intracardiac conduction in all parts of the heart, with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods were observed only in the ventricle. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction (see Warnings).

TAMBOCOR causes a dose-related and plasma-level-related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful 30–40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 μg/ml may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 μg/ml. Plasma levels above 0.7–1.0 μg/ml are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally.

In animals and isolated myocardium, a negative inotropic effect of flecainide has been demonstrated. Decreases in ejection fraction, consistent with a negative inotropic effect, have been observed after single administration of 200 to 250 mg of the drug in man; both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses (see Warnings).

Metabolism in Humans. Following oral administration, the absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range, 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life, with steady state levels approached in three to five days; once at steady state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one fifth as potent) and the meta-O-dealkylated lactam of flecainide (non-active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found in urine; only 5% of an oral dose is excreted in feces. In patients, free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 μg/ml).

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. (See Dosage and Administration.)

In patients with congestive heart failure (NYHA class III), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 14 hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar. (See Dosage and Administration.)

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 μg/ml. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs (see Precautions, Drug Interactions).

INDICATIONS AND USAGE:

TAMBOCOR is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

TAMBOCOR is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of TAMBOCOR, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, TAMBOCOR, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients depending on their cardiac status and underlying cardiac disease (see Dosage and Administration).

The effects of TAMBOCOR in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including TAMBOCOR, has been shown to have a favorable effect on mortality or sudden death.

CONTRAINDICATIONS:

TAMBOCOR is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm. Should complete heart block occur, TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Proarrhythmic Effects. TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias.

In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. Their frequency appears to be related to dose and to the underlying cardiac disease.

Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule (see Dosage and Administration).

Patients with less serious arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal.

The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).

Heart Failure. TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of preexisting CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg b.i.d. (see Dosage and Administration) and patients should be monitored carefully. Close attention must be given to maintenance of cardiac function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics; others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/ml.

Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose-related increases in PR, QRS, and QT intervals.

PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one third of patients may develop new first-degree AV heart block (PR interval ≥ 0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study, 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.15 seconds or more. Thus caution should be used when such intervals occur and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythmia associated with TAMBOCOR-induced QT prolongation and bradycardia.

Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest, and symptomatic bradycardia (1.2%); second-degree AV block (0.5%); and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block, or right bundle branch block associated with a left hemiblock occurs, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally threshold changes are within the range of multiprogrammable pacemakers and, when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture.

Electrolyte Disturbances: Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Pre-existing hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

PRECAUTIONS:

Drug Interactions: TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin, a 13% ± 19% increase in plasma digoxin levels occurred at six hours postdose.

In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, plasma flecainide levels were increased about 20% and propranolol levels were increased about 30% compared to control values. In this formal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects when the drugs were administered together the effects were additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive. In TAMBOCOR clinical trials, patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.

Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (eg, anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction.

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgment of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

Pregnancy: Pregnancy Category C. Flecainide has been shown to have teratogenic effects (club paws, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day respectively, however, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers: It is not known whether flecainide is excreted in human milk. Because many drugs are excreted in human milk and because of the drug's potential for serious adverse effects in infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.

Use in Patients with Hepatic Impairment: Studies to determine the effect of hepatic impairment upon the elimination of TAMBOCOR have not yet been completed. Because the drug undergoes extensive biotransformation (most likely in the liver), patients with significant hepatic impairment should not receive TAMBOCOR unless the potential benefits clearly outweigh the risks.

ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR, described in detail in Warnings section, were new or exacerbated ventricular arrhythmias which occurred in 7% of patients, and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unsustainable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest; about 1.2% all together (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 µg/ml.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign postmarketing surveillance studies, there have been rare reports of hepatic dysfunction, including reports of cholestasis and hepatic failure, and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects are based on a multicenter efficacy study, utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to noncardiac adverse effects.

Table 1

Most Common Adverse Effects in Patients Treated with TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 428 Patients at Any Dose	Incidence by Dose During Upward Titration: 200 mg/ Day (N = 426)	300 mg/ Day (N = 293)	400 mg/ Day (N = 100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance†	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.

†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400–600 mg/day, the incidence of these adverse experiences was similar, except for dizziness (32%) and visual disturbances (28%).

The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies: *Body as a Whole*—malaise, fever; *Cardiovascular*—tachycardia, sinus pause or arrest; *Gastrointestinal*—vomiting, diarrhea, dyspepsia, anorexia; *Skin*—rash; *Visual*—diplopia; *Nervous System*—hypothesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus; *Psychiatric*—anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients: *Body as a Whole*—Swollen lips, tongue and mouth, arthralgia, bronchospasm, myalgia; *Cardiovascular*—angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension; *Gastrointestinal*—flatulence; *Urinary System*—polyuria, urinary retention; *Hematologic*—leukopenia, thrombocytopenia; *Skin*—urticaria, exfoliative dermatitis, pruritus; *Visual*—eye pain or irritation, photophobia, nystagmus; *Nervous System*—twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor; *Psychiatric*—amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the T-wave, a reduction in myocardial rate and contractility, conduction disturbances, hypotension, and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol, mechanically assisted respiration, circulatory assists such as intra-aortic balloon pumping, and transvenous pacing in the event of conduction block. Because of the long plasma half-life of flecainide (12 to 27 hours in patients receiving usual doses) and the possibility of markedly nonlinear elimination kinetics at very high doses, these supportive treatments may need to be continued for extended periods of time. Hemodialysis is not an effective means of removing flecainide from the body.

DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, eg, low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels, in patients with normal renal and hepatic function, may not be achieved until the patient has received three to five days of therapy at a given dose. Therefore, increases in dosage should be made no more frequently than once every four days, since during the first two to three days of therapy the optimal effect of a given dose may not be achieved.

For sustained ventricular tachycardia patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg b.i.d. every four days until efficacy is achieved. Most such patients do not require more than 150 mg every 12 hours (300 mg/day) and the maximum dose is 400 mg/day.

For patients with symptomatic nonsustained ventricular tachycardia, couplets, or premature ventricular complexes the recommended starting dose is also 100 mg every 12 hours. This dose may be increased in increments of 50 mg b.i.d. every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day, and the plasma level is below 0.6 µg/ml, the dosage may be cautiously increased to a maximum of 600 mg/day.

Use of higher initial doses and more rapid dosage adjustments has resulted in an increased incidence of proarrhythmic events and congestive heart failure, particularly during the first few days of dosing (see Warnings). Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients, efficacy at the lower dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction (see Warnings). The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg b.i.d. every four days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

In patients with renal impairment, the initial dosage should be 100 mg every 12 hours. Dosage increases should be made cautiously at intervals greater than four days, observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change. It is recommended that plasma level monitoring be used to guide dosage adjustments (see below).

Based on theoretical considerations, rather than experimental data, the following suggestion is made: when transferring patients from another antiarrhythmic drug to TAMBOCOR, allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting TAMBOCOR at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 µg/ml. The probability of adverse experiences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 µg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Because elimination of flecainide from plasma may be slower in patients with severe chronic renal failure or severe congestive heart failure, plasma level monitoring may be especially helpful in these patients.

HOW SUPPLIED:

TAMBOCOR is supplied as white, round, scored tablets containing 100 mg of flecainide acetate and embossed with RIKER on one side and TR 100 on the other side.

TAMBOCOR, 100 mg/tablet, is available in bottles of 100—NDC #0089-0307-10.

Store at controlled room temperature 15°–30°C (59°–86°F) in a tight, light-resistant container.

TR-1

Manufactured by
Riker Laboratories, Inc./3M
St. Paul, Minnesota 55144-1000

Riker Laboratories, Inc./3M

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

ORIGINAL

REPORTS

3M

September 29, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong

Florence N. Wong
Regulatory Specialist

FNW/jlg

Enclosure - [redacted]

Certified Mail P 235 105 074

RECEIVED
OCT 9 1986
HFD-110
BUREAU OF DRUGS

Certified Mail P

Lullaby Waiver T
10/14

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	64	M	02	09	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

WORSENED CONGESTIVE HEART FAILURE, PLEURAL EFFUSION, DEATH
DEATH POSSIBLY DUE TO WORSENING CONGESTIVE HEART FAILURE.

07/24/86..PATIENT WAS A 64 YEAR OLD MALE ADMITTED ON 2/7/86 FOR A PERSISTENT RIGHT SIDED PLEURAL EFFUSION. HIS CARDAIC HISTORY BEGAN IN 1977 WHEN HE UNDERWENT QUADRUPLE ACBP. HE DID WELL UNTIL 12/85 WHEN HE DEVELLOPED ATRIAL FLUTTER, MANIFESTING AS CONGESTIVE HEART FAILURE. HE DID NOT CONVERT TO NSR WITH DIGOXIN AND QUINAGLUTE. SHORT RUNS OF V. TACH WERE ALSO NOTED. HE WAS ELECTRICALLY CARDIOVERTED ON 12/24/85 WITH SIGNIFICANT SYMPTOMATIC IMPROVEMENT. PROCAN SR WAS BEGUN FOR V. TACH. A CARDIAC CATH REVEALED PATENT GRAFTS, AN AKINETIC INFERIOR WALL,

13. RELEVANT TESTS LABORATORY DATA

ANATCMICAL DIAGNOSIS:
1. Ichemic heart disease, manifested by:
(a) Coronary artery atherosclerosis, Grade IV--RCA: 100% occlusion;
LAD: 80% occlusion; LCX: 100% occlusion.
i) Status-post aorto-cornonary bypass graft X 4 (1977) all

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*: 12/31/85 - 02/18/86

19. THERAPY DURATION: 39 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

CAPTOPRIL
FUROSEMIDE
POTASSIUM CHLORIDE
SODIUM WARFARIN
DIGOXIN
CHLORPROPAMIDE
NIFEDIPINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

ASHD; Myocardial infarction; Coronary bypass surgery; Cardiomegaly; CHF-Class III with breathlessness; Cardiove..sion; Sustained VT and Multifoca
l PVCs documented by Holter, telemetry and ECG.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 9/11/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

RV 71/4 PA 56/10 PCWP 25. EF WAS COMPUTED TO BE 37% PERSISTENT VENTRICULAR ARRHYTHMIAS NECESSITATED THE INITIATION OF FLECAINIDE ON 12/31/85, WITH SOME IMPROVEMENT. A MUGA ON 1/6/86 REVEALED A LVEF OF 25%. HE DID WELL AFTER DISCHARGE, EXCEPT FOR A BRIEF ADMISSION IN 1/86 FOR EXACERBATION OF CHF. VIGOROUS DIURESIS WAS CONTINUED AFTER DISCHARGE. ON 2/7/86 HE WAS ADMITTED FOR A PERSISTENT RIGHT PLEURAL EFFUSION AND COUGH. THE IMPRESSION ON ADMISSION WAS THAT OF A 64 Y/O MALE WITH CHF, VENTRICULAR ARRHYTHMIAS, AND A RIGHT SIDED PLEURAL EFFUSION PERSISTING DESPITE VIGOROUS DIURESIS. FURTHER INVESTIGATIVE STUDIES REGARDING THE ETIOLOGY OF THIS EFFUSION WERE PLANNED. THE METABOLIC ABNORMALITIES WERE FELT TO BE SECONDARY TO DEHYDRATION, AND

13. RELEVANT TESTS/LABORATORY DATA

grafts patent and arterialized; right graft with 50% narrowing.
ii) Vessels distal to bypass graft with Grade IV atherosclerosis:
RCA: 90% occlusion; LAD-A: 9% occlusion; LAD-B: 100% occlusion;
LCX: 95% occlusion.
(b) Old transmural myocardia infarction, left ventricle.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17 INDICATION(S) FOR USE

:RAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

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2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

CAUTIOUS FLUID REPLACEMENT WAS BEGUN. K WAS REPLACED ALSO. A SWAN-GANZ CATHETER REVEALED RV 80/3, PA 78/30, PCWP 32. FLECAINIDE WAS THOUGHT TO PLAY A ROLE IN THIS EXACERBATION OF CHF SO IT WAS DISCONTINUED ON 2/8/86 AT 23:15 ON 2/8/86 THE PATIENT BECAME UNRESPONSIVE. V TACH AND APNEA WERE NOTED. RESUSCITATIVE MEASURES WERE UNSUCCESSFUL.

13. RELEVANT TESTS/LABORATORY DATA

(c) Congestive cardiac failure (clinical).
2. Cardiomegaly (800 gm):
(a) Biventricular hypertrophy
(b) Hypertension (clinical)
(c) Fibrocalcific mitral valve disease (mild).

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines,biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17 INDICATION(S) FOR USE

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

RAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND./NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. IS DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

25.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

25b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
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ADVERSE REACTION REPORT
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2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

13. RELEVANT TESTS/LABORATORY DATA

3. Pulmonary atelectasis, bilateral: Pulmonary hypertension (secondary to 1. (c). Right pleural effusion (800 ml).
NOTE: Post-mortem blood and pleural cultures are negative.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000

(612)733-0633

9.1

November 12, 1986

3M

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/dls

Enclosure - [redacted]

Certified Mail P 235 106 228

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	54	F	07	19	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

RECURRENT SUSTAINED VENTRICULAR TACHYCARDIA, PROGRESSIVE HYPOTENSION, CARDIAC ARREST Death.
This 54 yOC. diabetic woman had history of severe coronary disease, anterior wall myocardial infarct, and was 3 months post circumflex coronary artery bypass graft doing well. She developed syncope and was found to be in sustained V-tach which responded temporarily but then changed again to sustained v-tach followed by cardiac arrest. This was converted and she was given one, 100 mg tablet of flecainide. Over the next 3 hours progressive hypotension developed. Fluids, dopamine and dobutamine failed to resolve the situation and she died. She had known low ejection fraction (30%). During the terminal event pulmonary pressure

13. RELEVANT TESTS/LABORATORY DATA
Please see #7, above.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [x] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE
100 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*
07-18-86 - 07-18-86

19. THERAPY DURATION
ONE DOSE

CONCOMITANT DRUGS AND HISTORY

NCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Please see #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
10/28/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

JAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

was not elevated. Potassiums were 4.3 and 3.9, glucose was 430, but CPK was not suggestive of re-infarct of myocardium. C. coli was present in urine, but this had been the case for some time.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

NCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

AY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

25.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

25b. TELEPHONE NO. *(Include area code)*

25c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

25d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

9.1

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000

(612)733-0633

ORIGINAL

November 19, 1986

REPORTS

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Reports
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/dls

Enclosure [redacted]

Certified Mail P 235 106 246

12/2

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
RENAL FAILURE, Death
Report from Riker UK clinical study [redacted]FRO GB-203 states cause of death as "renal failure". Patient history lists presence of ischemic heart disease. Further information requested.

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
UNKNOWN

17. INDICATION(S) FOR USE
UNKNOWN

THERAPY DATES *(From To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
10/28/86

24d. REPORT SOURCE (Check one)
- [X] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [ ] HEALTH PROFESSIONAL
- [ ] CONSUMER

15 DAY REPORT
- [X] YES
- [ ] NO

25a. REPORT TYPE
- [X] INITIAL
- [ ] FOLLOWUP

NOTE. Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

25.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

25b. TELEPHONE NO. *(Include area code)*
[redacted]

25c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES
- [ ] NO

25d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES
- [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-7)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
***RENAL FAILURE, BRONCHIAL PNEUMONIA* Death**
Report from Riker UK clinical study [redacted]RO GB-203 states cause of death as "renal failure and bronchial pneumonia". Further information requested.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
UNKNOWN

17. INDICATION(S) FOR USE
UNKNOWN

HERAPY DATES *(From To)*
UNKNOW - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
10/28/86

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

25d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

9.1

DEC 1 9

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA # 18-830
NAME OF DRUG: Tombocor (flecainide acetate) Tablets
SPONSOR: Riker
TYPE OF SUBMISSION: ADR
DATE OF SUBMISSION: November 6, 1986
DATE OF REVIEW: November 27, 1986
REVIEWER: Sughok K. Chun, M.D., HFN-110 S.K. Chun 12/17/86.

A. Resume:

#[redacted].
A63Y/M died of lung cancer

#[redacted]

FEVER, PLEURAL EFFUSION, ARTHRALGIA, ESINOPHILIA, VENTRICULAR FIB.
This 65 years-old woman was being treated with various drugs for atrial fibrillation without results. She was changed to flecainide. The atrial fibrillation was controlled, but ventricular fibrillation required cardioversion (flecainide still ongoing). After one to two weeks of flecainide therapy, she developed intermittent fever and arthralgia, pleural effusion, and eosinophilia. The symptoms soon became intolerable. Flecainide was stopped, and the symptoms resolved. Her ANA titer was not elevated.

WBC normal with a 5-8% eosinophilia; 30% eosinophilia in the pleural effusion.

#[redacted]
A65 Y/M was hospitalized for CVA.

cc:
Original NDA: 18-830
HFN-110
HFN-110/CSO
HFN-110/SChun/12/1/86
klb,'12/15,'86/00821

110

9.1

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000

(612)733-0633

November 6, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/dls

Enclosure - [redacted]

Certified Mail P 235 106 218

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	63	M	01	15	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

LUNG CANCER Death
PATIENT WAS DIAGNOSED AS HAVING LUNG CANCER 3 WEEKS FOLLOWING START OF FLECAINIDE ACETATE TREATMENT. ENTERED HOSPITAL, BECAME MORIBUND AND DIED ABOUT 3 WEEKS LATER. FLECAINIDE DOSING STARTED AT 150 MG BID AND WAS DECREASED TO 100 MG BID ON 12/29/85. MEDICATION USED DURING HOSPITALIZATION TO TREAT CARCINOMA-RELATED SYMPTOMS: SOLU-MEDROL, PREDNISONE, ALUPENT, MORPHINE SULFATE, COMPAZINE, AMPHOGEL, CALCIMAR, KEFLEX, AMINOPHYLLINE, XANAX AND KLOTRIX.

13. RELEVANT TESTS LABORATORY DATA

CT SCAN; SPUTUM SAMPLES; ECG SHOWED JUNCTIONAL RHYTHM
HYPERCALCEMIA; ELEVATED: SGPT, GGT, SGOT, CREATININE, BUN
DECREASED: HCT, PLATELETS, RBC

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

X CANCER
X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: 05DEC85 - 14JAN86

19. THERAPY DURATION: 40 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

BECLOMETHASONE DIPROPIONATE	?	ALBUTEROL	?
FUROSEMIDE		TERBUTALINE SULPHATE	?
THEOPHYLLINE	?	RANITIDINE	?
ACETAMINOPHEN	?	TRIAZOLAM	
NITROGLYCERIN	?	SULFAMETHOXAZOLE, TRIMETHOPRIM	~5WKS
MILK OF MAGNESIA-CASCARA	?	-	

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

PREMATURE VENTRICULAR COMPLEXES, NON-SUSTAINED VENT. TACHYCARDIA, VENT. FIBRILLATION, HISTORY OF MYOCARDIAL INFARCTION, SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE, ARTERIOSCLEROTIC HEART DISEASE.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 9/24/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26a. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

9.1

DEC 30 [illegible]

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA: 18-830

Name of Drug: Tambocor (flecainide acetate) Tablets

Sponsor: Riker Laboratory

Type of Submission: ADR

Date of Submission: October 23, 1986

Date of Review: November 10, 1986

Reviewer: Sughok K. Chun, M.D. (HFN-110)

Resume:

[redacted] by: [redacted]

Phone: [redacted]

PURPURA, RENAL FAILURES

This 73-year-old man was admitted to the hospital 5/25/86 for treatment of AMI. He was taking Quinidine, and Lasix . On 5/26/86, he developed VT for which he received two bolus injections of Lidocaine 50 mg and Pronestyl 750 mg by IV drip. In spite of this therapy, VT recurred. On 5/30/86 he was switched to oral Pronestyl, and Solu-Medrol. On 6/2/86, Pronestyl was discontinued and Lidocaine administered for recurring VT. On 6/3/86 Lidocaine was discontinued, a single dose of Tocainide was administered, in spite of which VT persisted. Tambocor 100 mg Q12H was started 6/3/86, and the dose was increased to 150 mg Q12H on 6/4/86, after which time the arrhythmia appeared to be under control. On 6/6/86, Purpura was noted on all four extremities, particularly on palms and soles, and Tambocor was discontinued. The patient's creatinine on admission was 1.4 mg/dl, but was noted to be steadily rising throughout his hospital course. On 6/13/86, his creatinine was 4 mg/dl and Lasix was discontinued. Purpura appears to be subsiding on 6/13/86. Six other drugs have been administered continuously.

SK Chun 12/29/86

Sughok K. Chun, M.D.

cc: Orig. NDA
HFN-110
HFN-110/CSO
HFN-110/SChun
ef:12/29/96:#0767g

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

ORIGINAL

October 23, 1986

3M

REPORTS

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/jlg

Enclosure - [redacted]

Certified Mail P 235 106 206

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	73	M	06	07	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Purpura, renal failure
This 73-year-old man was admitted to the hospital 05/25/86 for treatment of an acute myocardial infarction. He was already taking quinidine, and Lasix was initiated orally at a dose of 40mg daily; Lasix has been continued at varying doses since that time. On 05/26/86, he developed ventricular tachycardia for which he received two bolus injections of lidocaine 50mg and Pronestyl 750mg by IV drip. In spite of this therapy, ventricular tachycardia recurred. On 05/30/86 he was switched to oral Pronestyl, and Solu-Medrol was administered as well. On 06/02/86, Pronestyl was discontinued and lidocaine administered for recurring ventricular tachycardia. On 06/03/86 lidocaine was discontinued, a single

13. RELEVANT TESTS LABORATORY DATA
5/25/86 serum creatinine 1.4 mg/dl
6/13/86 serum creatinine 4.0 mg/dl
Hemoglobin=12gm, platlets=207,000, bleeding and prothrombin times normal

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: PAROX VENTRIC TACHYCARD

18. THERAPY DATES *(From/To)*: 06/03/86 - 06/07/86

19. THERAPY DURATION: 4 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
FUROSEMIDE
DIGOXIN
METOLAZONE
DIOCYTL SODIUM SULFOSUCCINATE
GEMFIBROZIL
DILTIAZEM HCL
FLURAZEPAM HCL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
History of pre-existing congestive heart failure.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED MANUFACTURER: 9/11/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 10-DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5-85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

dose of tocainide was administered, in spite of which ventricular tachycardia persisted. Tambocor 100mg Q12H was started 06/03/86, and the dose was increased to 150mg Q12H on 06/04/86, after which time the arrhythmia appeared to be under control. On 06/07/86 purpura was noted on all four extremities, particularly on palms and soles, and Tambocor was discontinued. The patient's creatinine on admission was 1.4 mg/dl, but was noted to be steadily rising throughout his hospital course. On 6/13/86 his creatinine was 4 mg/dl and Lasix was discontinued. Purpura appears to be subsiding on 06/13/86. Six other drugs have also been administered continuously (see concomitant medications below).
FDA PLEASE NOTE: Originally received as a non-15 day in JUN86, this

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

RAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

2[illegible] ATE RECEIVED MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25b. [illegible]AY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.	8.-12. CHECK ALL APPROPRIATE TO REACTION
[redacted] (PAGE 3)						☐ DIED DUE TO REACTION ☐ TREATED WITH Rx DRUG ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

case will reach you as an INITIAL report (non-15 day) as part of the third quarterly periodic report going to you the week of 13OCT86. However, on 11SEP86 the status changed to that of a 15-day report due to the information that the patient had died. This FOLLOW-UP report is being held in Medical Services a short time beyond the 15 day limit so that Regulatory does not forward it to you as a FOLLOW-UP before you have logged it in as an INITIAL report.(GBE)

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

RAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. ...AY REPORT ☐ YES ☐ NO

25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

25.-25a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

25b. TELEPHONE NO. *(Include area code)*

25c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

25d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

9.1-(F)

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000

(612)733-0633

October 27, 1986

3M

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Report
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/dls

Enclosure - [redacted]

Certified Mail P 235 106 209

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	62	M	06	30	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

~~*PULMONARY EMBOLI* DEATH~~
This man had a history of sustained ventricular tachycardia, myocardial infarcts and congestive heart failure; he was currently receiving furosemide and potassium when flecainide was started for his ventricular arrhythmia. After 18 days of flecainide therapy he was released from the hospital and upon arriving at home he collapsed and died. An autopsy revealed pneumonia and pulmonary emboli.

C

13. RELEVANT TESTS LABORATORY DATA

Autopsy Report: 1. Fibrotic aneurysmal dilatation, left ventricle, involving septum and apex with adherent thrombus and associated pulmonary emboli and infarcts, visceral congestion. 2. Focal pulmonary edema with organizing pneumonia.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines.biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*
06/12/86 - 06/30/86

19. THERAPY DURATION
18 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

FUROSEMIDE

POTASSIUM CHLORIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

History of myocardial infarcts; receiving treatment for malnourishment and sustained VT; congestive heart failure.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
10/ 3/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 5 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

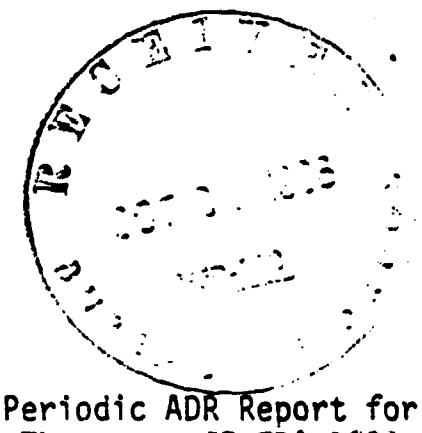
Riker Laboratories, Inc.

270-3A-01 3M Center
St. Paul, Minnesota 55144

9.1 P-3 ORIGINAL

3M

October 15, 1986



Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir or Madam:

Pursuant to 21 CRF 314.80, enclosed is the Periodic ADR Report for Tambocor® (flecainide acetate) NDA 18-830. There are 65 FDA-1639 forms in this submission, 58 of which are initial reports and seven are follow-up reports.

The time period covered by this report is June 11, 1986 to September 10, 1986.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/ds

12/22/86

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	68	M	05	25	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cause unknown.
Patient was a man in his late 60's with history of arteriosclerotic heart disease, bypass surgery, and angina. He had, for several years, been on a mexilitine trial but whose arrhythmia broke through. While in hospital, he was placed on flecainide with a good response and discharged. While working at home on 5/25/86, he died suddenly.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
??/??/?? - 05/25/86

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
6/11/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	66	M	04	25	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden Death (cause unkoown)
Patient with history of severe, ischemic cardiomyopathy, and serious congestive heart failure developed large MI [illegible] MAR86. Recurrent sustained and non-sustained V-tach developed 25APR86 which was controlled by flecainide 200mg/day as demonstrated on 19MAY86 by Holter monitor. Patient was clinically stable until he died suddenly on 23MAY86. The immediate cause of death was not determined. At time of death patient was also being treated with digoxin, Enalopril, Lasix and KCl. Physician feels it possible that flecainide was causally related to the death.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*: 04-25-86 - 05-23-86

19. THERAPY DURATION: 4 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN
FUROSEMIDE
NONE
POTASSIUM CHLORIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/13/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[x] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [x] NO

25a. REPORT TYPE
[x] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5.85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	79	M	06	06	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sudden Death (cause unknown)
Patient with history of diabetes, severe ischemic cardiomyopathy, myocardial infarct and severe congestive heart failure was found to have non-sustained ventricular tachycardia on Holter monitor 12MAY86. Treated with flecainide 200mg/day, the Holter monitor showed definite improvement by 29MAY86. Patient was also taking furosemide, spironolactone, potassium and Lente insulin. He died suddenly on 06JUN86, but the cause was not determined. The physician feels that there was a possible relationship between flecainide treatment and death.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*: 05-14-86 - 06-06-86

19. THERAPY DURATION: 3 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

FUROSEMIDE
INSULIN ZINC
SPIRONOLACTONE
POTASSIUM CHLORIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/13/86

24d. REPORT SOURCE *(Check one)*: ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT: ☐ YES ☒ NO

25a. REPORT TYPE: ☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	78	M	03	14	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Unresuscitatable Ventricular Arrhythmias
Patient with history of severe, ischemic cardiomyopathy, serious congestive failure and mild renal failure developed syncope and pre-syncope early in 1986. Was started as an outpatient on 12MAR86 with flecainide 200mg/day when malignant ventricular ectopy was diagnosed. This was soon increased to 300mg/day. On 14MAR86 patient developed syncope due to ventricular arrhythmia. He was hospitalized, but the arrhythmia proved to be refractory to multiple resuscitative efforts and he died. Physician considers that flecainide was probably causally related to terminal events.

13. RELEVANT TESTS/LABORATORY DATA
PRE-FLECAINIDE DIGOXIN LEVEL (03MAR86)=2.5

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*
03-10-86 - 03-14-86

19. THERAPY DURATION
4 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
DIGOXIN
HYDRALAZINE HCL
FURCSEMIDE
NITROGLYCERIN
CAPTOPRIL
METOLAZONE
SODIUM WARFARIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
6/13/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	75	F	05	24	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sustained ventricular tachycardia Death
This 73-year-old woman had history of myocardial infarction in 1968 and borderline cardiac failure being currently treated with digoxin and Lasix. She had been hypertensive for a number of years. She also suffered from signficant ventricular arrhythmia including couplets and short runs of ventricular tachycardia. These have been unresponsive to quinidine, Quinaglute, Norpace, Procainamido. She was admitted to hospital where Procainimide was discontinued and flecainide (100 mg b.i.d.) was started. Two and one-half days later, the dose was raised to 200 mg per day and she was discharged. The day following this, she called to complain of difficulty breathing and palpatations. On the way

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*: 05/21/86 - 05/25/86

19. THERAPY DURATION: 4 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN(LANOXIN) FUROSEMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Patient had myocardial infarctino in 1968. She suffered from hypertensive cardiovascular disease with a history of borderline congestive heart failure. Lasix and Lanoxin were being used for treatment of the latter. Her ventricular arrhythmias had been treated earlier with quinidine, disopyramide, procainamide and tocainide but these had caused side effects requiring their discontinuation.
MI 1968, CABG 1976, CHF NOV85, malignant vent. ectopy NOV85.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CE''ER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/20/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

to the hospital by ambulance, she developed v-tach which was converted but which arose again as sustained v-tach. The patient died.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	67	F	06	12	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

PROGRESSIVE FATIGUE,SUDDEN DEATH
This 67-year-old woman had history of mild to moderate hypertension and unifocal premature ventricular complexes. Treated for about 7 years with propranolol and disopyramide she developed fatigue and mild depression. Propranolol was discontinued but PVC's, which seemed worsened by exercise increased so that she could not continue garden work. Flecainide, 200mg/day, was started and within a week she "felt better than anytime in the past 20 years". She developed bronchitis treated first with erythromycin and then, when rash developed, with doxycycline. By this time, 12 days into the combination disopyramide/flecainide course, fatigue was developing. Three weeks into the course she went to a near-

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*: 05/21/86 - 06-12-86

19. THERAPY DURATION: 3 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
DOXYCYCLINE HCL — 8 DAYS — DISOPYRAMIDE — ~7 YEARS

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
She had mild hypertension (in 1979=180/96) and unifocal PVC's since at least 1979 for which she was treated with disopyramide and propranolol. Propranolol was discontinued in March 1986 due to increasing fatigue and slight depression. Flecainide (200mg/day) was added to the disopyramide (300mg/day) regimen on 21MAY86.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 7/16/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
by cabin with her friend, complained of fatigue and difficulty breathing whereupon she slumped in her chair and died.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	M	05	19	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

DEATH, CAUSE UNKNOWN
Patient died at home on the day of release from the hospital (05/19/86). The patient presented at the hospital with unstable angina and had ischemic cardiomyopathy; he had emergency coronary artery bypass graft 11 days prior to death; he was on pressors several days post-op; had no PVCs pre-op.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
200 MG	ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
05/10/86 - 05/19/86	10 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

GLUCOTROL
ASPIRIN
DIGOXIN
OXYCODONE HCL, ACETAMINOPHEN
DIPYRIDAMOLE
POTASSIUM CHLORIDE
FUROSEMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Noninsulin dependent diabetes mellitus.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER: 7/24/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [x] HEALTH PROFESSIONAL [ ] CONSUMER

25b. 15 DAY REPORT
- [ ] YES [x] NO

25a. REPORT TYPE
- [x] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5.85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	60	F	??	??	??

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cause unknown.
This woman had a history of short runs of ventricular tachycardia and multiple VPCs by Holter recording. She was also known to have a decreased ejection fraction. Upon treatment with Tambocor, she rapidly decreased the number of VPCs to zero, but died suddenly at home.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

No autopsy performed.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: 2 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Known decreased ejection fraction.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 8/ 5/86

24d. REPORT SOURCE *(Check one)*: ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT: ☐ YES ☒ NO

25a. REPORT TYPE: ☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFM-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	60	F	??	??	??

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cause unknown.
This woman, known to have a decreased ejection fraction, suffered from short runs of ventricular tachycardia. She was treated with flecainide for approximately three to five days and died suddenly at home.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTIO
- [ ] TREATED WITH Rx DRU
- [ ] RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
UNKNOWN	ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
UNKNOWN - UNKNOWN	3-5 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
8/ 5/86	[ ] FOREIGN [ ] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
[ ] YES [X] NO	[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	60	F	??	??	??

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cause unknown.
This woman, known to have a decreased ejection fraction, suffered from short runs of ventricular tachycardia. She was treated with flecainide for approximately three to five days and died suddenly at home.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTIO
- [ ] TREATED WITH Rx DRU
- [ ] RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
3-5 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
8/ 5/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [X] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	60	F	??	??	??

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cause unknown.
This woman, with decreased ejection fraction, was treated for ventricular arrhythmias with flecainide for a few days. She died at home.
More information is being sought.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 8/15/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

25b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	65	M	??	??	??

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cause unknown.
This 65-year-old man suffering from ventricular premature contractions, died shortly after starting flecainide. Further information is being sought.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*: UNKNOWN - UNKNOWN

19. THERAPY DURATION: UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 8/ 5/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

25.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

25b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	65	M	??	??	??

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cause unknown.
Patient was being treated for ventricular premature beats, when he died in hospital. More information being sought.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

18. THERAPY DATES *(From To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-[illegible] 3M CENTER
ST.PAUL, MN 55 44-1000

24a. NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
8/ 5/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25a. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26c. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	65	M	??	??	??

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cause unknown.
Additional information being sought.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND./NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
8/ 5/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]D	---	F	09	09	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Sustained Ventricular Tachycardia, Ventricular Fibrillation Death
This elderly woman has history of severe coronary artery disease which recently led to progressively severe angina culminating in an anterior wall myocardial infarction. Premature ventricular complexes, which were present before the MI, thereafter became more frequent and malignant. Flecainide, 200mg/day, was used to treat the arrhythmia, but after its start she developed sustained v-tach and v-fibrillation which failed attempts at conversion, and she died.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: ??-??-86 - 09-09-86

19. THERAPY DURATION: ?

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 9/10/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

25.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	75	M	06	04	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

REFRACTORY VENTRICULAR TACHYCARDIA Death
NOTE: Case reported directly to FDA by physician on 1639a ~10JUL86. This 75 y.o man had a complex history including carcinoma of prostate, anemia, senile dementia, coronary artery disease and history of atrial tachycardia as well as ventricular tachycardia associated with syncope. He had mild congestive heart failure controlled on digoxin and furosemide. He had failed treatment with procainamide, tocainide and disopyramide. He was hospitalized for general work up and change of antiarrhythmic medication. Procainamide was stopped and flecainide 200 mg per day started. Did well the first day while he was given 2 units of blood for his anemia. During that night he developed PVC's and lido-

13. RELEVANT TESTS LABORATORY DATA

Hematocrit 26 rising to 29 with 2 units of blood.
MCV=108. WBC=5.6. LDH 228.
EKG (pre-flecainide) 1st degree heart block with left bundle branch block. non-specific ST-T wave changes.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
200 MG	ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*	19. THERAPY DURATION
06-03-86 - 06-04-86	1 1/2 DAYS

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN(LANOXIN)
FUROSEMIDE
LIDOCAINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Please see #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
13-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
7/15/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

26a. REPORT TYPE
[X] INITIAL [ ] FOLLOW-UP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
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ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

caine was begun i.v. That morning he developed ventricular tachycardia which proved refractory to CPR, more lidocaine and bretylium and he died. Physicians impression as to cause of death was probable myocardial infarction with documented refractory ventricular tachycardia leading to electromechanical dissociation.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	73	M	06	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

CONGESTIVE HEART FAILURE, VENTRICULAR TACHYCARDIA, VENTRICULAR FIBRILLATION, CARDIAC ARREST Death.
At 73 years of age this man had history of myocardial infarct 13 years before, recent problem with bilateral carotid artery arteriosclerotic disease and had failed quinidine therapy for arrhythmia due to development of thrombocytopenia. On the day of the event he developed CHF followed by ventricular tachycardia which progressed to ventricular fibrillation and cardiac arrest. He was revived in the ER, flecainide was stopped and procainamide given for 7-8 days in the hospital. The latter was stopped and that night he developed supraventricular tachycardia which was controlled with verapamil and lidocaine. This then

13. RELEVANT TESTS LABORATORY DATA

flecainide plasma concentration on 13JUN86 awaited.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG? [X] YES [ ] NO [ ] NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
200 MG	ORAL	
17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA		[ ] YES [ ] NO [X] NA
18. THERAPY DATES *From To)*: 05-21-86 - 06-13-86	19. THERAPY DURATION: 23 DAYS	

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIPYRIDAMOLE
RANITIDINE
ACETYLSALICYLIC ACID

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Please see #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
6/27/86	[ ] FOREIGN [ ] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

25b. 15 DAY REPORT	25a. REPORT TYPE
[ ] YES [X] NO	[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL? [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.	8.-12. CHECK ALL APPROPRIATE TO REACTION
[redacted] (PAGE 2)						☐ DIED DUE TO REACTION ☐ TREATED WITH Rx DRUG ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

progressed to ventricular tachycardia again, ventricular fibrillation not responsive to increased doses of lidocaine, and the patient died. Blood was drawn in the ER for flecainide concentration, but those results were not known at time of report.

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
17. INDICATION(S) FOR USE		
18. THERAPY DATES *(From/To)*	19. THERAPY DURATION	☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)* ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER
25. 15 DAY REPORT ☐ YES ☐ NO	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	21	F	04	16	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

**Heart Block, Hypotension* ; Death
A 21-year-old female patient with mitral valve prolapse and catecholamine dependent ventricular tachycardia ingested approximately 2 Gm of Inderal and 12-16 Gm of Tambocor. Within one hour had blood pressure of 70/40 and pulse 70. Within 2 hours was in asystole with complete heart block; no response to medication, pacemaker, or internal heart massage.
25SEP86 Coding terms (shown within asterisks, above) changed to those shown which are more appropriate to event.

13. RELEVANT TESTS/LABORATORY DATA

07/21/86..AUTOPSY RESULTS: FLECAINIDE LEVELS (ALL UNITS IN MICROGRAMS/ML) SERUM 3.24;BLOOD 10.9;URINE 27.2;LIVER 256;BILE - PRESENT;VITREOUS HUMOR 7.4;GASTRIC 190MCG/KG. PROPRANOLOL LEVELS (ALL UNITS IN MICROGRAMS/ML.) BLOOD 1.1;URINE 1.7; LIVER 9.2;BILE - PRESENT;GASTRIC 190MG/KG.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X OVERDOSE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

15. DAILY DOSE
~16 GRAMS

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
04/15/86 - 04/16/86

19. THERAPY DURATION
1 DAY

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

PROPRANOLOL ONE DOSE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

None.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
7/21/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	04	06	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Ventricular fibrillation
This gentleman (age not reported) had history of diaghragmatic wall myocaruial infarct, triple coronary artery bypass surgery and mild, stable aortic stenosis. He also sufferred from recurrent atrial fibrillation for which he was given flecainide 400mg/day. Concommitant medications included Lopressor and quinidine. One month following start of flecainide, immediately following exercising in a gymnasium, he developed ventricular fibrillation and collapsed. This converted to incessant v-tach which proved refractory to lidocaine, bretylium and i.v. Pronestyl followed by death several hours after the event.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 400 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: ATRIAL FIBRILLATION

18. THERAPY DATES *(From/To)*: 03-04-86 - 04-06-86

19. THERAPY DURATION: 4 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
QUINIDINE POLYGALACTURONATE METOPROLOL TARTRATE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Remote history of diaphragmatic wall infarct, triple vessel bypass surgery and mild, stable aortic stenosis. He exercised regularly.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 7/14/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

11-F

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

ORIGINAL

REPORTS 3M

March 4, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Reports
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are five Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/dls

Enclosure - [redacted]

Certified Mail P 504 523 554

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	79	F	12	29	86

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ACUTE MYOCARDIAL INFARCTION, VENTRICULAR FIBRILLATION Death
This 79 y.o. female had entered and completed Riker study [redacted] ([redacted]). She had started on flecainide 100 mg bid during the study and experienced an adverse event ([redacted]) but continued taking flecainide. On 12/29/86, she was found unresponsive at home in ventricular fibrillation. The rescue squad applied CPR and defibrillation, administered epinephrine and sodium bicarbonate, and transported her to the ER where the code continued for 15 minutes. The total resuscitative effort lasted 40 minutes. The woman died with immediate case of death listed as acute myocardial infarction.

13. RELEVANT TESTS / LABORATORY DATA

Per [redacted] creatinine level 1.4 (upper normal); flecainide level on 10/23/86 0.67 mcg/ml.

II. SUSPECT DRUG(S) INFORMATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE: Ventri Premature Beats

THERAPY DATES *(From/To)*: 10/24/86 ~ 12/29/86

19. THERAPY DURATION: 2 MONTHS

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

CAPTOPRIL
POTASSIUM CHLORIDE
SODIUM LEVOTHYROXINE
FUROSEMIDE
NIFEDIPINE
NITROGLYCERIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above and adverse experience report IT-86-449.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 2/12/87

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

. AY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

11-1

Riker Laboratories, Inc.

270-3A-01 3M Center
St. Paul, Minnesota 55144
(612)733-0633

ORIGINAL

3M REPORTS

January 19, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Reports
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are seven Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/dls/1

Enclosure - [redacted]

Certified Mail P 235 106 351

RECEIVED
NATIONAL CENTER FOR DRUGS AND BIOLOGICS
FEB 03 1987
HFN-110

87 JAN 30 PM 2:00

CMM 2/6

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	68	M	08	24	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

LEFT VENTRICULAR FAILURE, ATRIAL FLUTTER, VENTRICULAR TACHYCARDIA, VENTRICULAR FIBRILLATION Death
This 68 y.o. male had a history of inferior myocardial infarction. He started taking flecainide on 8/18/86 at a dose of 200 mg per day. At some point he experienced a cardiac arrest (unknown whether before or after flecainide initiation). The events directly related to death began on 8/24/86; flecainide was discontinued 8/24/86. At the hospital, the patient was cardioverted to sinus bradycardia and received atropine and lignocaine. Further ventricular fibrillation required DC counter-shock leading to bradycardia. Continued ventricular fibrillation led to electromechanical dissociation. Ca gluconate and Na bicarbonate

13. RELEVANT TESTS LABORATORY DATA

Potassium 3.3mmol/liter (date unknown)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR FIBRILLATION

18. THERAPY DATES *(From To)*: 08/18/86 - 08/24/86

19. THERAPY DURATION: 6 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG? [ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

FUROSEMIDE	12 DAYS	POTASSIUM CHLORIDE	12 DAYS
MEXILETINE	7 DAYS	CIMETIDINE	
SULINDAC			
Digoxin			

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

History of old inferior myocardial infarction. See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 1/ 7/87

24d. REPORT SOURCE *(Check one)*: [X] FOREIGN [ ] STUDY [ ] LITERATURE [ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 7 DAY REPORT: [X] YES [ ] NO

25a. REPORT TYPE: [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL? [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

were given. The patient went into asystole, was given adrenaline and diazepam, and died on 8/28/86. Death was caused by left ventricular failure, atrial flutter, ventricular tachycardia, and ventricular fibrillation. The immediate cause of death, in the opinion of the physician, was ventricular fibrillation secondary to ischaemic heart disease and left ventricular failure.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

110

11-1-11-2-F

REPORTS

ORIGINAL

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000

3M

(612)733-0633

January 6, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Reports
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/dls

Enclosure - [redacted]

Certified Mail P 235 106 326

RECEIVED
NATIONAL CENTER FOR DRUGS AND BIOLOGICS
JAN 29 1987
HFN-110

Clm. 2/19

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	73	M	06	07	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

VASCULITIS DEATH

Patient (73-year-old man) was admitted to hospital with a complicated myocardial infarction. He developed congestive heart failure and hypotension requiring pressor agents. He also developed ventricular tachycardia and was treated by cardioversion and also received lidocaine, procainamide, and tocainide, all without satisfactory control. On 6/3/86 he was started on flecainide 100 mg bid. The patient was also on furosemide, diltiazem, metolazone, and nitrates. On 6/7/86, the patient was noted to have purpuric lesions (flecainide and metolazone were discontinued). The patient a that time was diagnosed as having hypersensitivity vasculitis. On 6/8/86 the skin lesions were again noted and

13. RELEVANT TESTS LABORATORY DATA

6/8/86 - platelet count normal

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*: 06/03/86 - 06/07/86

19. THERAPY DURATION: 5 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

FUROSEMIDE
METOLAZONE
NONE
DILTIAZEM HCL
NITROGLYCERIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

reported that the patient had angina pectoris and mild hypertension and elevated blood lipids prior to his hospitalization for the myocardial infarction and was receiving propranolol, clofibrate, and hydrochlorothiazide. The patient had had a resection of adenocarcinoma of the lung 18 months previously but was not undergoing radiation or chemotherapy.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

BAKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 12/30/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

platelet count was normal. Lopid, Colace, and diltiazem were discontinued. Digoxin, nitrates and ampicillin were continued. Within the next few days, the patient developed renal failure, fluid retention and progressively deteriorating course, which led to his death on 6/16/86. Consultant's order of drug suspicion=furosemide/metalazone/flecainide.
PREVIOUSLY REPORTED TO FDA VIA USP REPORTING SYSTEM, DOCUMENT #70702, WHICH ERRONEOUSLY IDENTIFIED THE DOSAGE FORM AS INTRAVENOUS.
FOLLOW-UP 30DEC86: Correction of dosage information which had been entered incorrectly.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

HERAPY DATES *(From/To)*	19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

11.1

MAY 22

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA: 18-330

Name of Drug: Tambocor (flecainide)

Sponsor: Riker Lab.

Type of Submission: Periodic ADR Report

Date of Submission: January 12, 1987

Date of Review: February 19, 1987

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

The time period covered by this report is September 11, 1986 to December 10, 1986.

FROM NON 15-DAY REPORTS

UNLABLED

REACTION TERMS	NUMBER OF REPORTS
CUSHINGOID FACIAL FEATURES	1
ECHO-OPAQUE VENTRICULAR SEPTAL DEPOSITS	1
HEPATIC FUNCTION ABN	1
HEPATITIS	1
MANIC DEPRESSIVE	1
PNEUMONIA	1
ANGIOEDEMA	1
CEREBROVASCULAR DISORDER	1

LABLED

	CARDIAC FAILURE	8
	ECG ABNORMAL	1
	SYNCOPE	3
	CONSTIPATION	1
	NAUSEA	1
	TINNITUS	1
	ARRHYTHMIA	3
	ARRHYTHMIA VENTRICULAR	2
	AV BLOCK	2
	BRADYCARDIA	3
	BUNDLE BRANCH BLOCK	3
	TACHYCARDIA	9
	HEPATIC FAILURE	1
	HEPATIC FUNCTION ABNORMAL	2
PLATELET, BLEEDING & CLOTTING DISORD	THROMBOCYTOPENIA	1
PSYCHIATRIC DISORDERS	AMNESIA	1
	CONFUSION	2
	IMPOTENCE	1
SKIN & APPENDAGES DISORDERS	RASH	1
	URTICARIA	1
URINARY SYSTEM DISORDERS	URINARY RETENTION	1
VISION DISORDERS	VISION ABNORMAL	1

NARRATIVE OF ACTION TAKEN

Current labeling appears to be covering well such events as have been reported in the first three quarterly reports based upon United States marketing. Based upon careful review of information received in this quarter, it appears that the experiences present no information which could be incorporated into current prescribing material on Tambocor to improve prescriber understanding or use of this agent.

S K Chun 5/15/87

Sughok K. Chun, M.D., HFN-110

cc: Orig. NDA: #18-830
HFN-110
HFN-110/CSO
HFN-110/SChun/2/19/87

NAI 6/4/87 GB

[redacted] *VASCULITIS* DEATH
Patient (73 y/m) was admitted to hospital with a complicated MI. He developed CHF and hypotension requiring pressor agents. He also developed VT and was treated by cardioversion and also received lidocaine, procainamide, and tocainide, all without satisfactory control. On 6/3/86 he started on flecainide 100 mg bid. The patient was also on furosemide, diltiazem, metolazone were (d/ced). The patient at that time was diagnosed as having hypersensitivity vasculitis. On 6/8/86 the skin lesions were again noted and platelet count was normal. Lopid, Colase, and diltiazem were d/ced. Digoxin, nitrates and ampicillin were continued. Within the next few days, the patient developed renal failure, fluid retention and progressively deteriorating course, which led to his death on 6/16/86. Consultants's order of drug suspicion=furosemide/metalazone/flecainide.

[redacted]
CHRONIC ACTIVE HEPATITIS
ELEVATED BILIRUBIN, ELEVATED SERUM ALKALINE PHOSPHATASE, SPIDER NEVI
This 51 y/m was being treated with F 200 mg/day for PVCs with bursts of VT. After two years of therapy, he was found to have elevated serum globulin, and alkaline phosphatase, ALT, globulin, and gamma, GT. 2-3 spider nevi were noted. A diganosis of chronic, active hepatitis was made and prednisone was prescribed for treatment. Present evidence is not thought to indicate primary biliary cirrhosis.

Elevated bilirubin 25; alkaline phosphatase 808; ALT 160 (normal 40); albumin 38; globuline 50; gamma GT 335 (normal 50); normal calcium. Auto-antibodies have shown positive mitrochrondrial antibody.

[redacted]
HEPATITIS
64 y/f entered hospital with shortness and breath and with aim to change her medication for treatment of frequent PVCs. She was currently on 4 gm procainamide daily. This was d/ced and F. 100 mg bid started. After 3 days of F increased to 400 mg/d, but after 2 days of reduced to 200 mg/d due to GI complaints. After 2 days of that, marked elevation of transaminases and bilirubin appeared without elevation of alk, phos. F was stopped. (Aminophylline and SOLU MEDROL d/c'ed when GI complaints appeared.) Diagnosed of hepatitis is entertained. On 10/13/86 patient died.

CUSHINGGOID FACIAL FEATURES
This 59 y/m who has history of CAD, - MI was started with F 100 mg bid four months ago for treatment of multi-focal PVCs. The arrhythmic response was prompt however, both he and his physician noted that he had developed facial features suggestive of cushinggoid appearance. Buffalo hump, striae or other features were not present. Subsequent to the initial report it was learned that patient had received a steroid shot for arthritis from another physician considered to explain these changes.

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000

P-4

REPORTS

ORIGINAL

January 12, 1987

3M

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir or Madam:

Pursuant to 21 CRF 314.80, enclosed is the Periodic ADR Report for Tambocor®(flecainide acetate) NDA 18-830. There are 45 FDA-1639 forms in this submission, 38 of which are initial reports and seven are follow-up reports.

The time period covered by this report is September 11, 1986 to December 10, 1986.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/ds/8f

Chm 2/19

110

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	64	F	06	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Hepatitis
64 y.o. woman entered hospital with shortness of breath and with aim to change her medication for treatment of frequent preaature ventricular contractions. She was currently on 4gm procainamide daily. This was discontinued and flecainide 100mg bid started. After 3 days flecainide increased to 400mg/d, but after 2 days of that flecainide reduced again to 200mg/d due to GI complaints. After 2 days of that, marked elevation of transaminases and bilirubin appeared without elevation of alk. phos. Flecainide stopped. (Aminophylline and SOLU MEDROL d/c'ed when GI complaints appeared.) Dignosis of hepatitis is entertained.
13OCT86 M.D. advised patient died. His suspicions of flecainide's

13. RELEVANT TESTS/LABORATORY DATA

23JUN86 Bilirubin 4.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*: 06-16-86 - 06-23-86

19. THERAPY DURATION: 7 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

AMINOPHYLLINE

METHYLPREDNISOLONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Shortness of Breath has been present some time and seems to relate to a primary pulmonary condition, not clearly defined, rather than to cardiac status. General cardiac status appears to be good without failure.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 10/13/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-700)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-5. REACTION ONSET MO. DA. YR.

6.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

involvement are reduced as many other medications were involved before and after its discontinuation. He promises a full report.

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	M	05	19	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

DEATH, CAUSE UNKNOWN
Patient died at home on the day of release from the hospital (05/19/86). The patient presented at the hospital with unstable angina and had ischemic cardiomyopathy; he had emergency coronary artery bypass graft 11 days prior to death; he was on pressors several days post-op; had no PVCs pre-op.

13. RELEVANT TESTS/LABORATORY DATA

Autopsy not done.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*: 05/10/86 - 05/19/86

19. THERAPY DURATION: 10 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?

☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

GLUCOTROL
ASPIRIN
DIGOXIN
OXYCODONE HCL, ACETAMINOPHEN
DIPYRIDAMOLE
POTASSIUM CHLORIDE
FUROSEMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Noninsulin dependent diabetes mellitus.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 9/23/86

24d. REPORT SOURCE *(Check one)*

☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT

☐ YES ☒ NO

25a. REPORT TYPE

☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?

☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	10	05	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

WORSENING OF ARRHYTHMIA* Death
This patient had preexisting renal dysfunction which required dialysis when flecainide was started at 100 mg bid for ventricular arrhythmia. After about 10 days of therapy the arrhythmia worsened and the patient subsequently died. Results of a serum flecainide level assay had not been received when the patient died (6-7 days after the sample had been sent in).

13. RELEVANT TESTS LABORATORY DATA

Awaiting flecainide concentration report.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X **LIFE THREATENING**

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

THERAPY DATES *(From/To)*: 09/26/86 - 10/05/86

19. THERAPY DURATION: 10 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Renal failure requiring dialysis.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 10/ 7/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	69	F	10	02	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

LEFT BUNDLE BRANCH BLOCK, 3RD DEGREE AV BLOCK, CHF DEATH
The patient's ectopy was not controlled with quinidine and verapamil, and was switched to verapamil and flecainide. The ectopy was then well controlled but after four days of therapy, LBBB appeared and by Day 5, congestive heart failure and 3rd degree AV block occurred; death occurred shortly thereafter. The reporter questioned the possibility of a drug interaction with verapamil (CHF and AV block may occur with both drugs).

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
100 MG	ORAL

17. INDICATION(S) FOR USE

VENTRI PREMATURE BEATS

THERAPY DATES *(From/To)*	19. THERAPY DURATION
09/28/86 - 10/02/86	5 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?

- [ ] YES
- [x] NO
- [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

- [ ] YES
- [ ] NO
- [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

VERAPAMIL HCL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

End stage pulmonary interstitial fibrosis

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
10/ 8/86	☐ FOREIGN ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
☐ YES ☒ NO	☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?

☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (1-[illegible]-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	07	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***PACEMAKER EXIT BLOCK* DEATH**
This patient had a pacemaker in place when flecainide was started. Difficulty was encountered in establishing a new pacemaker threshold and the patient subsequently died.

13. RELEVANT TESTS LABORATORY DATA

None known.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X **LIFE THREATENING**

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: UNKNOWN

THERAPY DATES *(From/To)*: ??/??/86 - ??/??/86

19. THERAPY DURATION: UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 10/16/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	10	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

PROARRHYTHMIA Death
This man of unknown age was experiencing ventricular arrhythmia (type unknown) and had poor ejection fraction said to be in the area of 10%. Shortly following initiation of flecainide therapy (dose and duration presently unknown) he experienced a proarrhythmic event and died. More information is being sought concerning the dosing, past history, the event and concommitant medications.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

THERAPY DATES *(From/To)*: 10-??-86 - 10-28-86

19. THERAPY DURATION: UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [x] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Very low ejection fraction.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 11/ 3/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[x] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [x] NO

25a. REPORT TYPE
[x] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	??	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cause unknown
Patient described by physician as "very sick" was started on flecainide while in hospital and died. Physician did not feel death was due to the drug.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

18. THERAPY DATES *(From/To)*
??-??-86 - ??-??-86

19. THERAPY DURATION
??

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-930

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
9/26/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [x] HEALTH PROFESSIONAL
- [ ] CONSUMER

25b. 15 DAY REPORT
- [ ] YES
- [x] NO

25a. REPORT TYPE
- [x] INITIAL
- [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

25b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES
- [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES
- [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	??	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, Cause unknown
Patient was described by physician as "very sick". Started on flecainide in hospital and died. Physician did not believe death was due to the drug.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

THERAPY DATES *(From/To)*
??-??-86 - ??-??-86

19. THERAPY DURATION
??

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-930

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
9/26/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	65	M	05	02	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cause unknown.
This 65 y.o. man, believed to have generally good cardiac status, was experiencing multifocal premature ventricular complexes for which he was prescribed flecainide 100 mg bid. About a week after starting the drug he stepped out of the shower and died suddenly. No autopsy was obtained. The physician is uncertain as to a causative role of flecainide in this death.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 2.0 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*: 04-26-86 - 05-02-86

19. THERAPY DURATION: 1 WEEK

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 9/26/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	37	M	09	12	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#VENTRICULAR TACHYCARDIA, VENTRICULAR FIBRILLATION# Death
This 37 y.o. man with good left ventricular function was in hospital for treatment of recurrent ventricular tachycardia. He was started on flecainide 200mg/day which put the arrhythmia under control but with some non-sustained v-tach remaining. On the fourth day of treatment ventricular tachycardia returned and progressed to ventricular fibrillation from which he could not be resuscitated. No autopsy was obtained and no flecainide concentrations determined.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*: 09-08-86 - 09-12-86

19. THERAPY DURATION: 4 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 9/12/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25b. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE [redacted] ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	67	M	12	09	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

HEPATIC DYSFUNCTION Death
This 67 y.o. man had long history of severe cardiac disease complicated by chronic obstructive pulmonary disease. He had history of coronary artery bypass surgery and failure controlled with digoxin and furosemide. At the time of the event he was in hospital taking a number of medications (see below) and verapamil had been used for a short period. While in hospital he received flecainide 100mg bid for ventricular arrhythmias, but during the five days following strart of dosing he "went rapidly downhill" and died. Information was obtained from an assistant to the physician who was enquiring about all of the drugs the patient had been taking -- particularly with respect to their affect

13. RELEVANT TESTS LABORATORY DATA

No autopsy was obtained.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

THERAPY DATES *(From/To)*: 12-04-86 - 12-09-86

19. THERAPY DURATION: 5 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN(LANOXIN)
PHENYTOIN
PREDNISONE
FUROSEMIDE
DIPYRIDAMOLE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Please see #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 12/10/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

he liver. She could not be more specific about what role the liver was suspected have played in the end events. Thus, pending further information, the event, "hepatic dysfunction" is presumptive. No autopsy was obtained.

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
17. INDICATION(S) FOR USE	
18. THERAPY DATES *(From/To)*	19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)* ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER
25. 15 DAY REPORT ☐ YES ☐ NO	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

11.1-11.2-F

Regulatory Affairs
Riker Laboratories, Inc.

Building 27C-3A, 3M Center
St. Paul, Minnesota 55144-1000

(612)733-0633

ORIGINAL

REPORTS 3M

December 15, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Reports
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are four Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/dls

Enclosure - [redacted]

Certified Mail P 235 106 296

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	95	M	5	7	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

RENAL FAILURE, LEFT VENTRICULAR FAILURE Death
This 95 y.o. male was admitted to the hospital 5/6/86 at the request of his general practioner for non-specific deterioration. He had been receiving flecainide for approximately 20 months at 200mg/day. On 5/7/86 he experienced left ventricular failure and renal failure as evidenced by urinary retention. Flecainide was decreased to 50mg/day and then discontinued, both on 5/7/86. The patient died on 5/8/86 of left ventricular failure, ischemic heart disease, and renal failure. Underlying cause of death is believed to be atherosclerotic cardiovascular disease.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [x] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Lab tests taken 5/6/86: Urea 47.9 Potassium 6.4 Alk phos 417 iu/l
ALT 1650 iu/l GLT 62 iu/l Creatinine 388

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
100 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

THERAPY DATES *(From/To)*
24SEP84 - 07MAY86

19. THERAPY DURATION
20 MONTHS

20 DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

FUROSEMIDE	2 MONTHS	POTASSIUM CHLORIDE	2 MONTHS
AMOXICILLIN	1 DAY	MORPHINE	1 DAY

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
12/10/86

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

e. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 09:0-0X01
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	83	M	9	9	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***RENAL FAILURE, BRONCHIAL PNEUMONIA* Death**
This 83 y.o. male was admitted to the hospital on 7/25/85 because of onset of immobility, chest infection, and dehydration. He had been receiving flecainide since 4/16/85. On 8/28/85 his general condition began to deteriorate but then showed improvement until 9/6/85. General deterioration, dizziness, and shortness of breath occurred until 9/9/85 when sudden deterioration led to death. Immediate cause of death is believed due to renal failure and bronchial pneumonia.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [x] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Lab tests (date unknown): Hemoglobulin 11.1 Urea 19.1
Creatinine 310
Serum flecainide 0.415 mcg/ml
PR interval 0.24 sec
QRS interval 0.16 sec (LBBB)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE
100 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

THERAPY DATES *(From/To)*
16APR85 - 09SEP85

19. THERAPY DURATION
5 MONTHS

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

TEMAZEPAM	**6 WEEKS**	**ERYTHROMYCIN**	**2 WEEKS**
FUROSEMIDE	**6 WEEKS**	**AMILORIDE**	**6 WEEKS**
Asilone	6 WEEKS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
12/10/86

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted]

2. AGE YRS. 87

3. SEX F

4.-6. REACTION ONSET: MO. 10 DA. 25 YR. 85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***CEREBRAL EMBOLUS, BRONCHOPNEUMONIA* Death**
This 87 y.o. female was started on flecainide 100mg bid 10/16/85 for the treatment of atrial flutter. On 10/21/85 flecainide was increased to 150mg bid. On 10/25/85 the patient's condition deteriorated due to an embolus to the left side of the brain with slight right side weakness (cerebrovascular accident) and pneumonia. Amoxicillin was started on 10/26/85 for treatment of the pneumonia. At 8:00am on 10/28/85 the patient experienced a second cerebrovascular accident to the right side of the brain with left hemiparesis. Condition deteriorated until the patient died on 10/29/85. The immediate cause of death is believed to be bronchopneumonia resulting from the first cerebrovascular accident with

13. RELEVANT TESTS/LABORATORY DATA
QRS interval shows incomplete RBBB (date unknown)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☒ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: **300 MG**

16. ROUTE OF ADMINISTRATION: **ORAL**

17. INDICATION(S) FOR USE: **ATRIAL FLUTTER**

THERAPY DATES *(From/To)*: **16OCT85 - 28OCT85**

19. THERAPY DURATION: **12 DAYS**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

AMOXICILLIN	**2 DAYS**	**PROPOXYPHENE, ACETAMINOPHEN**	**5 WEEKS**
PROCHLORPERAZINE	**2 DAYS**	**Colofac**	**5 WEEKS**
Prothiaden	**5 WEEKS**	**LACTULOSE**	**5 WEEKS**

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST. PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: **18-830**

24b. MFR CONTROL NO. [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 12/10/86

24d. REPORT SOURCE *(Check one)*: ☒ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT: ☒ YES ☐ NO

25a. REPORT TYPE: ☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFR-7301)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA | YR.

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
underlying cause of death being atherosclerotic cardiovasular disease.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	M	5	13	85

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#OCCULSION OF CORONARY ARTERY# Death
This 70 y.o. male was started on flecainide 150 mg bid on 2/19/85 for the treatment of paroxsymal atrial fibrillation. He was seen by the physician on 3/26/85 at which time he appeared very well with no symptoms. On 5/13/85 the patient died very suddenly at home. Autopsy showed atheromatous occlusion of the right coronary artery.

13. RELEVANT TESTS/LABORATORY DATA

Autopsy. See #7 above.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: ATRIAL FIBRILLATION

18. THERAPY DATES *(From/To)*: 19FEB85 - 13MAY85

19. THERAPY DURATION: 3 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?

- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ISOSORBIDE DINITRATE	3 MONTHS	TRIAMTERENE/HYDROCHLOROTHIAZIDE	3 MONTHS
DIAZEPAM	3 MONTHS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 12/10/86

24d. REPORT SOURCE *(Check one)*

- [X] FOREIGN [ ] STUDY [ ] LITERATURE
- [ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT

- [X] YES [ ] NO

25a. REPORT TYPE

- [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

12.1 SEP 8 1987

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA: 18-830

Name of Drug: Tombocor (flecainide Acetate) Tablets

Sponsor: Riker

Type of Submission: ADR

Date of Submission: August 3, 1987

Date of Assignment: August 28, 1987

Date of Review: August 29, 1987

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

*[redacted]

Possible Drug Interaction (theophylline), Impaired Renal Function. This 80 y/m was hospitalized on 7/3/87 for exacerbation of COPD and treated witn aminoglycoside. While hospitalized a recurrent VT was found and flecainide (F) was started on 7/17/87. Concomitant medications consisted of theophylline, isoetharine HCl, ipathropium bromide, prednisone and acetaminophen. He was released from hospital on 7/11/87 and readmitted on 7/15/87 with evidence of theophylline toxicity (symptoms to be obtained) and serum theophylline level of 28.4 mcg/ml compared to 11.8 mcg/ml prior to F. The impaired, but improving renal status was thought due to ibuprofen which was stopped prior to F use.

	LABORATORY DATA	
	BUN	CREATININE
7/11/87	38	1.3
7/15/87	26	1.2

[redacted] *APNEA, CYANOSIS*

This one month old infant was born with irreversible severe VT. F was started at a dose of 6 mg q 8h which effectively controlled the tachycardia. Two weeks after discharge, on 7/18/87, the child suddenly experienced 3 episodes of apnea and cyanosis lasting a total of ten min. The child was hospitalized and has not had any further episodes within the last three days. Flecainide level was 0.91 mgc/ml. Follow-up information was requested.

Comments:

Case [redacted] is the first ADR for a new born baby. I called the sponsor on 8/29/87 and asked whether the sponsor gave any guidance to dosing of infant and any animal studies in new born with flecainide. The sponsor will look into it and will let us know.

S K Chun 9/2/87

Sughok K. Chun, M.D., HFN-110

cc:
Orig. NDA 18-830
HFN-80/DDIR
HFN-110
HFN-110/CSO
HFN-110/SChun/8/26/87
klr/8/26/87/09141

12.1

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612) 736-5016

REPORTS D

3M

August 3, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are four (4) Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Enclosure: 15 Day Reports
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Certified Mail P 648 917 322

8/19

RECEIVED
AUG 27 1987
HFD-110
FOOD & DRUG ADMIN

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFI-730)
ROCKVILLE MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ACUTE MYOCARDIAL INFARCTION
This patient was started on flecainide 200 mg daily as part of a study for control of non-sustained ventricular tachycardia. The dose may have been increased but the maximum allowed in the study was 400 mg daily. This patient had a history of coronary artery disease and angina. During the study, the patient died of acute myocardial infarction.

Literature report: "Flecainide in the treatment of nonsustained ventricular tachycardia"; Annals of Internal Medicine 1986, 105, 493-498.

13. RELEVANT TESTS/LABORATORY DATA
None.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200-400 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
7/22/87

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☒ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

5 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

Flecainide in the Treatment of Nonsustained Ventricular Tachycardia

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Thirty-two patients received flecainide acetate for nonsustained ventricular tachycardia after having had unsuccessful treatment with a mean of four antiarrhythmic drugs. The mean left ventricular ejection fraction was 41% in 27. Thirty-one patients had organic heart disease, and 22 patients had arrhythmia-related symptoms. Total suppression of ventricular tachycardia occurred in 22 patients. Thirty patients were discharged from the hospital receiving flecainide at a mean (± SD) dosage of 315 ± 76 mg/d and 26 of these patients attained a mean trough plasma drug level of 567 ± 254 ng/mL. One patient had proarrhythmia and 3 had worsening of heart failure. Twenty-two patients remained in the trial for a mean follow-up of 13 ± 7 months. Five patients died (1 suddenly) during the follow-up period. Our data indicate that flecainide suppresses refractory nonsustained ventricular tachycardia in 69% of patients who have organic heart disease. Serious adverse effects were minimized by initiation of treatment in the hospital and careful surveillance of electrocardiograms and plasma drug levels.

FLECAINIDE ACETATE is a new drug classified generally as a Ic antiarrhythmic agent because of its pronounced negative dromotropic effect on cardiac tissues in the absence of marked alterations in repolarization (1). A few cases of its use in treating recurrent sustained and nonsustained ventricular tachycardia have been reported, but clinical experience with this drug in the United States remains limited (2-7). We describe the combined experience of three arrhythmia centers that have used flecainide to treat patients with nonsustained ventricular tachycardia who had had previous unsuccessful treatment with other antiarrhythmic drugs.

We examined 32 patients who were part of a larger group enrolled in a trial of flecainide for the treatment of ventricular tachyarrhythmias. The results of this trial in patients who had recurrent, sustained ventricular tachycardia or out-of-hospital cardiac arrest have been presented in a separate report (3).

Patients and Methods

Seventeen men and 15 women aged 32 to 76 years (mean ± SD, 56 ± 14) who had recurrent, nonsustained ventricular tachycardia participated in the study between 1 January 1982 and 31 December 1984 at the Jewish Hospital at Washington University in St. Louis, the Medical College of Wisconsin Hospitals in Milwaukee, and Hermann Hospital at the University of Texas Medical School in Houston.

Nonsustained ventricular tachycardia was defined as six or more consecutive ventricular complexes occurring at a rate of more than 100 beats/min, lasting less than 30 seconds, and not requiring artificial termination because of hemodynamic instability. Twenty patients had coronary artery disease that was diagnosed by electrocardiographic findings of infarction in 6 and by angiographic documentation of coronary stenoses in 14. Fifteen patients had sustained myocardial infarctions lasting from 1 to 180 months (mean, 48 ± 55) before entry into trial and 5 patients had stable angina pectoris. Seven patients had mitral valve prolapse, 3 had congestive cardiomyopathy, 1 had rheumatic valvular disease, and 1 had no structural heart disease. Twenty-two of these patients had symptoms believed to be arrhythmia related. The commonest symptom, palpitation, occurred in 18 patients. Other presenting symptoms of syncope, near syncope, and shortness of breath correlated with recorded arrhythmias in 4 patients. Previous unsuccessful antiarrhythmic therapy included the use of one to eight drugs (mean, four). Failure of previous antiarrhythmic therapy was due to intolerance or ineffectiveness as determined by clinical criteria that included the use of telemetry monitoring and ambulatory electrocardiograms. When patients were referred after several unsuccessful drug trials, attempts by the investigators to confirm intolerance or inefficacy of previously administered drugs generally were not made unless they thought inappropriate doses had been given before referral. Left ventricular ejection fraction measured in 27 patients ranged from 18% to 60% (mean, 41% ± 13%).

Patients who had PR intervals of more than 0.28 seconds, second or higher degree atrioventricular blocks, creatinine clearances of less than 20 mL/min, or digitalis-induced arrhythmias, and patients who were pregnant or of childbearing potential were excluded from study participation. Efforts were made to avoid the concomitant use of calcium channel blockers or the enrollment of patients totally dependent on artificial pacing. In all patients flecainide was the only antiarrhythmic drug used.

STUDY PROTOCOL

The patients were admitted to a telemetry unit after having had electrocardiographic determination of nonsustained ventricular tachycardia, and were continuously monitored throughout the hospital phase of the trial. After granting informed consent, they had pretreatment evaluations, during which all antiarrhythmic drug treatment was discontinued. This evaluation included a patient history, physical examination, 12-lead electrocardiogram, roentgenogram of the chest, ophthalmologic examination, and measurement of left ventricular function by radionuclide ventriculography or, when indicated, contrast angiography. Twenty-four hour ambulatory electrocardiographic recordings, taken after a clearance from previous antiarrhythmic treatment involving at least five drug half-lives, were repeated during treatment with the highest tolerated dose of flecainide. All tapes were analyzed at a central computerized facility (Cardio Data Systems, Haddonfield, New Jersey).

Flecainide treatment was then begun orally at an initial dosage of 100 mg every 12 hours. If the drug was well tolerated but ventricular ectopy persisted, the dosage was increased in 100-mg/d increments every 2 to 4 days. For the patients enrolled in the study during the first year, the maximum daily dose was limited to 600 mg. The administrators of the drug decreased this limit to 400 mg for all patients enrolled in 1983 and 1984 because of proarrhythmic effects that occurred during treat-

▶ From Jewish Hospital at Washington University Medical Center, St. Louis, Missouri, Medical College of Wisconsin Hospitals, Milwaukee, Wisconsin, and Hermann Hospital at the University of Texas Medical School, Houston, Texas.

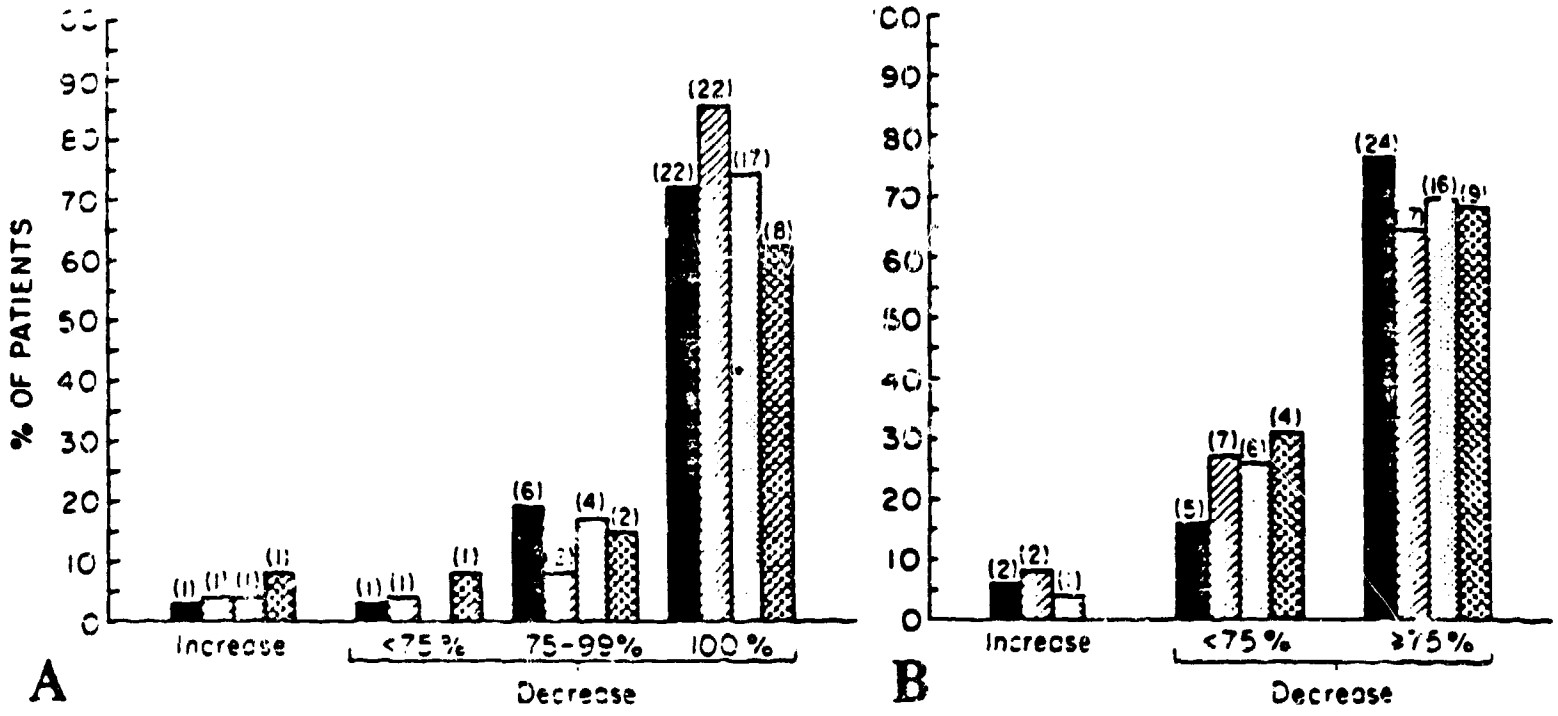

Figure 1. Percentage of patients, compared with baseline, who showed reductions in ventricular tachycardia events (*panel A*) and premature ventricular complexes (*panel B*) on 24-hour ambulatory electrocardiographic recordings. Values given for 31 patients at discharge (*solic bars*), 26 patients at 3 months (*hatched bars*), 23 patients at 6 months (*dotted bars*), and 13 patients at 12 months (*cross-hatched bars*)

ment with higher doses. In addition, an interval of 4 days was required between each dose increment. On long-term treatment, only one of the patients reported here received dosages of higher than 400 mg/d. Twelve-lead electrocardiograms were recorded on 25-mm/s paper speed and the PR, QRS, and QTc intervals were measured using calipers before each increase in dosage. Trough plasma flecainide levels were determined in 26 patients before each dosage increment and at the maximum tolerated dose before discharge from the hospital by the laboratory of S. F. Chang (Riker Laboratories, Inc., St. Paul, Minnesota). Details of this liquid chromatographic method have been published (8-10). If patients had [illegible] histories of exercise-induced or exercise-exacerbated ar[illegible]mia, they were given symptom-limited treadmill tests be[illegible]scharge from the hospital to confirm the effectiveness of treatment during exercise.

Long-term treatment with flecainide was offered after a 75% or greater suppression of episodes of nonsustained ventricular tachycardia, as determined on predischarge ambulatory electrocardiographic [illegible] (that for 24-hour ambulatory electrocardiographic monitoring, ventricular tachycardia was defined as more than three consecutive ventricular complexes); a 75% or greater measured reduction in premature ventricular complexes; and good subjective tolerance of the drug in doses found effective according to these criteria.

Patients discharged on flecainide were seen regularly in outpatient clinics for long-term monitoring of drug safety and efficacy and for verification of compliance. Efficacy was verified by patient questioning and repeating 24-hour ambulatory electrocardiographic monitoring 1 month after discharge and thereafter at 3-month intervals (Figure 1). A 12-lead electrocardiogram and blood specimens were obtained at each visit for determination of hematologic and biochemical profiles. Compliance was verified by measurement of plasma drug levels. Follow-up radionuclide angiograms were ordered for patients who were in New York Heart Association class III or IV or for patients who developed signs or symptoms of congestive heart failure.

DATA ANALYSIS

We stored data in a statistical analysis system database using the Washington University mainframe computer system (IBM, Poughkeepsie, New York) and analyzed data using *t*-tests. Pooled values are reported as mean ± SD.

Results

Of the 32 patients in the study, 30 completed the in-hospital phase of the trial and received flecainide after discharge from the hospital. Flecainide treatment was discontinued for early ineffectiveness in 1 patient and because of a proarrhythmic effect in 1 (*see* below). The dosage at discharge ranged from 200 to 500 mg/d (mean, 315 ± 76). Trough plasma flecainide levels, measured in 26 patients, ranged from 203 to 1121 ng/mL (mean, 567 ± 254).

CHANGES ON ELECTROCARDIOGRAMS

Comparison of 12-lead electrocardiographic recordings before and during flecainide treatment showed a statistically significant increase in the mean PR interval from 172 ± 5 ms to 203 ± 6 ms ($p = 0.0001$), and in QRS duration from 98 ± 3 ms to 118 ± 6 ms ($p = 0.0003$). No statistically significant change in heart rate or corrected QT interval occurred during flecainide treatment. These electrocardiographic changes are summarized in Table 1.

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

We analyzed baseline and predischarge 24-hour ambulatory electrocardiograms in 31 patients (Table 2). Total suppression of ventricular tachycardia (more than three consecutive ventricular complexes) was achieved in 22 patients, and a greater than 75% suppression was achieved in 6 patients. One patient had a marked reduction in premature ventricular complexes and a less than 75% suppression of episodes of ventricular tachycardia, but remained in the trial because of the marked shortening and slowing of the runs. One patient left the trial

because of a marked increase both in premature ventricular complexes and in the number of episodes of ventricular tachycardia that occurred during treatment. One patient who had had previous electrocardiographic documentation of ventricular tachycardia, but no episodes of ventricular tachycardia recorded on the baseline or predischarge study ambulatory electrocardiograms, had a more than 85% reduction in premature ventricular complexes. Flecainide decreased the number of premature ventricular complexes by 75% or more in 24 patients, and by less than 75% in 5 additional patients. These findings and a comparison of the observations on ambulatory electrocardiograms obtained during long-term treatment are shown in Figure 1.

ADVERSE EFFECTS

Twenty-three patients had cardiac or noncardiac adverse effects during the in-hospital phase of the trial (Table 3). The commonest cardiac adverse effect was worsening of preexisting congestive heart failure, which occurred in three patients. This effect was controlled in each patient by an adjustment in dose of diuretics. These patients had left ventricular ejection fractions before treatment of 23%, 23%, and 36%, respectively. New rate-related left bundle branch block was seen in three patients during flecainide treatment. One patient had a proarrhythmic response consisting of an eightfold increase in the number of ventricular tachycardia episodes, a sixfold increase in the number of premature ventricular complexes over 24 hours, and the development of nonsustained ventricular tachycardia during an exercise test, which had not been seen before treatment with flecainide.

The commonest noncardiac side effect, blurring of vision, occurred in 14 patients and was associated with dizziness or headache in 5 patients. Other less frequent side

Table 1. Changes in Electrocardiographic Recordings in 32 Patients Given Flecainide for Nonsustained Ventricular Tachycardia*

	Baseline*	After Treatment*	*p* Value
Heart rate, *beats/min*	72 ± 3	69 ± 2	NS
PR interval, *ms*	172 ± 5	203 ± 6	0.0001
QRS duration, *ms*	98 ± 3	118 ± 6	0.0003
QTc interval, *ms*	456 ± 9	449 ± 7	NS

* Values expressed as mean ± SD. NS = not significant.

Table 2. Results of 24-Hour Ambulatory Electrocardiographic Monitoring in 32 Patients Given Flecainide for Nonsustained Ventricular Tachycardia

Patient Number	Diagnosis	Before Treatment			After Treatment			Dose	Plasma Level
		Premature Ventricular Complexes	Couplets	Runs*	Premature Ventricular Complexes	Couplets	Runs		
		n			*n*			*mg*	*ng/mL*
1	Coronary artery disease	4364	8	0	558	2	0	200	598
2	Mitral valve prolapse	3041	146	50	1468	0	0	500	986
3	Mitral valve prolapse	7309	283	4	1256	1	0	200	927
4	Coronary artery disease	2555	60	8	10	0	0	300	379
5	Mitral valve prolapse	31 552	5630	71	2486	62	0	300	527
6	Coronary artery disease	9804	5	1	13 225	6	0	200	465
7	Cardiomyopathy	11 602	429	34	2399	56	5	300	279
8	Mitral valve prolapse	28 758	629	29	20 427	5	0	300	883
9	Primary electrical disorder	11 521	108	2	1520	0	0	400	ND†
10	Coronary artery disease	12 966	74	9	2837	8	1	200	203
11	Coronary artery disease	11 121	676	95	964	205	4	300	463
12	Mitral valve prolapse	1909	15	2	119	0	0	300	515
13	Coronary artery disease	20 759	1941	356	885	4	1	300	1121
14	Coronary artery disease	15 647	0	5	6	0	0	400	ND
15	Coronary artery disease	1811	68	2	43	0	0	400	ND
16	Coronary artery disease	33 303	2452	291	15	0	0	400	ND
17	Coronary artery disease	4444	612	366	550	0	0	300	478
18	Coronary artery disease	2701	208	3	303	10	0	200	851
19	Coronary artery disease	49 269	3136	3280	8689	94	1	300	333
20	Coronary artery disease	35 403	5034	109	1642	30	0	300	369
21	Coronary artery disease	51 137	3040	434	126	0	0	200	ND
22	Coronary artery disease	13 746	2028	190	43	0	0	300	400
23	Coronary artery disease	31 476	1938	197	23 428	144	16	400	494
24	Cardiomyopathy	3600	100	16	97	14	11	300	747
25	Cardiomyopathy	6865	194	12	37 274	690	94	300	273
26	Coronary artery disease	2566	252	22	139	0	0	400	426
27	Coronary artery disease	8496	224	2	12	2	0	400	ND
28	Coronary artery disease	11 112	366	7	51	0	0	300	490
29	Rheumatic valvular disease	13 420	1160	64	1070	112	0	400	1052
30	Mitral valve prolapse	2666	1028	40	...	...	...	400	416
31	Mitral valve prolapse	4827	208	3	14	0	0	300	458
32	Coronary artery disease	28 864	2518	22	14 165	16	0	300	622

* Three consecutive ventricular complexes.
† ND = not determined

Table 3. Adverse Effects of Flecainide in 32 Patients with Nonsustained Ventricular Tachycardia

	Patients*
	n
Proarrhythmia	1
Congestive heart failure	3
Rate-related left bundle branch block	3
Blurring of vision	14
Headache	4
Dizziness	5
Weakness	1
Fatigue	1
Nausea	2
Insomnia	1
Vertigo	1
Tinnitus	1

* Of the 32 patients, 23 had adverse effects and treatment was discontinued because of adverse effects in 1. Note that the same patient may have had more than one side effect

effects were nausea, insomnia, weakness, fatigue, vertigo, and tinnitus. None of these noncardiac side effects were severe enough to warrant discontinuation of treatment and they responded to either a decrease in dose of flecainide or a change in drug dispensation from twice to three times a day.

LONG-TERM TREATMENT

Thirty patients completed the in-hospital phase of the trial and received long-term treatment. Of the 30 patients who entered the outpatient phase of the study, 22 remained in the trial at follow-ups ranging from 4 to 28 months (mean, 13 ± 7). The courses of patients during the in-hospital and long-term phases of the treatment are shown in Figure 2. Dosages of flecainide were decreased during follow-up in 5 patients because of recurrent noncardiac side effects. Two of these five patients had undesirably high plasma levels of flecainide (1121 and 1752 ng/mL). Three patients required dosage increases to maintain total suppression of complex forms of ventricular ectopy during ambulatory monitoring. Mean plasma flecainide levels increased from 604 ng/mL to 714 ng/mL in 8 patients who had measurements at discharge from the hospital and 6 months afterwards with no intercurrent change in drug dosage; the change is not statistically significant.

Flecainide treatment was discontinued in one patient at his request after 11 months of successful therapy. Treatment also was discontinued in one patient after 4 months because of persistent chest wall paresthesia, constipation, and impotence. The relationship of these symptoms to the use of flecainide is unclear because some symptoms have persisted after withdrawal of the drug. In one patient, treatment had to be discontinued for late ineffectiveness at 12 months.

Five patients died during the follow-up period. One patient died suddenly after 7 months of treatment, 4 weeks after a 24-hour ambulatory electrocardiogram had shown total suppression of ventricular tachycardia and complex ectopy. Two patients died of acute myocardial infarctions and one patient died on the way to the hospital after an episode of prolonged chest pain. Among the three patients who died after ischemic events, two had histories of recurrent angina pectoris, and one died of hemodynamic consequences of the infarction. The fifth patient who died during flecainide treatment had become critically ill from intractable respiratory insufficiency. The flecainide plasma level had increased from 875 ng/mL 2 weeks earlier to 2306 ng/mL at the time of death, during which time the patient had been receiving a stable dosage of flecainide. The patient died of a combination of intractable respiratory insufficiency and hypotensive ventricular rhythm of 110 beats/min that probably had been caused by toxic amounts of flecainide. None of the patients had any biochemical or hematologic adverse effects during follow-up.

LEFT VENTRICULAR FUNCTION

Of the 32 patients enrolled in the trial, 27 had measurements of left ventricular ejection fraction done before initiation of therapy. Fifteen had left ventricular ejection fractions of 40% or greater, and 12 had fractions of less than 40%. All 12 patients who had ejection fractions of less than 40% were discharged on flecainide, and 4 died during follow-up. One died suddenly, 1 died after a prolonged ischemic episode, 1 died during an acute myocardial infarction, and 1 died of respiratory failure. At a mean follow-up of 12 months, 8 of the patients who had marked left ventricular dysfunction were still receiving flecainide and had significant suppression of ventricular

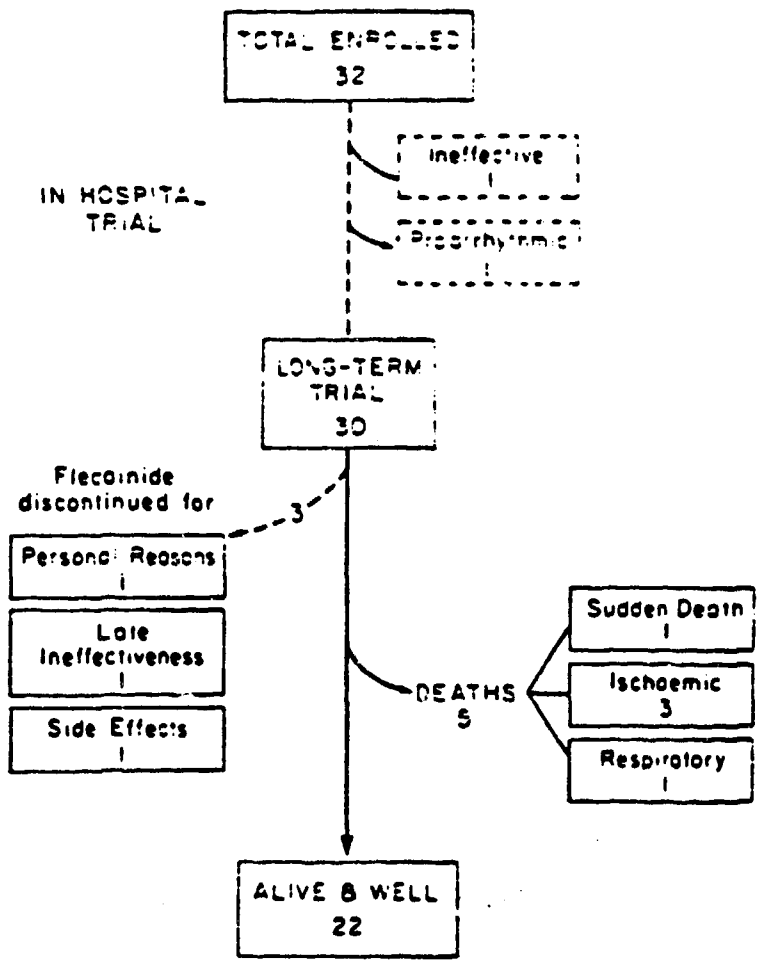

Figure 2. Flow diagram showing the results of in-hospital and long-term trials using flecainide to treat nonsustained ventricular tachycardia (mean follow-up, 13 months; range, 4 to 28).

Table 4. Analysis of Flecainide Treatment in 32 Patients by Diagnosis and Ventricular Function

	Patients		Results of Treatment		
	Total	Discharged on Flecainide	Treatment Discontinued	Eventual Death	Sudden Death
	n				
Diagnosis					
Coronary artery disease	20	20	2	3	1
Other	12	10	1	1	0
Left ventricular ejection fraction					
< 40%	12	12	0	3	1
≥ 40%	15	13	1	0	0
Not measured	5	5	2	1	0

tachycardia. Of the 15 patients who did not have marked left ventricular dysfunction (ejection fraction of 40% or greater), 13 were discharged from the hospital receiving flecainide. One patient from this group had flecainide treatment discontinued during long-term follow-up because of late ineffectiveness, and 12 have remained on treatment with adequate suppression of ventricular tachycardia. None of the patients from this group died. The outcome in relation to left ventricular function is shown in Table 4.

CORONARY ARTERY DISEASE

Of the 32 patients, 20 had coronary artery disease and all were discharged from the hospital receiving flecainide. Four of these patients died (1 suddenly) and the others remained on flecainide, achieving adequate suppression of ventricular tachycardia throughout follow-up. Of the 12 patients who had other diagnoses, 10 were discharged from the hospital receiving flecainide. Treatment was later discontinued in 1 of these patients due to subjective intolerance. One patient who had no coronary artery disease died of intractable respiratory insufficiency and 9 remained on flecainide with adequate suppression of ventricular tachycardia. Results are summarized in Table 4.

Discussion

The limited clinical experience accumulated thus far in the United States with the use of flecainide has shown the drug to be safe and highly effective in suppressing chronic, stable ventricular ectopy in patients who have no advanced organic heart disease (11, 12). The true efficacy and safety of an antiarrhythmic drug, however, can only be measured when it is given to patients at risk who, in general, have overt structural or ischemic heart disease associated with high-grade ventricular ectopy or sustained tachyarrhythmias. The proarrhythmic and myocardial depressant potentials of an antiarrhythmic drug will be reflected best in these patients. Reports from earlier trials of flecainide in high-risk patients raised concerns of an unacceptably high incidence of major proarrhythmic complications (7). Our observations in this group of patients indicate that flecainide can achieve long-term suppression of nonsustained ventricular tachycardia in a high percentage of patients with ischemic or structural heart disease even after several previous unsuccessful antiarrhythmic trials, and even in the presence of significant left ventricular dysfunction. Furthermore, proarrhythmic or other limiting adverse effects occurred infrequently. We believe that the low rate of serious complications in our trial, similar to that seen by others (13), is attributable to our strict adherence to the following rules: treatment was initiated in the hospital; dosage began with no more than 200 mg/d and loading doses were not used; increases in dosage were not made more often than every 4 days; dosages higher than 400 mg/d were not given; and plasma levels higher than 1 μg/mL were avoided. We therefore recommend following these rules when flecainide therapy is initiated in patients who have ventricular arrhythmias associated with advanced organic heart disease.

A negative inotropic effect with worsening of signs and symptoms of congestive heart failure can be an adverse effect from antiarrhythmic therapy and was seen in 3 of our patients. This side effect, which was anticipated on the basis of studies done by Legrand and colleagues (14) and Josephson and colleagues (15), occurred only in the presence of preexisting left ventricular dysfunction and was alleviated after adjustment of standard therapy for congestive heart failure. Flecainide must be used with caution in the treatment of patients who have severely depressed left ventricular function and an unstable cardiac output that causes variations in renal elimination of the drug. This mechanism may have resulted in flecainide accumulating to toxic levels in our patient who died of respiratory insufficiency.

Unlike serious adverse effects, nonlimiting side effects (visual ones, in particular) occurred frequently and required rearrangement of therapy for several patients. Overall, however, the drug was well tolerated on a long-term basis and few patients abandoned the trial because of side effects. Recently, Meinertz and associates (16) reported a long-term increase in plasma concentration of flecainide with no change in total daily dosage. In our study, a small rise in plasma flecainide level was measured in eight patients between discharge from the hospital and 6 months of follow-up, which suggests that even after 4 days of treatment, stable levels may not have been reached in some patients.

LIMITATION OF THE STUDY

Our trial was not controlled because strict comparisons with the effects of other antiarrhythmic agents were not its intent. Thus, our results should not be interpreted as demonstrative of the superior antiarrhythmic activity of

flecainide over other agents. Earlier randomized comparative trials in a low-risk population did, however, show a greater efficacy of flecainide in suppressing ventricular ectopy compared with that derived from both quinidine and disopyramide (12, 17).

A few patients included in this report had three or fewer episodes of ventricular tachycardia during baseline electrocardiographic monitoring. The short- and long-term elimination of nonsustained ventricular tachycardia in such patients thus may have been a reflection of mere spontaneous variability of the arrhythmia. In general, however, these patients had been selected for entry into the study because of frequently recurrent ventricular tachycardia as well as refractoriness to antiarrhythmic treatment. The absence of complex and high-grade ventricular ectopy on ambulatory electrocardiographic recordings during long-term treatment therefore was most likely a reflection of drug effect.

Although we tried to enroll patients who had symptoms, we recognize that suppression of symptoms as an endpoint of treatment in patients who have nonsustained tachyarrhythmias is unreliable and highly subjective, particularly when the trial does not involve controls. Therefore, we preferred to base our assessment of drug effect on 24-hour electrocardiographic measurements. In many of our patients, however, the effective control of arrhythmia was associated with the disappearance of symptoms, particularly palpitations, and these results contributed to the high compliance to, and acceptance of, long-term treatment.

Although one patient who received long-term treatment with flecainide died suddenly, this trial does not contribute information on the value of antiarrhythmic therapy in patients who have organic heart disease and a history of nonsustained ventricular tachyarrhythmias; only a large-scale placebo-controlled study could resolve this issue. In the meantime, if treatment is indicated for a patient who has nonsustained ventricular tachycardia, flecainide represents one of six choices available to the clinician. Because of its potentially serious side effects, we urge caution in its use, particularly in the early phase of treatment in patients who have underlying myocardial disease.

CONCLUSIONS

Results of this study indicate that flecainide can provide effective long-term suppression of nonsustained ventricular tachycardia in almost 70% of patients with organic heart disease. Adverse effects occurred in several patients initially, but tended to be nonlimiting. Aggravation of heart failure occurred in 9% of patients. Although proarrhythmic complications occurred infrequently, we recommend the initiation of treatment with flecainide in the hospital where the rhythm can be monitored. In addition, plasma drug levels should be surveyed closely both during the initial phase of treatment and during long-term follow-up.

▶ Requests for reprints should be addressed to Rodolphe Ruffy, M.D., Arrhythmia Service, Jewish Hospital at Washington University Medical Center, 216 S. Kingshighway, St. Louis, MO 63110.

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DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ACUTE MYOCARDIAL INFARCTION
This patient was started on flecainide 200 mg daily as part of a study for control of non-sustained ventricular tachycardia. The dose may have been increased but the maximum allowed in the study was 400 mg daily. This patient had a history of coronary artery disease and angina. During the study, the patient died of acute myocardial infarction.

Literature report: "Flecainide in the treatment of nonsustained ventricular tachycardia"; Annals of Internal Medicine 1986, 105, 493-498.

13. RELEVANT TESTS/LABORATORY DATA
None.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200-400 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
7/22/87

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☒ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Flecainide in the Treatment of Nonsustained Ventricular Tachycardia

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Thirty-two patients received flecainide acetate for nonsustained ventricular tachycardia after having had unsuccessful treatment with a mean of four antiarrhythmic drugs. The mean left ventricular ejection fraction was 41% in 27. Thirty-one patients had organic heart disease, and 22 patients had arrhythmia-related symptoms. Total suppression of ventricular tachycardia occurred in 22 patients. Thirty patients were discharged from the hospital receiving flecainide at a mean (± SD) dosage of 315 ± 76 mg/d and 26 of these patients attained a mean trough plasma drug level of 567 ± 254 ng/mL. One patient had proarrhythmia and 3 had worsening of heart failure. Twenty-two patients remained in the trial for a mean follow-up of 13 ± 7 months. Five patients died (1 suddenly) during the follow-up period. Our data indicate that flecainide suppresses refractory nonsustained ventricular tachycardia in 69% of patients who have organic heart disease. Serious adverse effects were minimized by initiation of treatment in the hospital and careful surveillance of electrocardiograms and plasma drug levels.

FLECAINIDE ACETATE is a new drug classified generally as a Ic antiarrhythmic agent because of its pronounced negative dromotropic effect on cardiac tissues in the absence of marked alterations in repolarization (1). A few cases of its use in treating recurrent sustained and nonsustained ventricular tachycardia have been reported, but clinical experience with this drug in the United States remains limited (2-7). We describe the combined experience of three arrhythmia centers that have used flecainide to treat patients with nonsustained ventricular tachycardia who had had previous unsuccessful treatment with other antiarrhythmic drugs.

We examined 32 patients who were part of a larger group enrolled in a trial of flecainide for the treatment of ventricular tachyarrhythmias. The results of this trial in patients who had recurrent, sustained ventricular tachycardia or out-of-hospital cardiac arrest have been presented in a separate report (3).

Patients and Methods

Seventeen men and 15 women aged 32 to 76 years (mean ± SD, 56 ± 14) who had recurrent, nonsustained ventricular tachycardia participated in the study between 1 January 1982 and 31 December 1984 at the Jewish Hospital at Washington University in St. Louis, the Medical College of Wisconsin Hospitals in Milwaukee, and Hermann Hospital at the University of Texas Medical School in Houston.

Nonsustained ventricular tachycardia was defined as six or more consecutive ventricular complexes occurring at a rate of more than 100 beats/min, lasting less than 30 seconds, and not requiring artificial termination because of hemodynamic instability. Twenty patients had coronary artery disease that was diagnosed by electrocardiographic findings of infarction in 6 and by angiographic documentation of coronary stenoses in 14. Fifteen patients had sustained myocardial infarctions lasting from 1 to 180 months (mean, 48 ± 55) before entry into trial and 5 patients had stable angina pectoris. Seven patients had mitral valve prolapse, 3 had congestive cardiomyopathy, 1 had rheumatic valvular disease, and 1 had no structural heart disease. Twenty-two of these patients had symptoms believed to be arrhythmia related. The commonest symptom, palpitation, occurred in 18 patients. Other presenting symptoms of syncope, near syncope, and shortness of breath correlated with recorded arrhythmias in 4 patients. Previous unsuccessful antiarrhythmic therapy included the use of one to eight drugs (mean, four). Failure of previous antiarrhythmic therapy was due to intolerance or ineffectiveness as determined by clinical criteria that included the use of telemetry monitoring and ambulatory electrocardiograms. When patients were referred after several unsuccessful drug trials, attempts by the investigators to confirm intolerance or inefficacy of previously administered drugs generally were not made unless they thought inappropriate doses had been given before referral. Left ventricular ejection fraction measured in 27 patients ranged from 18% to 60% (mean, 41% ± 13%).

Patients who had PR intervals of more than 0.28 seconds, second or higher degree atrioventricular blocks, creatinine clearances of less than 20 mL/min, or digitalis-induced arrhythmias, and patients who were pregnant or of childbearing potential were excluded from study participation. Efforts were made to avoid the concomitant use of calcium channel blockers or the enrollment of patients totally dependent on artificial pacing. In all patients, flecainide was the only antiarrhythmic drug used.

STUDY PROTOCOL

The patients were admitted to a telemetry unit after having had electrocardiographic determination of nonsustained ventricular tachycardia, and were continuously monitored throughout the hospital phase of the trial. After granting informed consent, they had pretreatment evaluations, during which all antiarrhythmic drug treatment was discontinued. This evaluation included a patient history, physical examination, 12-lead electrocardiogram, roentgenogram of the chest, ophthalmologic examination, and measurement of left ventricular function by radionuclide ventriculography or, when indicated, contrast angiography. Twenty-four hour ambulatory electrocardiographic recordings, taken after a clearance from previous antiarrhythmic treatment involving at least five drug half-lives, were repeated during treatment with the highest tolerated dose of flecainide. All tapes were analyzed at a central computerized facility (Cardio Data Systems, Haddonfield, New Jersey).

Flecainide treatment was then begun orally at an initial dosage of 100 mg every 12 hours. If the drug was well tolerated but ventricular ectopy persisted, the dosage was increased in 100-mg/d increments every 2 to 4 days. For the patients enrolled in the study during the first year, the maximum daily dose was limited to 600 mg. The administrators of the drug decreased this limit to 400 mg for all patients enrolled in 1983 and 1984 because of proarrhythmic effects that occurred during treat-

▶ From Jewish Hospital at Washington University Medical Center, St. Louis, Missouri, Medical College of Wisconsin Hospitals, Milwaukee, Wisconsin; and Hermann Hospital at the University of Texas Medical School, Houston, Texas.

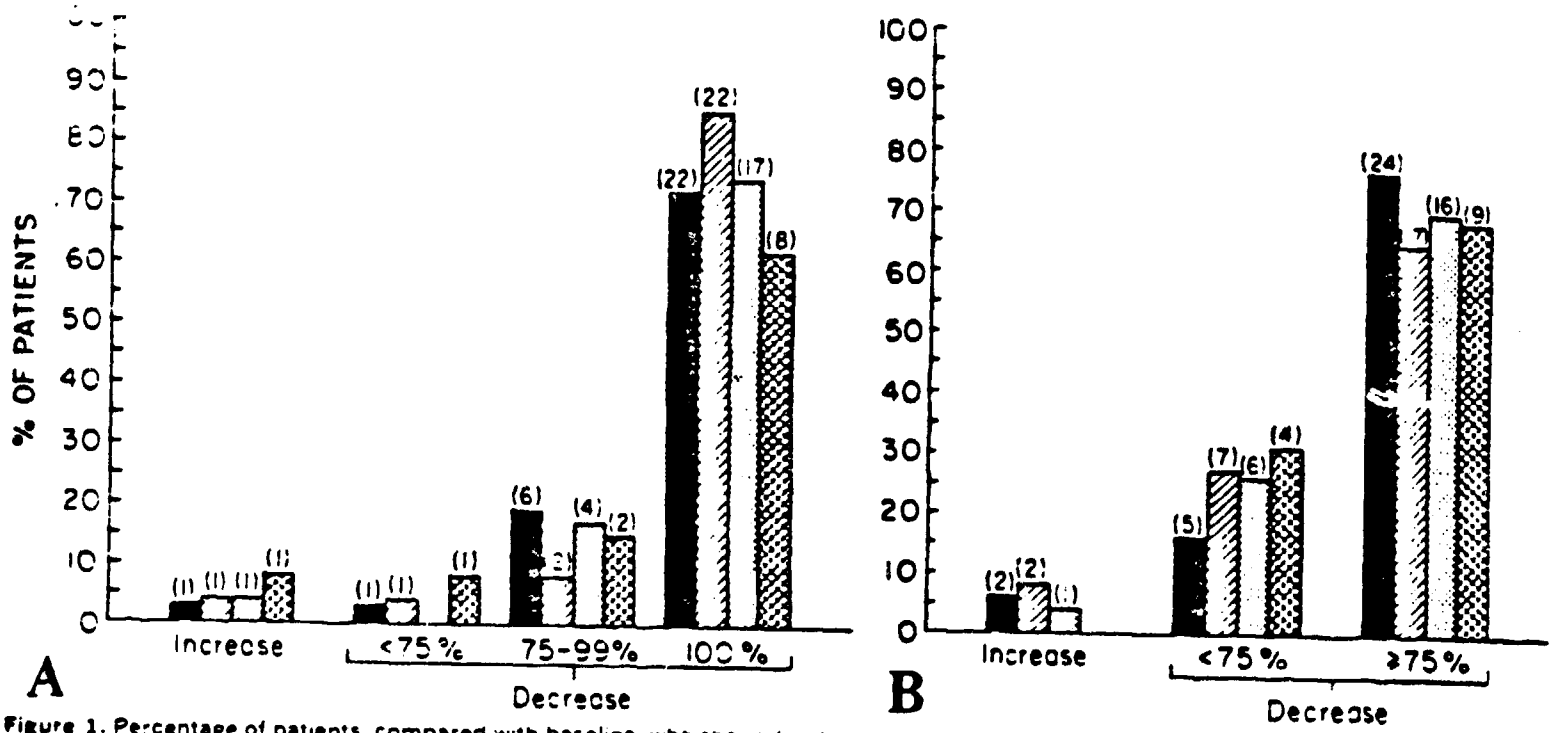

Figure 1. Percentage of patients, compared with baseline, who showed reductions in ventricular tachycardia events (*panel A*) and premature ventricular complexes (*panel B*) on 24-hour ambulatory electrocardiographic recordings. Values given for 31 patients at discharge (*solid bars*), 26 patients at 3 months (*hatched bars*), 23 patients at 6 months (*dotted bars*), and 13 patients at 12 months (*cross-hatched bars*).

ment with higher doses. In addition, an interval of 4 days was required between each dose increment. Only one of the patients reported here received dosages of higher than 400 mg/d. Twelve-lead electrocardiograms were recorded on 25-mm/s paper speed and the PR, QRS, and QTc intervals were measured using calipers before each increase in dosage. Trough plasma flecainide levels were determined in 26 patients before each dosage increment and at the maximum tolerated dose before discharge from the hospital by the laboratory of S. F. Chang (Riker Laboratories, Inc., St. Paul, Minnesota). Details of this liquid chromatographic method have been published (8-10). If patients had had histories of exercise-induced or exercise-exacerbated arrhythmia, they were given symptom-limited treadmill tests before discharge from the hospital to confirm the effectiveness of treatment during exercise.

Long-term treatment with flecainide was offered after a 75% or greater suppression of episodes of nonsustained ventricular tachycardia as determined by predischarge ambulatory electrocardiographic recordings (note that for 24-hour ambulatory electrocardiographic monitoring, ventricular tachycardia was defined as more than three consecutive ventricular complexes); a 75% or greater measured reduction in premature ventricular complexes, and good subjective tolerance of the drug in doses found effective according to these criteria.

Patients discharged on flecainide were seen regularly in outpatient clinics for long-term monitoring of drug safety and efficacy and for verification of compliance. Efficacy was verified by patient questioning and repeating 24-hour ambulatory electrocardiographic monitoring 1 month after discharge and thereafter at 3-month intervals (Figure 1). A 12-lead electrocardiogram and blood specimens were obtained at each visit for determination of hematologic and biochemical profiles. Compliance was verified by measurement of plasma drug levels. Follow-up radionuclide angiograms were ordered for patients who were in New York Heart Association class III or IV or for patients who developed signs or symptoms of congestive heart failure.

DATA ANALYSIS

We stored data in a statistical analysis system database using the Washington University mainframe computer system (IBM, Poughkeepsie, New York) and analyzed data using *t*-tests. Pooled values are reported as mean ± SD.

Results

Of the 32 patients in the study, 30 completed the in-hospital phase of the trial and received flecainide after discharge from the hospital. Flecainide treatment was discontinued for early ineffectiveness in 1 patient and because of a proarrhythmic effect in 1 (*see* below). The dosage at discharge ranged from 200 to 500 mg/d (mean, 315 ± 76). Trough plasma flecainide levels, measured in 26 patients, ranged from 203 to 1121 ng/mL (mean, 567 ± 254).

CHANGES ON ELECTROCARDIOGRAMS

Comparison of 12-lead electrocardiographic recordings before and during flecainide treatment showed a statistically significant increase in the mean PR interval from 172 ± 5 ms to 203 ± 6 ms ($p = 0.0001$), and in QRS duration from 98 ± 3 ms to 118 ± 6 ms ($p = 0.0003$). No statistically significant change in heart rate or corrected QT interval occurred during flecainide treatment. These electrocardiographic changes are summarized in Table 1.

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

We analyzed baseline and predischarge 24-hour ambulatory electrocardiograms in 31 patients (Table 2). Total suppression of ventricular tachycardia (more than three consecutive ventricular complexes) was achieved in 22 patients, and a greater than 75% suppression was achieved in 6 patients. One patient had a marked reduction in premature ventricular complexes and a less than 75% suppression of episodes of ventricular tachycardia, but remained in the trial because of the marked shortening and slowing of the runs. One patient left the trial

because of a marked increase both in premature ventricular complexes and in the number of episodes of ventricular tachycardia that occurred during treatment. One patient who had had previous electrocardiographic documentation of ventricular tachycardia, but no episodes of ventricular tachycardia recorded on the baseline or predischarge study ambulatory electrocardiograms, had a more than 85% reduction in premature ventricular complexes. Flecainide decreased the number of premature ventricular complexes by 75% or more in 24 patients, and by less than 75% in 5 additional patients. These findings and a comparison of the observations on ambulatory electrocardiograms obtained during long-term treatment are shown in Figure 1.

ADVERSE EFFECTS

Twenty-three patients had cardiac or noncardiac adverse effects during the in-hospital phase of the trial (Table 3). The commonest cardiac adverse effect was worsening of preexisting congestive heart failure, which occurred in three patients. This effect was controlled in each patient by an adjustment in dose of diuretics. These patients had left ventricular ejection fractions before treatment of 23%, 23%, and 36%, respectively. New rate-related left bundle branch block was seen in three patients during flecainide treatment. One patient had a proarrhythmic response consisting of an eightfold increase in the number of ventricular tachycardia episodes, a sixfold increase in the number of premature ventricular complexes over 24 hours, and the development of nonsustained ventricular tachycardia during an exercise test, which had not been seen before treatment with flecainide.

The commonest noncardiac side effect, blurring of vision, occurred in 14 patients and was associated with dizziness or headache in 5 patients. Other less frequent side

Table 1. Changes in Electrocardiographic Recordings in 32 Patients Given Flecainide for Nonsustained Ventricular Tachycardia*

	Baseline*	After Treatment*	*p* Value
Heart rate, *beats/min*	72 ± 3	69 ± 2	NS
PR interval, *ms*	172 ± 5	203 ± 6	0.0001
QRS duration, *ms*	98 ± 3	118 ± 6	0.0003
QTc interval, *ms*	456 ± 9	449 ± 7	NS

* Values expressed as mean ± SD. NS = not significant.

Table 2. Results of 24-Hour Ambulatory Electrocardiographic Monitoring in 32 Patients Given Flecainide for Nonsustained Ventricular Tachycardia

Patient Number	Diagnosis	Before Treatment			After Treatment			Dose	Plasma Level
		Premature Ventricular Complexes	Couplets	Runs*	Premature Ventricular Complexes	Couplets	Runs		
		n			*n*			*mg*	*ng/mL*
1	Coronary artery disease	4764	8	0	558	2	0	200	598
2	Mitral valve prolapse	3041	146	50	1468	0	0	500	986
3	Mitral valve prolapse	7309	283	4	1256	1	0	200	927
4	Coronary artery disease	2555	60	8	10	0	0	300	379
5	Mitral valve prolapse	31 552	5630	71	2486	62	0	300	527
6	Coronary artery disease	9804	5	1	13 225	6	0	200	465
7	Cardiomyopathy	11 602	429	34	2399	56	5	300	279
8	Mitral valve prolapse	28 258	629	29	20 427	5	0	300	883
9	Primary electrical disorder	11 521	108	2	1520	0	0	400	ND†
10	Coronary artery disease	12 966	74	9	2837	8	1	200	203
11	Coronary artery disease	11 121	676	95	964	205	4	300	463
12	Mitral valve prolapse	1909	15	2	119	0	0	300	515
13	Coronary artery disease	20 759	1941	356	885	4	1	300	1121
14	Coronary artery disease	15 647	0	5	6	0	0	400	ND
15	Coronary artery disease	1811	68	2	43	0	0	400	ND
16	Coronary artery disease	33 303	2452	291	15	0	0	400	ND
17	Coronary artery disease	4444	612	366	550	0	0	300	478
18	Coronary artery disease	2701	208	3	303	10	0	200	851
19	Coronary artery disease	49 269	3136	3280	8689	94	1	300	333
20	Coronary artery disease	35 403	5034	109	1642	30	0	300	369
21	Coronary artery disease	51 137	3040	434	126	0	0	200	ND
22	Coronary artery disease	13 746	2028	190	43	0	0	300	400
23	Coronary artery disease	31 476	1938	197	23 428	144	16	400	494
24	Cardiomyopathy	3600	100	16	97	14	11	300	747
25	Cardiomyopathy	6865	194	12	37 274	690	94	300	273
26	Coronary artery disease	2566	252	22	139	0	0	400	426
27	Coronary artery disease	8496	224	2	12	2	0	400	ND
28	Coronary artery disease	11 112	366	7	51	0	0	300	490
29	Rheumatic valvular disease	13 420	1160	64	1070	112	0	400	1052
30	Mitral valve prolapse	2666	1028	40	. . .	. .	. . .	400	416
31	Mitral valve prolapse	4827	208	3	14	0	0	300	458
32	Coronary artery disease	28 864	2518	22	14 165	16	0	300	622

* Three consecutive ventricular complexes.
† ND = not determined

Table 3. Adverse Effects of Flecainide in 32 Patients with Nonsustained Ventricular Tachycardia

	Patients*
	n
Proarrhythmia	1
Congestive heart failure	3
Rate-related left bundle branch block	3
Blurring of vision	14
Headache	4
Dizziness	5
Weakness	1
Fatigue	1
Nausea	2
Insomnia	1
Vertigo	1
Tinnitus	1

* Of the 32 patients, 23 had adverse effects and treatment was discontinued because of adverse effects in 1. Note that the same patient may have had more than one side effect.

effects were nausea, insomnia, weakness, fatigue, vertigo, and tinnitus. None of these noncardiac side effects were severe enough to warrant discontinuation of treatment and they responded to either a decrease in dose of flecainide or a change in drug dispensation from twice to three times a day.

LONG-TERM TREATMENT

Thirty patients completed the in-hospital phase of the trial and received long-term treatment. Of the 30 patients who entered the outpatient phase of the study, 22 remained in the trial at follow-ups ranging from 4 to 28 months (mean, 13 ± 7). The courses of patients during the in-hospital and long-term phases of the treatment are shown in Figure 2. Dosages of flecainide were decreased during follow-up in 5 patients because of recurrent noncardiac side effects. Two of these five patients had undesirably high plasma levels of flecainide (1121 and 1752 ng/mL). Three patients required dosage increases to maintain total suppression of complex forms of ventricular ectopy during ambulatory monitoring. Mean plasma flecainide levels increased from 604 ng/mL to 714 ng/mL in 8 patients who had measurements at discharge from the hospital and 6 months afterwards with no intercurrent change in drug dosage; the change is not statistically significant.

Flecainide treatment was discontinued in one patient at his request after 11 months of successful therapy. Treatment also was discontinued in one patient after 4 months because of persistent chest wall paresthesia, constipation, and impotence. The relationship of these symptoms to the use of flecainide is unclear because some symptoms have persisted after withdrawal of the drug. In one patient, treatment had to be discontinued for late ineffectiveness at 12 months.

Five patients died during the follow-up period. One patient died suddenly after 7 months of treatment, 4 weeks after a 24-hour ambulatory electrocardiogram had shown total suppression of ventricular tachycardia and complex ectopy. Two patients died of acute myocardial infarctions and one patient died on the way to the hospital after an episode of prolonged chest pain. Among the three patients who died after ischemic events, two had histories of recurrent angina pectoris, and one died of hemodynamic consequences of the infarction. The fifth patient who died during flecainide treatment had become critically ill from intractable respiratory insufficiency. The flecainide plasma level had increased from 875 ng/mL 2 weeks earlier to 2306 ng/mL at the time of death, during which time the patient had been receiving a stable dosage of flecainide. The patient died of a combination of intractable respiratory insufficiency and hypotensive ventricular rhythm of 110 beats/min that probably had been caused by toxic amounts of flecainide. None of the patients had any biochemical or hematologic adverse effects during follow-up.

LEFT VENTRICULAR FUNCTION

Of the 32 patients enrolled in the trial, 27 had measurements of left ventricular ejection fraction done before initiation of therapy. Fifteen had left ventricular ejection fractions of 40% or greater, and 12 had fractions of less than 40%. All 12 patients who had ejection fractions of less than 40% were discharged on flecainide, and 4 died during follow-up. One died suddenly, 1 died after a prolonged ischemic episode, 1 died during an acute myocardial infarction, and 1 died of respiratory failure. At a mean follow-up of 12 months, 8 of the patients who had marked left ventricular dysfunction were still receiving flecainide and had significant suppression of ventricular

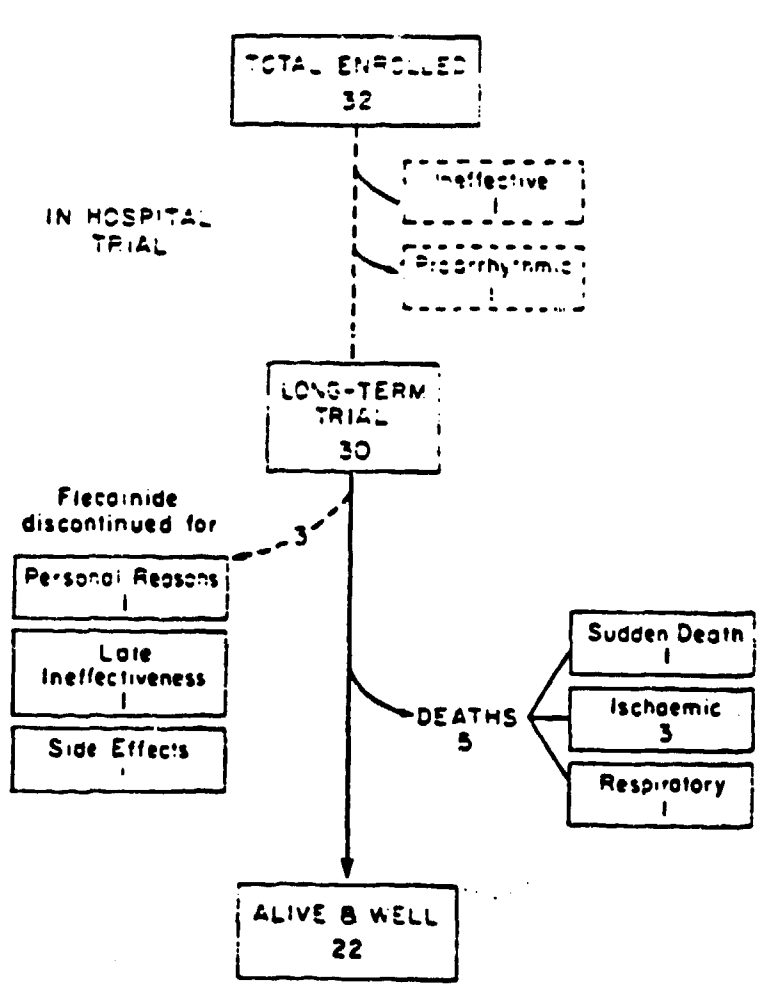

Figure 2. Flow diagram showing the results of in-hospital and long-term trials using flecainide to treat nonsustained ventricular tachycardia (mean follow-up, 13 months; range, 4 to 28).

Table 4. Analysis of Flecainide Treatment in 32 Patients by Diagnosis and Ventricular Function

	Patients		Results of Treatment		
	Total	Discharged on Flecainide	Treatment Discontinued	Eventual Death	Sudden Death
	n				
Diagnosis					
Coronary artery disease	20	20	2	3	1
Other	12	10	1	1	0
Left ventricular ejection fraction					
< 40%	12	12	0	3	1
≥ 40%	15	13	1	0	0
Not measured	5	5	2	1	0

tachycardia. Of the 15 patients who did not have marked left ventricular dysfunction (ejection fraction of 40% or greater), 13 were discharged from the hospital receiving flecainide. One patient from this group had flecainide treatment discontinued during long-term follow-up because of late ineffectiveness, and 12 have remained on treatment with adequate suppression of ventricular tachycardia. None of the patients from this group died. The outcome in relation to left ventricular function is shown in Table 4.

CORONARY ARTERY DISEASE

Of the 32 patients, 20 had coronary artery disease and all were discharged from the hospital receiving flecainide. Four of these patients died (1 suddenly) and the others remained on flecainide, achieving adequate suppression of ventricular tachycardia throughout follow-up. Of the 12 patients who had other diagnoses, 10 were discharged from the hospital receiving flecainide. Treatment was later discontinued in 1 of these patients due to subjective intolerance. One patient who had no coronary artery disease died of intractable respiratory insufficiency and 9 remained on flecainide with adequate suppression of ventricular tachycardia. Results are summarized in Table 4.

Discussion

The limited clinical experience accumulated thus far in the United States with the use of flecainide has shown the drug to be safe and highly effective in suppressing chronic, stable ventricular ectopy in patients who have no advanced organic heart disease (11, 12). The true efficacy and safety of an antiarrhythmic drug, however, can only be measured when it is given to patients at risk who, in general, have overt structural or ischemic heart disease associated with high-grade ventricular ectopy or sustained tachyarrhythmias. The proarrhythmic and myocardial depressant potentials of an antiarrhythmic drug will be reflected best in these patients. Reports from earlier trials of flecainide in high-risk patients raised concerns of an unacceptably high incidence of major proarrhythmic complications (7). Our observations in this group of patients indicate that flecainide can achieve long-term suppression of nonsustained ventricular tachycardia in a high percentage of patients with ischemic or structural heart disease even after several previous unsuccessful antiarrhythmic trials, and even in the presence of significant left ventricular dysfunction. Furthermore, proarrhythmic or other limiting adverse effects occurred infrequently. We believe that the low rate of serious complications in our trial, similar to that seen by others (13), is attributable to our strict adherence to the following rules: treatment was initiated in the hospital; dosage began with no more than 200 mg/d and loading doses were not used; increases in dosage were not made more often than every 4 days; dosages higher than 400 mg/d were not given; and plasma levels higher than 1 μg/mL were avoided. We therefore recommend following these rules when flecainide therapy is initiated in patients who have ventricular arrhythmias associated with advanced organic heart disease.

A negative inotropic effect with worsening of signs and symptoms of congestive heart failure can be an adverse effect from antiarrhythmic therapy and was seen in 3 of our patients. This side effect, which was anticipated on the basis of studies done by Legrand and colleagues (14) and Josephson and colleagues (15), occurred only in the presence of preexisting left ventricular dysfunction and was alleviated after adjustment of standard therapy for congestive heart failure. Flecainide must be used with caution in the treatment of patients who have severely depressed left ventricular function and an unstable cardiac output that causes variations in renal elimination of the drug. This mechanism may have resulted in flecainide accumulating to toxic levels in our patient who died of respiratory insufficiency.

Unlike serious adverse effects, nonlimiting side effects (visual ones, in particular) occurred frequently and required rearrangement of therapy for several patients. Overall, however, the drug was well tolerated on a long-term basis and few patients abandoned the trial because of side effects. Recently, Meinertz and associates (16) reported a long-term increase in plasma concentration of flecainide with no change in total daily dosage. In our study, a small rise in plasma flecainide level was measured in eight patients between discharge from the hospital and 6 months of follow-up, which suggests that even after 4 days of treatment, stable levels may not have been reached in some patients.

LIMITATION OF THE STUDY

Our trial was not controlled because strict comparisons with the effects of other antiarrhythmic agents were not its intent. Thus, our results should not be interpreted as demonstrative of the superior antiarrhythmic activity of

flecainide over other agents. Earlier randomized comparative trials in a low-risk population did, however, show a greater efficacy of flecainide in suppressing ventricular ectopy compared with that derived from both quinidine and disopyramide (12, 17).

A few patients included in this report had three or fewer episodes of ventricular tachycardia during baseline electrocardiographic monitoring. The short- and long-term elimination of nonsustained ventricular tachycardia in such patients thus may have been a reflection of mere spontaneous variability of the arrhythmia. In general, however, these patients had been selected for entry into the study because of frequently recurrent ventricular tachycardia as well as refractoriness to antiarrhythmic treatment. The absence of complex and high-grade ventricular ectopy on ambulatory electrocardiographic recordings during long-term treatment therefore was most likely a reflection of drug effect.

Although we tried to enroll patients who had symptoms, we recognize that suppression of symptoms as an endpoint of treatment in patients who have nonsustained tachyarrhythmias is unreliable and highly subjective, particularly when the trial does not involve controls. Therefore, we preferred to base our assessment of drug effect on 24-hour electrocardiographic measurements. In many of our patients, however, the effective control of arrhythmia was associated with the disappearance of symptoms, particularly palpitations, and these results contributed to the high compliance to, and acceptance of, long-term treatment.

Although one patient who received long-term treatment with flecainide died suddenly, this trial does not contribute information on the value of antiarrhythmic therapy in patients who have organic heart disease and a history of nonsustained ventricular tachyarrhythmias; only a large-scale placebo-controlled study could resolve this issue. In the meantime, if treatment is indicated for a patient who has nonsustained ventricular tachycardia, flecainide represents one of six choices available to the clinician. Because of its potentially serious side effects, we urge caution in its use, particularly in the early phase of treatment in patients who have underlying myocardial disease.

CONCLUSIONS

Results of this study indicate that flecainide can provide effective long-term suppression of nonsustained ventricular tachycardia in almost 70% of patients with organic heart disease. Adverse effects occurred in several patients initially, but tended to be nonlimiting. Aggravation of heart failure occurred in 9% of patients. Although proarrhythmic complications occurred infrequently, we recommend the initiation of treatment with flecainide in the hospital where the rhythm can be monitored. In addition, plasma drug levels should be surveyed closely both during the initial phase of treatment and during long-term follow-up.

▶ Requests for reprints should be addressed to Rodolphe Ruffy, M.D., Arrhythmia Service, Jewish Hospital at Washington University Medical Center, 216 S. Kingshighway, St. Louis, MO 63110.

References

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12.1

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

ORIGINAL

REPORTS

3M

April 8, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Reports
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/dls

Enclosure - [redacted]

Certified Mail P 504 523 605

RECEIVED
APR 22 1987
HFN-110
NATIONAL CENTER FOR DRUGS AND BIOLOGICS

Withdrawn re F. TT-87-124.
4-17

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	69	M	3	2	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ELEVATED LIVER ENZYMES, RENAL FAILURE, CARDIAC ARREST Death
This man, with a history of diabetes and hypertension, was being treated with tocainide 400 mg tid for six weeks. He was experiencing nausea and vomiting which led to hospitalization on 3/14/87. On admission, his liver function tests were normal. The liver was enlarged but without evidence of cirrhosis. Ascites was not present. Tocainide was discontinued and flecainide 200 mg daily was started on 3/17/87. After four doses, the man continued to have nausea and vomiting; flecainide was discontinued and tocainide was restarted. After tocainide was restarted, liver transaminase was found to be elevated. SGOT was elevated to more than 1100; SGPT was slightly elevated. Bilirubin was not significantly

13. RELEVANT TESTS/LABORATORY DATA

Liver function tests were normal while receiving tocainide (6 weeks). Following four doses of flecainide and restarting of tocainide, SGOT was elevated to more than 1100, transaminase was increased, SGPT was slightly elevated, and bilirubin was not significantly affected.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☑ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*: 03/17/87 - 03/18/87

19. THERAPY DURATION: 2 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☑ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☑ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

HYDRALAZINE HCL
RANITIDINE
SODIUM NITROPRUSSIDE
DIGOXIN
DOBUTAMINE HYDROCHLORIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See 87 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

2 E RECEIVED MANUFACTURER: 3/24/87

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☑ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☑ YES ☐ NO

25a. REPORT TYPE
☑ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS (In Confidence)	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

affected. The man continued to deteriorate with renal failure secondary to liver failure. On 3/20/87 the man experienced cardiac arrest, was resuscitated, but later died. (It should be noted that medications prior to admission included concomitant tocainide, digoxin, furosemide, hydralazine, alprazolam, theophylline, diltiazem, nitroglycerin paste, and chlorpropamide.)

8.-12. CHECK ALL AF PROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Flecanide-Induced Immune Neutropenia

Documentation of a Hapten-Mediated Mechanism of Cell Destruction

Wolfram E. Samlowski, MD; Richard N. Frame, MD; Gerald L. Logue, MD

• Immune-mediated granulocytopenia due to cardiac antiarrhythmic medications is a rare, but potentially dangerous, event. This article characterizes the first case, to our knowledge, of severe granulocytopenia associated with the administration of flecanide acetate, a new class I antiarrhythmic drug. Immunologic studies determined that flecanide was capable of binding to the surface of normal neutrophils. The patient's serum contained an IgG antibody that could specifically bind to the haptenized neutrophils, presumably mediating enhanced destruction of mature granulocytes both in the serum and within the bone marrow. Cessation of flecanide therapy resulted in resolution of the granulocytopenia. The titer of antineutrophil antibody in the patient's serum decreased to background levels within the next five months. Similar antibodies were not found in serum from nonsensitized individuals. The capacity of flecanide to bind to normal neutrophils may prove to be a significant risk factor for the subsequent development of antineutrophil antibodies and agranulocytosis in patients receiving this drug. Careful hematologic monitoring of all patients who are receiving this medication is, therefore, strongly urged.

(*Arch Intern Med* 1987;147:383-384)

Class I antiarrhythmic medications, such as procainamide hydrochloride and quinidine sulfate, have occasionally caused severe, life-threatening neutropenia (< 500 neutrophils per microliter of peripheral blood).[1-8] The mechanism of granulocyte destruction in such cases is frequently immunologically mediated.[5-8] Flecanide acetate, a congener of procainamide, is an experimental class I antiarrhythmic agent that is currently undergoing clinical trials. It has no known hematologic toxicity.[10-12] We have recently observed the first case, to our knowledge, of severe neutropenia and selective marrow depletion of mature granulocytes in association with the ingestion of this drug. Studies were performed to attempt to identify the mechanism by which flecanide therapy mediated the destruction of granulocytes.

REPORT OF A CASE

A 66-year-old man came to the rheumatology clinic complaining of a sore throat and nonproductive cough that had been present for two days. He had a history of psoriatic arthritis, controlled by indomethacin therapy and methotrexate administered orally (5 mg three times per week) for the past five years. There was no prior evidence of hematologic, renal, or hepatic dysfunction on frequent laboratory evaluations. A routine complete blood cell count during this visit to the clinic demonstrated profound leukopenia (leukocyte count of 1400/mm³ [1.4 × 10⁹/L]), and the patient was admitted to the hospital for hematologic evaluation.

The patient's medical history was significant for essential hypertension, which was well controlled with hydrochlorothiazide therapy. Three months prior to admission, he suffered an inferior-wall myocardial infarction, complicated by frequent premature ventricular contractions, including coupled ectopic beats. He agreed to enter a randomized, double-blind trial of antiarrhythmic agents. He received flecanide acetate, a new class I antiarrhythmic drug (100 mg orally, three times per day) with a marked diminution in the frequency of premature ventricular contractions and couplets. Metaprolol was also added to his medication regimen to improve blood pressure control. At the time flecanide therapy was initiated, the leukocyte count was 7800/mm³ (7.8 × 10⁹/L).

Physical examination on admission revealed an elderly man with the cutaneous stigmata of psoriasis, mainly over the extensor aspects of his limbs. He was afebrile, with minimal pharyngeal erythema, without exudates or adenopathy. Cardiopulmonary and abdominal examinations were unremarkable. Symmetrical deformation of multiple joints, particularly in hit fingers, was present.

Complete blood cell count disclosed the following values: leukocytes, 1400/mm³ (1.4 × 10⁹/L), with 24% (0.24) mature granulocytes, 2% (0.02) band cells, 44% (0.44) lymphocytes, 14% (0.14) monocytes, and 10% (0.10) eosinophils; hematocrit, 38% (0.38); and platelets, 161 000/mm³ (161 × 10⁹/L). Sequential blood cell counts are plotted in the Figure. Results of a multiphasic chemistry profile (SMA-20) were entirely normal. Urinalysis and chest roentgenograms were unremarkable.

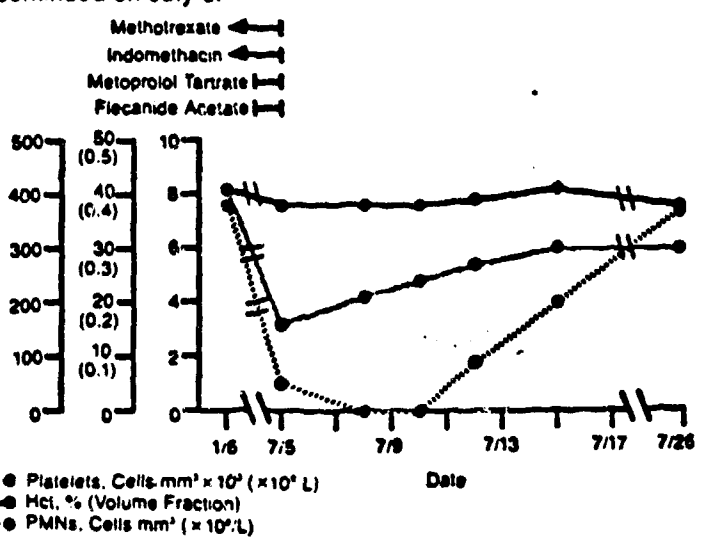
On admission, all medications were discontinued, and a biopsy of the iliac crest bone marrow was performed, which revealed a fatty marrow with sparse foci of normally cellular marrow, containing predominantly erythroid precursors (myeloid to erythroid ratio approximating 1:1). Erythroid morphology was normal. The myeloid series demonstrated normal morphology, but there was total absence of the more mature granulocyte forms. Megakaryocytes appeared to be normal both in number and morphology.

The patient remained asymptomatic and afebrile for the duration of his hospitalization, and peripheral blood leukocyte and absolute neutrophil counts began to improve by the seventh hospital day. He was discharged on the tenth hospital day with a neutrophil count of 4250/mm³ (4.25 × 10⁹/L).

RESULTS

The patient's serum was assessed for antigranulocyte antibodies on two dates, using previously published techniques.[13] The first sample was obtained during the period of granulocytopenia. At this time, IgG antibodies were present in the patient's serum, which bound to the surface of normal donor neutrophils following incubation of the cells with either 3.3 mg/mL or 0.33 mg/mL of flecanide acetate (Table). Incubation of neutrophils with normal serum or buffer, either in the presence or absence of flecanide,

Time course of flecanide-induced granulocytopenia. Patient's absolute neutrophil count (mature polymorphonuclear neutrophils [PMNs] and band cells), platelet count, and hematocrit (Hct) are plotted vs time. Drug therapies that might have contributed to granulocytopenia are stated in upper portion of Figure. Dosages were as follows: methotrexate, 15 mg/wk; indomethacin, 50 mg three times daily; metoprolol tartrate, 50 mg three times daily; and flecanide acetate, 100 mg three times daily. All medications were discontinued on July 5.



Accepted for publication Sept 10, 1986.

From the Division of Hematology/Oncology, Department of Medicine, University of Utah and the Veterans Administration Medical Center, Salt Lake City (Drs Samlowski and Frame), and the Division of Hematology, Department of Medicine of the State University of New York at Buffalo and Buffalo General Hospital (Dr Logue).

Reprints not available.

Granulocyte-Bound IgG*			
	Reagent Added		
	Flecanide Acetate, 3.3 mg/mL	Flecanide Acetate, 0.33 mg/mL	Buffer
Serum obtained during granulocytopenia, 1:10 dilution	240.9 ± 16.7	147.2 ± 4.8	114.3 ± 21.5
Serum obtained during convalescence, 1:10 dilution	94.1 ± 6.5	. . .	89.2 ± 8.1
Control serum, 1:10 dilution	93.4 ± 5.7	67.4 ± 6.1	60.7 ± 7.4
Buffer	51.1 ± 9.7	36.4 ± 5.1	30.6 ± 5.2

*Granulocyte-bound IgG in grams of staphylococcal protein A (SPA) bound per granulocyte times 10^{19}. Binding of radioiodinated SPA to normal paraformaldehyde-fixed neutrophils (2×10^7/mL) that had been previously incubated (60 minutes at 37°C) with equal volume of flecanide acetate (either 3.3 mg/mL or 0.33 mg/mL) or buffer and then extensively washed, was assayed as previously described.[13] Significant increase in SPA binding was observed subsequent to incubation of flecanide-exposed neutrophils with patient's serum, indicating specific binding of an IgG antibody. The results are the mean ± SEM of triplicate assays. Binding of SPA to neutrophils in presence of patient's serum and 3.3 mg/mL of flecanide acetate was statistically different from both the binding of SPA without the addition of drug ($P<.01$) and from antibody-binding derived from normal serum ($P<.001$) at either flecanide dilution by Student's *t* test.

resulted in significantly lower IgG binding. Although the studies shown in the Table were performed utilizing a 1:10 dilution of normal serum, to minimize nonspecific antibody adsorption to neutrophils, similar results were obtained when higher concentrations of serum were used. Parallel assays in the presence of normal serum or buffer did not result in significantly increased binding of radioiodinated staphylococcal protein A. Neutrophils that were exposed to each of the other medications which the patient was taking, including methotrexate, hydrochlorothiazide, metoprolol, or indomethacin at either 1.0 or 0.1 mg/mL, failed to demonstrate any potentiation of immunoglobulin binding in the presence of either the patient's serum or the control serum (data not shown). Additionally, increases in neutrophil-bound IgM and C3 complement[14] could not be detected on the surface of the flecanide-haptenated cells following incubation with the patient's serum (data not shown). Assay of a second serum sample, obtained during convalescence five months after the cessation of flecanide therapy, revealed the virtual disappearance of the flecanide-specific antibody (Table).

COMMENT

Drug-induced granulocytopenia is a rare and potentially fatal complication of antiarrhythmic drugs. Among the class I antiarrhythmic drugs, the incidence of this complication varies widely. Procainamide therapy causes granulocytopenia in the range of 0.6% to 4.4% of patients to whom this drug is administered.[8] The incidence of granulocytopenia induced by quinidine sulfate therapy is harder to establish, but numerous case reports document its occurrence.[4-7] Lidocaine hydrochloride therapy has not been associated with granulocytopenia, but therapy with tocainide hydrochloride, a congener of lidocaine, has been reported to produce this complication in approximately 0.18% of treated patients.[14] No reports of granulocytopenia or agranulocytosis associated with newer therapeutic agents, such as flecanide or encanide, have, as yet, been reported in the literature, to our knowledge.[10-12]

We observed a patient with the delayed onset of granulocytopenia, which we believe to be related to the administration of flecanide therapy. This patient developed a severe reduction in circulating neutrophils three months after institution of flecanide therapy. A bone marrow examination revealed normal erythroid and immature myeloid maturation, but a striking lack of mature granulocytes. The hematologic findings were most compatible with selective, immunologically mediated destruction of mature granulocytes in the peripheral blood and the bone marrow. Since the patient was receiving multiple medications that have previously been associated with granulocytopenia, immunologic testing was performed to determine which drug was the responsible agent.

The immunologic studies in our patient revealed that the granulocytopenia was mediated by haptenization of flecanide onto the surface of normal neutrophils. The hapten-neutrophil complex was quite stable, and could not be easily eluted from the cell surface by extensive washing of the neutrophils. This hapten was recognized by specific antibodies in our patient's serum, and resulted in a marked increase in the ability of antibody to bind to neutrophils. Fixation of the IgG antibody from the serum of our patient on the cell surface probably resulted in the immunologic destruction of the granulocytes. None of the other medications that the patient was taking was found to increase antibody binding to normal neutrophils.

The most important finding in this case is the observation that flecanide, a new investigational class I antiarrhythmic drug, is capable of haptenizing normal neutrophils from random donors. The fact that our patient was capable of immunologically recognizing such hapten-coated neutrophils suggests that this drug may cause similar complications in other patients. Further studies need to be performed to establish the frequency of clinically significant granulocytopenia following the administration of flecanide therapy. We recommend that if flecanide therapy is utilized, it be used cautiously, with regular assessment of blood cell counts to detect the potential onset of hematologic complications.

This study was supported in part by a Veterans Administration Research Associate Award, an American Cancer Society (New York) clinical fellowship, a National Institutes of Health (Bethesda, Md) grant (1RO1-AM31895-03), and the Richard Wahle Endowment Research Fund of the State University of New York at Buffalo.

The helpful editorial suggestions of James P. Kushner, MD, are sincerely appreciated.

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Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)736-5016

ORIGINAL REPORTS

3M

July 10, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is a Follow-up Adverse Reaction Report (Form FDA 1639) pertaining to a serious and unlabeled adverse experience which occurred in association with the use of the subject product. Also attached is the initial report which originally was thought to be a non-15-day report, and was being held for the periodic ADR report. Subsequently, when more information became available it was decided that the ADR was indeed a 15-day report. Therefore, both reports are included herein.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Attached - Initial 15 day report - [redacted]
Follow-up report

Certified Mail P 235 106 394

RECEIVED
JUL 28 1987
HFN-11C
CENTER FOR DRUGS AND BIOLOGICS

7/31

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	64	M	01	23	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

WORSENED CONGESTIVE HEART FAILURE, HYPERTHYROIDISM Death

This 64 y.o. male had a history of congestive heart failure and PVC's which were not controlled with quinidine or procainamide. Flecainide was started 10/86 at 100 mg bid with good control. On 1/23/87 the man had increased congestive heart failure (ie, shortness of breath, rales, and pedal edema) and evidence of hyperthyroidism. The man was admitted to the hospital. The cardiologist did not recommend discontinuation of flecainide. Follow-up information shows that this man w[illegible] diagnosed with severe refractory CHF, cardiomyopathy with poor ejection fraction, and hepatic encephalopathy. The man died on 2/12/87. The physician stated twice that these incidents were not related to flecainide.

13. RELEVANT TESTS LABORATORY DATA

Thyroid function tests prior to flecainide therapy - T3 34.8; T4 8.7
Following three months of flecainide - T3 48; T4 10.6; FTI 5.1

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTIO
- [ ] TREATED WITH Rx DRU
- [x] RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*: 10/??/86 - 02/12/87

19. THERAPY DURATION: 4 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN(LANOXIN)
SPIRONOLACTONE
CAPTOPRIL
BUMETANIDE
ISOSORBIDE DINITRATE
TRAZODONE HCL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 3/19/87

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

12.1

AUG 12

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA #18-830 TOMBOCOR (flecainide acetate) Tab.

Sponsor: Riker

Type of Submission: Periodic ADR Report (March 11-June 10, 1987)

Date of Submission: 7/15/87

Date of Review: 8/6/87

Reviewer: Sughok K. Chun, M.D. HFN-110

A. Resume:

Pertinent ADRs to be noted are:

[redacted] 69 Y/M
PAIN, TENDERNESS, SWELLING IN BREAST, UNILATERAL

Onset of persistent, constant pain in left breast after 4+ mo on F. Gradual appearance of swelling & gradually increasing tenderness of nipple & areola of left breast; no discharge.

No history of prior episode of breast swelling or tenderness. Speciality consultation to be sought regarding management.

Concomitant Rx: digoxin 1+ yrs, atenolol, 1+ yrs.

[redacted] Age ?/M
NAUSEA, BLURRED VISION

F was started two weeks ago at 100 mg bid. The dose was increased to 150 mg bid with good control of the arrhthmia. The man began to experience blurred vision and severe nausea with resulting weight loss. The physician prescribed trimethoperzamide for nausea. When F dose was reduced to 100 mg bid nausea was completely abated without anti-nausea Rx.

[redacted] 77 Y/F
HYPOTENSION

The initial F dose was 100 mg bid, but when seen at one wk BP had fallen from 120/80 to 90/60. F dose was reduced to 100 mg daily,but at the end of another wk her BP was 70/50. F was d/ced, and BP returned to normal level.

[redacted] 38 Y/F
NAUSEA, UNFOCUSED VISION, DIZZINESS, VERTIGO

Pts VT was well controlled with F 100 mg bid but she experienced nausea, unfocused vision, dizziness due to the vision problem, and vertigo beginning

with the 1st day of Rx. She is also taking metoprolol tartrate. Her previous antiarrhthmics also caused nausea and visual disturbasnces. After 7 days of F Rx the ADR are still occurring with day-to-day variation (especially the nausea) but she prefers to continue F Rx.

[redacted]
TORSADE DE POINTE

A 70 Y/F with longstanding myocardial disease developed CHF & VF, treated with lidocaine which induced profound bradycardia. Several other antiarrhthmic drugs were tried, none of which were successful. F was started at 100 mg bid. On the 4th day Torsade de Pointe developed; F was d/ced & Torsade subsided shortly. Amiodarone was given, and Lanoxin, Capoten, a diuretic, & potassium continued. Five days later the patient died.

[redacted] Age ?/?
DIZZINESS, ATRIAL FLUTTER

Tnis pt, with mitral valve prolapse, was started on F 100 mg bid for VT. The pt noted dizziness which resolved with a reduction in dosage to 50 mg bid. One wk after this decrease in dose, the pt was noted to have atrial flutter.

[redacted] Age ?/?
ATRIAL FLUTTER

This patient, with Hx CABG and mild CHF, was started on F 50 mg bid for the Rx of PVC's with frequent couplets. The pt tolerated F well but after 1 wk of Rx, the pt was noted to have atrial flutter. The pt had no prior atrial arrhthmia.

[redacted] 59 Y/M
DIAPHORESIS

Pt noted markedly increased perspiration following taking the 3rd dose of F, with no abatement with passage of time & continued use of F. Paroxysmal atrial tachycardia, for which F was prescribed, seems well controlled, and the patient states that he has noted no other untoward symptoms. About a month later his ECG showed persistence of PAT, and F dosage was increased to 100 mg tid.

[redacted] 58 Y/M
ANGINA PECTORIS

A physician with Hx of mild angina during the past 10 mo, developed symptomatic episodic VT recently. F 100 mg bid was started. In 2nd day of F, VT was suppressed, but he now experienced more severe exertional angina. F was discontinued, and angina improved.

[redacted] 55 Y/M
FEVER

Onset on 3rd day of F Rx, with oral temperature reaching 102F. GU infection was discovered and Rx with ampicillin.

[redacted] 66 Y/F
HYPOTENSION

Pt was under treatment in Intensive Care Unit of hospital for adult respiratory distress syndrome, complicating diabetes, chronic renal failure & angina. She developed symptomatic PVCs & F 100 mg/day was ordered. Following the second dose, BP dropped to 60/0. She was given dopamine iv, & BP had returned to her normal 110/70 4 h later. Recurrent episodes of hypotension led to d/c of F after 2 more days; BP remained stable after that.

[redacted] 50+ Y/F
RASH

Started on low dose F for the control of PVC and bursts of VT. Within 48 h of initiation of F, she developed a severe skin rash. F was d/ced, and steroids prescribed to treat the rash. The rash resolved with no further problems.

[redacted] 57 Y/M
JOINT PAIN, SLIGHTLY ELEVATED SGOT & SGPT

F for about 1 1/2 mo at 200 mg/day he began to experience joint pains. Concomitant medication nadolol. This man has previously been treated with quinidine and beta-blockers but he has not had any evidence of lupus nor has he had a Hx of arthritis. He took aspirin for several days for the arthritis and it resolved entirely within 1 wk in spite of continuing on F Rx. Slightly elevated hepatic enzyme levels were noted.

Lab Data at onset of joint pain:

ESR - 20
ANA + 1:256 (nomogenous)
GLOBULIN - 4.2
SGOT - 56 and SGPT -88

[redacted] 72 Y/M
CHOLESTATIC JAUNDICE

Apparent at the end of 6 wks of F Rx, he felt quite sick, & icterus was evident (see laboratory data). F was discontinued 8/5/86. When he was seen again 8/14/86 jaundice had vanished, he felt good & all test results were returning to normal. Pindalol was reinstituted to control his arrhthmia.

LABORATORY DATA

DATE	BILIRUBIN (1.5)	ALK. P'TASE (37-108)	SGOT (10-27)	SGPT (7-46) (normal range)
5/22/86	0.2	normal	normal	normal
8/4/86	3.0	292	41	92
8/14/86	0.9	181	normal	normal

8/4/86 Ultrasound scan of gall bladder & biliary tree: NORMAL

[redacted] 77 Y/F
VENT. TACH, UNRESUSCITATABLE, HYPOTENSION Death

Hospitalized for CHF, unstable angina and non-sustained VT (frequent runs of 3-5 extopic beats). Treatments with both lidocaine & quinidine were ineffective. Studies revealed severe 2-vessel CAD, & double coronary artery bypass operation was performed. Postoperatively, episodes of VT continued to be troublesome, & procainamide was administered without success. F 100 mg bid orally was started, & the arrhythmia was reduced to occasional couplet/single ectopies. On the 3rd day of F, sustained monomorphic VT set in, which was resistant to repeated electroconversion attempts. A temporary pacemake was implaced, but it was ineffective. Bretyllium was given IV and cardiac rhythm was apparently stable for the following 6 hours, during which the pt was conscious but hypotensive, requiring IV Rx to improve BP. Sustained irreversible VT recurred, & death followed shortly.

[redacted] 44 Y/F
QRS WIDENING, BRADYCARDIA, HYPOTENSION Overdose

The pt took 20 Tabs F at 23:00 hrs on 4/22/87 in an apparent suicide attempt. She was seen in the emergency room the following morning where some tablets were suctioned from her stomach and activated charcoal was administered. She was in generally good health prior to the event. Her QRS was very wide and she had bradycardia of about 60/min. A brief period of hypotension developed which was controlled with isoproterenol. Treatment was conservative and aimed at allowing the drug to washout. Two plasma samples were taken for F assay. By 23 h after tablet ingestion the QRS had returned to about normal and a sinus rhythm was present. The following morning the pt signed herself out of the hospital.

LABORATORY DATA

DATE	PLASMA FLECAINIDE ACET.* (MICROGM/ML)	QRS (MILLISECONDS)
23APR87	5.3	.36
23APR87	3.19	.15
24APR87	1.62	.09
24APR87	2.13(a)	

Therapeutic level = 0.2-1.0 microgm/ml

(a) Called J. M. Fox on 8/10/87 for the correct data.

[redacted] 65 Y/M
WEAKNESS, EDEMA

The pt who has COPD was receiving F 300 mg daily for control of VT. After initiation of F, he begain to develop proximal muscle weakness & pretibial edema. The weakness progressed so that the man would fall & not able to get up. F was d/ced & mexilitene started. Edema has disappeared & weakness has improved.

[redacted] Age ?/F
JAUNDICE

Started on F 200 mg daily for the control of PVC's. She was also taking a number of concimitant medications. Because of non-cardiac problems the pt was hospitalized. While in the hospital, the diagnosis of jaundice was made. F, as the last agent added to her regimen, was d/ced. The jaundice began to reverse.

[redacted] 66 Y/M
WEAKNESS OF LOWER LIMBS

This physician started taking F 200 mg daily 3 wks ago for the control of paroxatrial fibrillation. After 3 days of Rx, he noted extreme weakness of the lower limbs after minimal exertion (ie, climbing a flight of stairs). He stated that these periods of weakness would last approximately 10 seconds, and would subside when he sat down. He did not notice any sweating, dyspnea, or arrhythmia. The man decreased F dose to 100 mg daily; the episodes of weakness disappeared. He continued F with low dose.

[redacted] 34 Y/F
CONSTIPATION

The pt with mitral valve prolapse was hospitalized for appendicitis, and F and propranolol was started. During the following 11 wks she did not have a bowel movement without using an enema. The constipation resolved after F was stopped. Rx of the arrhythmia continued with procainamide and propranolol.

[redacted] Age ?/M
INCREASED SGOT & SGPT, DRUG INTERACTION?

This man with a Hx of gouty arthritis was being treated with F at 200 mg/day since September, 1986. He was also receiving triamterene/HCTZ.

On 5/10/87 probenecid/colchicine was added to his Rx because of a flare of his gout. On this date his SGOT was 58 and uric acid was 10.6. About 1 mo later his SGOT was 87 and SGPT was 101. F and probenecid/colchicine were d/ced at that time to allow the gout to clear. The F serum level in Nov. 1986 was 0.47 mcg/ml; the 5/14/87 level was 0.59 mcg/ml.

[redacted] 68 Y/F
BLURRED & DARKENED VISION

F initiated at 100 mg bid 2 weeks ago. Dosage was increased to 150 mg bid after 8 days, because of resistance of arrhythmia, which have improved since but not entirely gone. On 6.3.87 the pt informed her doctor that she had been noticing diminished ("darkened") vision in her left eye, with some blurring. Examination by ophthalmologist today revealed perimacular edema, interpreted as due to "fluid leakage"; right ocular fundus was normal. F was d/ced 6/3/87, & progress will be followed.

[redacted] 48 Y/M
VT, BBB, UNRESUSC. VENT. FIB. Death

The pt was admitted to the hospital with a Hx or HTN, VT, and syncope, seizures possibly secondary to VT. Enalapril maleat Rx was ongoing. While hospitalized he experienced no dysrhythmias and all tests (Stress, Echo, ECG, Carotid flow) were normal. On day 2 of hospitalization, F and diltiazem were started and he was discharged later in the day. Two wks later the pt was again admitted to the hospital with seizures, syncope, and VT. Diltiazem was stopped the next day (F and enalapril still ongoing). At 0045 hours on day 3 of this hospitalization he had sudden onset of CBBB with rare PVCs which converted to NSR at 0046 hours without intervention. The pt was alert and asymtomatic but 20 min later he developed VT which did not respond to cardioversion. He went into VF and expired at 0205 hours. Result of a plasma F level taken at 0600 or 1800 hours (unclear in record) the day prior to death was 0.3 mcg/ml.

NARRATIVE SUMMARIES

Distribution of FDA 1639's*

	U.S. Spontaneous	Clinical	Foreign Spontaneous	Total
Serious -				
Unlabeled (15-day)	11	16	10	37
Labeled	20	NA	NA	20
Nonserious	22	NA	NA	22
Total	53	16	10	79

* There were 2 literature reports this quarter which are not included in this table.

The total number of reports, including those from literature, submitted this quarter was similar to that submitted to that submitted for the previous quarter. The most notable change was a drop in the number of nonserious, U.S. spontaneous reports from 35 during the previous quarter to 22 in the present.

ANALYSES OF DEATH

FDA 1639 Reports Submitted Containing Death as an Outcome

	U.S. Spontaneous	Clinical	Foreign Spontaneous	Total
Unlabeled (15-day)	3	2	1	6
Labeled	7*	0	0	7
Total	10	2	1	13

* Includes 4 "Death, Cause Unknown", which are arbitrarily included among the "labeled" events.

NARRATIVE OF ACTION TAKEN

After review of the adverse reaction reports received this quarter, it is concluded that current U.S. prescribing information for flecainide acetate tablets continues to describe safety information appropriately and, therefore, is not in need of revision at this time.

The most common ADRs was due to negative inotropic effect of F to cause hypotension. Gynecomastia, increased liver enzymes/alk. phosph./serum bilirubin should be noted.

S K Chun 8/11/87

Sughok K. Chun, M.D.

cc: Orig
HFN-110
HFN-110/CSO
HFN-110/SChun/8/6/87;8/11/87
clb/8/7/87;8/11/87/1665k

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)736-5016

REPORTS!

3M

P-6

July 15, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

ORIGINAL

Dear Sir/Madam:

Pursuant to 21 CFR 314.80, enclosed is the Periodic ADR Report in duplicate for Tambocor® (flecainide acetate) NDA 18 830. There are 42 FDA-1639 forms in this submission, 38 of which are initial reports and four are follow-up reports.

The time period covered by this report is March 11, 1987 to June 10, 1987.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

FDA CONTROL NO.
ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	73	F	04	07	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

*VENT. TACH, UNRESUSCITATABLE, HYPOTENSION*Death.
Hospitalized for congestive heart failure, unstable angina and non-sustained ventricular tachycardia (frequent runs of 3-5 ectopic beats). Treatments with both lidocaine & quinidine were ineffectual. Studies revealed severe 2-vessel coronary artery disease, & double coronary artery bypass operation was performed. Postoperatively, episodes of VT continued to be troublesome, & procainamide was administered intravenously, but without success. Flecainide 100mg bid orally was started, & the arrhythmia was reduced to occasional couplet/singlet ectopics. On the 3rd day of flecainide therapy, sustained monomorphic VT set in, which was resistant to repeated electroconversion attempts. A temporary

13. RELEVANT TESTS LABORATORY DATA

4/7/87: (prior to onset of sustained ventricular tachycardia)

Blood levels (meq/L)	Na	K	Cl	CO2
	132	5.2	104	21

Digoxin - 2.0ng/ml
Flecainide - not obtained.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*: 04/04/87 - 04/07/87

19. THERAPY DURATION: 3 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NITROGLYCERIN
DIGOXIN
FUROSEMIDE
POTASSIUM CHLORIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

History of Pulmonary Edema, Nephrosclerosis, inferior Myocardial Infaret (8-10 years ago). Anemia of chronic disease.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/16/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

pacemaker was implaced, but it was ineffective. Bretyllium was given IV and cardiac rhythm was apparently stable for the following 6 hours, during which the patient remained conscious but hypotensive, requiring IV treatment to improve blood pressure. Sustained irreversible VT then recurred, & death followed shortly.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTIC
- ☐ TREATED WITH Rx DRU
- ☐ RESULTED IN, OR PROLONGED, INPATIE HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
17. INDICATION(S) FOR USE	
18. THERAPY DATES *(From/To)*	19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)* ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER
25. 15 DAY REPORT ☐ YES ☐ NO	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

NOTE. Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	50	F			

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

DEATH, cause undetermined.
Patient was under treatment with flecainide for control of ventricular arrhythmia. She was also taking atenolol. History of myocardial infarction several years ago.

13. RELEVANT TESTS LABORATORY DATA

Coronary arteriogram several years ago (at the time of the myocardial infarction?)revealed normal coronary arterial system.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTIO
- [ ] TREATED WITH Rx DRU
- [ ] RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From To)*: / / - / /

19. THERAPY DURATION: UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ATENOLOL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: NDA 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/20/87

24d. REPORT SOURCE *(Check one)*

☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT

☐ YES ☒ NO

25a. REPORT TYPE

☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?

☐ YES ☐ NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-			

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
DEATH, cause undetermined

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

18. THERAPY DATES *(From To)*
/ / - / /

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/20/87

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [X] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-			

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
DEATH, cause undetermined.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTIC
- [ ] TREATED WITH Rx DRU
- [ ] RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15 DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

18. THERAPY DATES *(From To)*
/ / - / /

19 THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

II. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/20/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE. Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-			

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
DEATH, cause undetermined.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTIO
- [ ] TREATED WITH Rx DRU
- [ ] RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

18. THERAPY DATES *(From/To)*
/ / - / /

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/20/87

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [X] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	95	F	03	??	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

DIGOXIN TOXICITY DEATH
This 95 y/o woman was started on flecainide at 200 mg/day for ventricular arrhythmia. She was also receiving digoxin and has a history of CHF, syncope and PVCs. Flecainide was given for about 3 weeks and for 3-4 days prior to death she was on a monitor but the final record was lost therefore the cause of death was not recorded. The physician suspects digoxin toxicity occurred; digoxin serum levels have not been reported and the causal relationship between flecainide and digoxin remains undetermined (physicians opinion).

13. RELEVANT TESTS/LABORATORY DATA

NONE REPORTED

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [X] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- [X] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
200 MG	ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*	19. THERAPY DURATION
02/ /87 - 03/ /87	3 WEEKS

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

I. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Premature ventricular contractions; syncopy; chronic congestive heart failure.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
3/12/87	[ ] FOREIGN [ ] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
[ ] YES [X] NO	[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6 REACTION ONSET MO.	DA.	YR.
[redacted]	48	M	10	18	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#PVCs, VENT.TACH, BUNDLE BRANCH BLOCK, UNRESUSC. VENT. FIB.=DEATH
This 48 y/o man was admitted to the hospital with a history of hypertension, V. tachycardia, and syncope,seizures possibly secondary to V tach. Enalapril maleate therapy was ongoing. While hospitalized he experienced no dysrhythmias and all tests run (Stress, Echo, ECG, Carotid flow) were normal. On day 2 of hospitalization, flecainide acetate and diltiazem HCL were started and he was discharged later in the day. Two weeks later the patient was again admitted to the hospital with seizures, syncope, and ventricular tachycardia. Diltiazem was stopped the next day (flecainide and enalapril still ongoing). At 0045 hours on day 3 of this hospitalization he had sudden onset of CBBB with rare PVCs which

13. RELEVANT TESTS LABORATORY DATA
SEE #7, ABOVE

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*
10/04/86 - 10/20/86

19. THERAPY DURATION
16 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
ENALAPRIL HCL
DILTIAZEM HCL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
NDA 18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/23/87

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [x] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [x] NO

25a. REPORT TYPE
- [ ] INITIAL [x] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS (In Confidence)	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

converted to normal sinus rhythm at 0046 hours without intervention. The patient was alert and asymtomatic but 20 minutes later he developed ventricular tachycardia which did not respond to cardioversion. He went into ventricular fibrillation and expired at 0205 hours. Result of a plasma flecainide level taken at 0600 or 1800 hours (unclear in record) the day prior to death was 0.3 mcg/ml. Result of a level taken after death has not been reported.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)736-5016

12.1

July 15, 1987

REPORTS!

3M

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

ORIGINAL

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is a Follow-up Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

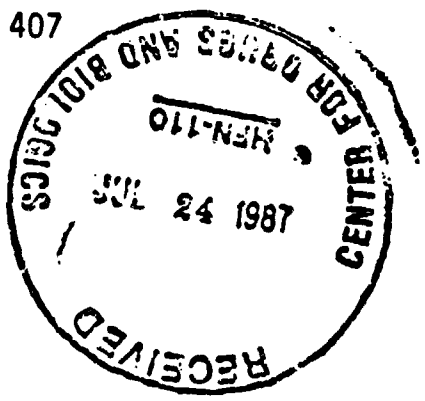
Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Attachments: Follow-up Report
[redacted] (initial sent 4/16/87)

Certified Mail P 235 106 407



DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	75	M	03	13	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ATRIAL FIBRILLATION, CARDIAC ARREST Death.
This 75 y.o. man was started on flecainide 300 mg daily in February 1987 for the control of intermittent atrial fibrillation. He had been in normal sinus rhythm at his last check-up. On 3/13/87, after three to four weeks of therapy, he was admitted to the hospital with atrial fibrillation and went into cardiac arrest. He was successfully resuscitated but suffered irreversible brain death during the resuscitation attempt and died. He had no evidence of myocardial ischemia. In the opinion of the physician, "it is difficult to implicate flecainide in the patient's death" because of the complexity of the situation.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
ATRIAL FIBRILLATION

18. THERAPY DATES *(From To)*
02/??/87 - 03/13/87

19. THERAPY DURATION
3-4 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
DIGOXIN
SODIUM WARFARIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
NDA 18-830

24b. MFR CONTROL NO.
[redacted]

DATE RECEIVED MANUFACTURER
6/30/87

24d. REPORT SOURCE *(Check one)*
- [X] FOREIGN [ ] STUDY [ ] LITERATURE
- [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	??		

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
#CARDIAC ARREST# Death
This man was being treated with flecainide (dose and duration unknown) for the control of intermittent atrial fibrillation. He had been in normal sinus rhythm at his last check-up. Three weeks later he was admitted to the hospital in cardiac arrest and was successfully resuscitated. However, he suffered irreversible brain death during the resuscitation attempt and died. The physician states that "it is difficult to implicate flecainide in the patient's death" because normal sinus rhythm was restored.

13. RELEVANT TESTS LABORATORY DATA
None.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
??

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
ATRIAL FIBRILLATION

18. THERAPY DATES *(From To)*
?? - ??

19. THERAPY DURATION
??

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

CONCOMITANT DRUGS AND HISTORY

CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

DATE RECEIVED BY MANUFACTURER
4/ 3/87

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA: 18-830

Name of Drug: Tombocor (Flecainide) Tabs

Sponsor: Riker

Type of Submission: ADR

Date of Submission: 6/16,6/17,6/29/87

Date of Review: 7/7/87

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

[redacted] DIZZY, VISUAL DISTURBANCES, HEADACHE, FATIGUE, ASTHENIA, NAUSEA, GOUT FLARE, POSSIBLE DRUG INTERACTION
This man with a HX of gout was treated with F at 200 mg/day when an acute podgra developed with an elevated uric acied. The gout was initially treated with indomethacin but then changed to allopurinol. Shortly thereafter the above symptoms developed and were tolerated for 4-5 days before the allopurinol was stopped and the symptoms resolved within 3-4 days. Allopurinol had been used in the past without any untoward complications. F continued throughout and is still ongoing. The reporter suspected a drug interaction with allopurinol.

[redacted]: Literature report (German): DMW 1984, 109. Jg., Nr. 48
JAUNDICE, POSSIBLE DRUG INTERACTION
This 61 Y/M was started on F 200 my daily with concurrent lidocaine for PVCs. Medical HX includes virus B hepatitis & MI in 1977, identification of IgA paraprotein in 1977, & angina pectoris. In 1984 patient was readmitted to the hospital with a second MI, followed by advent of VPCs for which F 100 mg bid was given. About 30 days later he complained of itching & within a few days became icteric. Diagnosis: cholestatic jaundice. F was stopped after 36 days, but chlorpromazine, being given concomitantly, was continued. Itching was treated with prednisone & IV clemastin. Jaundice resolved slowly: patient was discharged 7 weeks after onset, though still icteric (see bilirubin data). When seen 2+ months later, jaundice had cleared & all liver function test results were normal. The authors speculate as to the possibility of a drug interaction between F & chlorpromazine.

LABORATORY DATA

	Bilirubin	Alk Phos	GPT	GOT	Y-GT	LAP
Prior to jaundice	0.3,0.7mg/dl	normal	normal	normal		
During jaundice	8.3 mg/dl	585 U/l	71 U/l	58 U/l	143 G/l	70U/l
At discharge	4.3mg/dl					

[redacted] ELEVATED LIVER ENZYMES, RENAL FAILURE, CARDIAC ARREST, DEATH

A 60 Y/M with diabetes and HTN, was being treated with tocainide 400 mg tid for 6 wks. He was experiencing nausea/vomiting which led to hospitalization on 3/14/87. On admission, his liver function tests were normal. The liver was enlarged but without evidence of cirrhosis. Ascites was not present. Tocainide was d/ced and F 200 mg daily was started on 3/17/87. After four doses, the man continued to have nausea/vomiting; F was d/ced and tocainide was restarted. After tocainide was restarted, liver transaminase was found to be elevated. SGOT-1100+; SGPT was slightly elevated. Bilirubin was not significantly affected. The man continued to deteriorate with renal failure. On 3/20/87 the man experienced cardiac arrest, was resuscitated, but later died. Concomitant Medications: tocainide, digoxin, furosemide, hydralazine, alprazolam, theophylline, diltiazem, nitroglycerin paste, and chlorpropamide.)

[redacted] EPIGASTRIC PAIN, FEVER, CONFUSION, FLARE OF GOUT

This 64 Y/M was hospitalized 12/2/85 for investigation and treatment of epigastric pain. He was dischared after upper GI x-rays (negative) and ECG (myocardial infarct ruled out) and admitted to another hospital with fever, multiarticular gout, and confusion. Gout was treated with colchicine. He was treated with F for 6 mos.

[redacted] PERIPHERAL NEUROPATHY

This 68 Y/M has a complicated HX of CHF, second-degree AV block, left hemiblock, renal insufficiency, anemia, nephritis of probable viral origin, and sustained VT. He suffered a severe MI in this first week of April 1987. A pacemaker was placed during his hospitalization. His hospital stay was lengthened because of a para-influenza infection, pneumonia with respiratory failure, and a left-side CVA. F 200 mg daily was started on 4/12/87 for control of VT. The man was discharged from the hospital on 5/22/87. On 6/12/87 he was diagnosed with peripheral neuropathy as evidenced by toe drop, loss of sensattion in the lower legs, and paresis.

[redacted] PERICARDIAL TAMPONADE, CYSTITIS, PYELITIS, ELEVATED LIVER ENZYMES, FEVER HEPATITIS

This 61 Y/F was started on F 200 mg tid on 12/21/84 for the control of VT. On 1/16/85 F was d/ced because of drug intoxication. (Previously reported in [redacted]). She showed no liver function disturbance. Captopril was given for six days in January; the pt developed a rash and captopril was d/ced In February 1985 F was restarted at 50 mg tid. In March 1985 the woman developed pericardial tamponade; in May cystitis, possible pyelitis, elevated liver enzymes (ALAT, ASAT, LDH, AF), and fever. Biopsy showed acute hepatitis. F was d/ced. Liver enzyme values returned to normal. In August 1985, after D/C of F, she developed congestive cardiomyopathy following hypertensive cardiomyopathy. In October 1985, she once again developed fever, abnormal liver function tests, hepatitis, and erythema nodosum possibly related to tuberculosis.

S.C. Chun 7/9/87

Sughok K. Chun, M.D., HFN-110

cc: Orig. NDA: 18-830
HFN-110
HFN-110/CSO
HFN-110/SChun/6/29/87
mkm/7/7/87/3114r

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)736-5016

REPORTS

ORIGINAL

3M

June 16 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-83[illegible]

Dear Sir/Madam:

Enclosed is a Follow-up Adverse Reaction Report (Form FDA 1639) pertinent to an adverse experience which occurred in association with the use of the subject product. The initial Adverse Reaction Report was submitted to the FDA on April 8, 1987.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

Attachments: Follow-up 15-Day Alert Report - [redacted]
Initial 15-Day Alert Report (sent 4/8/87)

Certified Mail P 504 523 658

7/7

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6 REACTION ONSET MO.	DA.	YR.
[redacted]	60	M	3	?	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ELEVATED LIVER ENZYMES, RENAL FAILURE, CARDIAC ARREST Death
This man, with a history of diabetes and hypertension, was being treated with tocainide 400 mg tid for six weeks. He was experiencing nausea and vomiting which led to hospitalization on 3/14/87. On admission, his liver function tests were normal. The liver was enlarged but without evidence of cirrhosis. Ascites was not present. Tocainide was discontinued and flecainide 200 mg daily was started on 3/17/87. After four doses, the man continued to have nausea and vomiting; flecainide was discontinued and tocainide was restarted. After tocainide was restarted, liver transaminase was found to be elevated. SGOT was elevated to more than 1100; SGPT was slightly elevated. Bilirubin was not significantly

13. RELEVANT TESTS LABORATORY DATA

Liver function tests were normal while receiving tocainide (6 weeks). Following four doses of flecainide and restarting of tocainide, SGOT was elevated to more than 1100, transaminase was increased, SGPT was slightly elevated, and bilirubin was not significantly affected.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines-biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: 03/17/87 - 03/18/87

19. THERAPY DURATION: 2 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

HYDRALAZINE HCL
RANITIDINE
SODIUM NITROPRUSSIDE
DIGOXIN
DOBUTAMINE HYDROCHLORIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See 87 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

DATE RECEIVED / MANUFACTURER: 3/24/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

MAGNESIUM AND ALUMINUM HYDROXIDES ONGOING

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*

☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT

☐ YES ☐ NO

25a. REPORT TYPE

☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

☐ YES ☐ NO

25d. ARE YOU A HEALTH PROFESSIONAL?

☐ YES ☐ NO

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM PEVIEW

NDA# 18-830

Name of Drug: Tombocor (Flecainide) Tablets

Sponsor: Riker

Type of Submission: ADR

Date of Submission: March 18, 1987

Date of Review: April 22, 1987

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

*[redacted]
PROTHROMBIN TIME DECREASED, DRUG INTERACTION
This 45 y/man was hospitalized to start flecainide for VT. Concomitant drugs were HCTZ, Captopril, Albuterol inhaler and sodium warfarin. Prothromblin times of 24-25 seconds were maintained because of previous aortic valve replacement. Within five days after F was started the prothrombin times had decreased to normal (about 12 seconds) even though there were no other therapy changes. Two weeks after F was stopped the prothrombin times were back to the pre-F levels of 24-25 sec. without adjusting the sodium warfarin. The patients cardiac status had improved by discharge and did not need antiarrhythmic therapy.

*[redacted]
TORSADE DE POINTES, CARDIAC ARREST Death
This 87 y/man was being treated with F 200 mg daily. Six days after initiation of therapy, he was brought to ER with torsades de pointes. He was treated with IV lidocaine. Eight hours later he experienced cardiac arrest and died. No F levels were taken. The torsade may be related to possible elevated F levels due to the patient's low weight and poor renal function. Lidocaine level taken prior to death was elevated. This, in conjunction with concomitant diltiazem and F, may have contributed to the death.

Sughok K. Chun, M.D.

cc: Orig. NDA #18-817
HFN-110
HFN-110/CSO
HFN-110/SChun/3/22/87
klb/4/30/87/08421

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

REPORTS

ORIGINAL

3M

March 18, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Reports
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are two Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/dls

Enclosure - [redacted], [redacted]

Certified Mail P 504 523 571

RECEIVED
APR 15 1987
HFN-110
NATIONAL CENTER FOR DRUGS AND BIOLOGICS

1987 MAR 27 P 12:53

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	87	M	03	??	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

TORSADE DE POINTES, CARDIAC ARREST* Death
This 87 y.o. man was being treated with flecainide 200 mg daily. Six days after initiation of therapy, he was brought to the emergency room with torsade de pointes. He was treated with IV lidocaine. Eight hours later he experienced cardiac arrest and died. No flecainide levels were taken. The clinical pharmacist following this case feels that the torsade may be related to possible elevated flecainide levels due to the patient's low weight and poor renal function. Lidocaine level taken prior to death was elevated. This, in conjunction with concomitant diltiazem and flecainide, may have contributed to the death.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☒ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

18. THERAPY DATES *(From/To)*
03/??/87 - 03/??/87

19. THERAPY DURATION
6 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

CONCOMITANT DRUGS AND HISTORY

CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
DILTIAZEM HCL
LIDOCAINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
3/ 9/87

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

5 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

13.1

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

ORIGINAL

REPORTS
D

3M

November 25, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are two (2) Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Enclosure: 15 Day Reports
- [redacted]
- [redacted]

Certified Mail P 504 523 764

CENTER FOR
RECD
DEC 08 1987
MPN-ATU
DRUGS AND BIOLOGICS

[illegible]
DEC -7 [illegible] 12:27

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-720)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

HEART BLOCK, MYOCARDIAL INFARCTION, CARDIOGENIC SHOCK Death
This man was enrolled in a study as a stabilized post-infarction patient with ventricular arrhythmias. He was started on flecainide(dose unknown) He developed complete heart block while receiving sub-therapeutic doses of flecainide. A permanent pacemaker was inserted. Two weeks after completing the study while continuing his flecainide therapy, the man suffered another myocardial infarction which resulted in cardiogenic shock and death.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
11/11/87

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEC - 2 1987

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

MEDICAL OFFICER'S SHORT FORM REVIEW

NDA# 18,830

DRUG: Flecainide, TAMBOCOR

SPONSOR: Riker

TYPE OF SUBMISSION: ADR

DATE OF SUBMISSION: November 10, 1987

DATE OF ASSIGNMENT: November 23, 1987

DATE OF REVIEW: November 24, 1987

REVIEWER: Sugnok K. Chun, M.D.

A. RESUME:

[redacted] FEVER UNKNOWN ORIGIN, GRANULOMATOUS MYELOPATHY, NONSPECIFIC HEPATITIS

This 69 y/m with a Hy of anterior MI. CABG, CHF, PAFIB, non-susVT, COPD experienced fever, chills, and weakness 15 days after participation in a clinical trial using Flec for the Rx of paroxysmal A fib. The pt was admitted to Medical Center on 7/9/87 for evaluation of fever of unknown origin. Anemia and elevated liver enzymes (SGPT 83, SGPT 133) were present on admission. He was diagnosed to have nonspecific hepatitis on 7/22/87 after liver and bone marrow biopsies showed nonspecific hepatitis and ill-defined noncaseating granuloma, respectively. HBc Ab was positive. Procainamide was discontinued after 24 days of Rx. He was observed for an additional week and was then discharged in good condition. Follow-up liver enzymes will be drawn in one month. The pt began using Flec on 2/24/87 at 25mg bid. Liver enzymes were normal and concomitant medications included digoxin, verapamil, Lasix, aspirin, potassium and flurazepam. Flec was stopped on 3/22/87 and then restarted on 4/23/87 at 50mg bid. The dose was increased to 100mg bid on 5/21/87 and was continued at this dose until D/C for proarrhythmia on 6/17/87. Liver enzymes (SGOT 61, SGPT 158) were elevated at this final visit, Procainamide 500 mg qid was begin on 6/29/87.

[redacted] INTERSTITIAL PULMONATY FIBROSIS, HEMOPTYSIS, NAUSEA, ANOREXIA, FEVER, DYSPNEA

This 63 y/m has a HX of MI, pulmonary embolism, thrombophlebitis, CHF and malignant arrhythmias. He was hospitalized on 01-16-87 for hemoptysis, nausea, anorexia, fevers and increasing dyspnea. He was placed on a respirator and all oral medication was stopped. His condition progressively worsened and he expired on 02/10/86. The immediate cause of death was listed on the death certificate as shock due to sepsis and respiratory insufficiency associated with amiodarone. He had been on Flecainide 50mg bid for 17 days. It is the opinion of the investigator that the event was not due to Flec RX.

[redacted] BULLOUS RASH, SWELLING, ITCHING, ERYTHEMA MULTIFORME BULLOSM
This 86 y/m with a Hy of PVC was hospitalized for syncope (not controlled by other antiarrhythmics used) and found to have sustained VT. He was started on flec (200 mg/day) which controlled the arrhythmia very well but after about 6 wks he began to develop sewlling, itching and a rash. The rash persisted after flec was stopped; therefore, when his cardiac status worsened, flec was estarted. The rash continued and about a month later he was hospitalized in tne care of a dermatologist. Bullous erythema multiforme was diagnosed and a rather modest 10 day course of decreasing systemic steriod RX caused marked improvement. The dermatologist reported the pt nad "target" lesions on the upper body, a secondary infection in a lesion on one foot, impending exfoliation, and rash was becoming "generelized in a very disturbing way" when the steroid therapy was started. The pt's condition was rapidly reversed by steroids, although flec was continued. The dermatologist stated that recovery would not have been so prompt if flec had caused the condition and suggested an alternative etiology of cardiovascular-associated stasis dermatitis and subsequent secondary infection which led to bullous erythema multiforme. The pt is still experiencing itching and irritable skin but flec is ongoing and the lesions are not worsening. Concomitant medication continued furosemide, digoxin and KCL.

[redacted] PERIPHERAL NEUROPATHY
This 68 y/m has a Hy of CHF, second-degree AV block, left hemiblock, renal insufficiency, anemia, nephritis of probable viral origin, and sustained VT. He suffered a severe MI in the first week of April 1987. A pacemaker was placed during his hospitalization. His hospital stay was lengthened because of a para-influenza infection, pneumonia with respiratory failure, and a left-sided CVA. Flec 200 mg daily was started on 4/12/87 for control of VT. The man was discharged from the hospital on 5/22/87. On 6/12/87 he was diagnosed with peripheral neuropathy as evidenced by the toe drop, loss of sensation in the lower legs, and paresis. 8/7/87 Follow-up shows that flec was discontinued. The neuropathy has shown some reduction, but is not totally gone.

Sughok K. Chun 12/1/87
Sughok K. Chun, M.D.

cc: Orig./NDA
HFN-110
HFN-110/CSO
HFN-110/SKC
ayg/11/25/87/0023a/12/01/87

13.1

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

ORIGINAL

REPORTS
(2)

3M

November 10, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is an Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experience which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Enclosure: 15 Day Report [redacted]

Certified Mail P 504 523 743

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CENTER FOR
REC'D
NOV 19 1987
HFN-110
DRUGS AND BIOLOGICS

11/24

CENTER FOR
REC'D
DRUGS AND BIOLOGICS

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	57	F	03	15	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

MALAISE, SYNCOPE, VENTRICULAR TACHYCARDIA, VENTRICULAR FIBRILLATION, COMA, CONVULSION Death

This 57 y.o. woman had a history of hypercholesterolemia and gastro-intestinal reflux. On 03FEB87 she was started on flecainide 200 mg daily for control of PVC's. On 15MAR87 she experienced sudden malaise followed by loss of consciousness and was taken to the hospital where neurological examination showed coma with no reflexes and bilatoral mydriasis. The woman went into ventricular fibrillation and was treated with DC shock, intravenous bicarbonate, and epinephrine. She experienced four additional episodes of ventricular tachycardia and ventricular fibrillation. She was again treated with DC shocks and converted to

13. RELEVANT TESTS / LABORATORY DATA

Potassium=3.8 meq/L
Brain scan showed no obvious lesions and no intracerebral hemorrhage.
Plasma flecainide levels were not measured.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*: 02/03/87 - 03/15/87

19. THERAPY DURATION: 5 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

GEMFIBROZIL
CIMETIDINE
TRIMETAZIDINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-831

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 11/ 2/87

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 31[illegible].30.

V. INITIAL REPORTER *(In confidence)*

26. 26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	57	F	03	15	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

MALAISE, SYNCOPE, VENTRICULAR TACHYCARDIA, VENTRICULAR FIBRILLATION, COMA, CONVULSION Death

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13. RELEVANT TESTS LABORATORY DATA

Potassium=3.8 meq/L
Brain scan showed no obvious lesions and no intracerebral hemorrhage.
Plasma flecainide levels were not measured.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*: 02/03/87 - 03/15/87

19. THERAPY DURATION: 5 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

GEMFIBROZIL
TRIMETAZIDINE
CIMETIDINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 11/ 2/87

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID. INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS. 3. SEX

4-6. REACTION ONSET: MO. DA. YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

sinus rhythm (pulse rate=90;systolic blood pressure=110) Neurologic exam showed a very deep coma (stage IV) with myosis, lack of pupillary and corneal reflex, and complete abolition of tendon reflex. No cyanosis or cardiac failure were observed. The woman next experienced clonic movements in the left hemibody followed by a generalized seizure. This was treated with thiopentone sodium after failure of diazepam. The woman slipped into another coma and died 48 hours later.

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

10. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

27c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT ☐ YES ☐ NO

25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

13.1

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

ORIGINAL

REPORTS

(D)

3M

November 10, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor ®(flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are six (6) Follow-up Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Attachments: Follow-up Report
- [redacted] (initial sent 8/13/87)
- [redacted] (initial sent 9/17/87)
- [redacted] (initial sent 6/1/87)
- [redacted] (initial sent 6/16/87)
- [redacted] (follow-up sent 9/17/87)
- [redacted] (initial sent 6/17/87)
- [redacted] (follow-up sent 8/13/87)
- [redacted] (initial sent 10/27/87)

1987 NOV 18 AM 12:42

Certified Mail P 504 523 745

11/24

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NOV 19 1987
HFN-110
DRUGS AND BIOLOGICS

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	63	M	01	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

HEMOPTYSIS, NAUSEA, ANOREXIA, FEVER, DYSPNEA, INTERSTITIAL FIBROSIS
This 63 year old white male has a medical history of Myocardial Infarction, Pulmonary Embolism, Thrombophlebitis, Class I Congestive Heart Failure, and Malignant Arrhythmias. He was hospitalized on 01-16-87 for hemoptysis, accompanied by nausea, anorexia, fevers and increasing dyspnea. He was placed on a respirator and all oral medication was stopped. His condition progressively worsened and he expired on 02-10-86. The immediate cause of death was listed on the death certificate as shock due to sepsis and respiratory insufficiency associated with amiodarone. He had been on Flecainide 50mg bid for 17 days. It is the opinion of the investigator that the event was not

13. RELEVANT TESTS LABORATORY DATA
TEMPERATURE: 101.4
CHEST X-RAY: DIFFUSE BILATERAL INTERSTITAL INFILTRATES.
LABS: WBC-16,900, WITH 79% PMN, 6%-BANDS , PLATELETS-343,000, HGB-12.2.
BLOOD GASES: PH-7.47, PCO2-33, PO2-45, BICARB-2[redacted].
AUTOPSY: INTERSTITIAL FIBROSIS (PULMONARY)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 100MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*: 12/31/85 - 01/16/86

19. THERAPY DURATION: 17 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ATENOLOL	7 DAYS	ACETAMINOPHEN	36 DAYS
ASPIRIN	18 DAYS	AMIODARONE	34 DAYS
PROPRANOLOL	14 DAYS	SODIUM WARFARIN	15 DAYS
DIOCYTL SODIUM SULFOSUCCINATE	21 DAYS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

4c. DATE RECEIVED BY MANUFACTURER: 11/ 3/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

25c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1985

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID.INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET: MO. | DA. | YR.

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

due to Flecainide therapy.
11/3/87: Indication for flecainide treatment was - sustained & non-sustained ventricular tachycardia, & history of ventricular fibrillation

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTIC
- ☐ TREATED WITH Rx DRU
- ☐ RESULTED IN, OR PROLONGED, INPATIE HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-700)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS (In Confidence)	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	63	M	01	15	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
HEMOPTYSIS
This 63 year old white male has a medical history of Myocardial Infarction, Pulmonary Embolism, Thrombophlebitis, Class I Congestive Heart Failure, and Malignant Arrhythmias. He was hospitalized on 01-16-87 for hemoptysis, accompanied by nausea, anorexia, fevers and increasing dyspnea. He was placed on a respirator and all oral medication was stopped. His condition progressively worsened and he expired on 02-10-86. The immediate cause of death was listed on the death certificate as shock due to sepsis and respiratory insufficiency associated with amiodarone. He had been on Flecainide 50mg bid for 17 days. It is the opinion of the investigator that the event was not

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CHEST X-RAY: DIFFUSE BILATERAL INTERSTITAL INFILTRATES.
LABS: WBC-16,900, WITH 79% PMN, 6%-BANDS , PLATELETS-343,000, HGB-12.2.
BLOOD GASES: PH-7.47, PCO2-33, PO2-45, BICARB-24.
AUTOPSY: INTERSTITIAL FIBROSIS (PULMONARY)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
100MG

16. ROUTE OF ADMINISTRATION
ORAL

INDICATION(S) FOR USE
CARDIAC DYSRHYTHMIA NOS

THERAPY DATES *(From/To)*
12/31/85 - 01/16/86

19. THERAPY DURATION
17 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ATENOLOL	7 DAYS	ACETAMINOPHEN	36 DAYS
ASPIRIN	18 DAYS	AMIODARONE	34 DAYS
PROPRANOLOL	14 DAYS	SODIUM WARFARIN	15 DAYS
DIOCYTL SODIUM SULFOSUCCINATE	21 DAYS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
9/ 4/87

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID: INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
due to Flecainide therapy.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT ☐ YES ☐ NO

25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	72	M	04	27	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

OCCLUSION OF CORONARY ARTERY Death
This 72 y.o. man had a history of ischemic heart disease, left ventricular failure, and sustained ventricular tachycardia since 1980. He experienced episodes of palpitations and angina, approximately once per month, with each lasting more than 30 minutes. He had no history of myocardial infarction. Flecainide 200 mg daily was started on 6/17/85. Plasma flecainide levels remained at about 0.3 mcg/ml throughout therapy On 4/27/87, the man died suddenly at home. Results at autopsy show cause of death to be atheromatous occlusion of the right coronary artery.
9/10/87 Added blood pressure readings(Lab Data) 11/3/87 Deleted hypertension as side effect;blood pressures do not support as SE of flecainide.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

Plasma flecainide levels throughout two years of therapy: 0.3 mcg/ml

Date	Blood Pressure
23DEC85	170/80
27MAR86	190/90
03JUN86	140/80

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
06/17/85 - 04/27/87

19. THERAPY DURATION
22 MONTHS

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

TRIAMTERENE/CYCLOTHIAZIDE	>2 YEARS	ISOSORBIDE DINITRATE	>2 YEARS
NITROGLYCERIN	>2 YEARS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See 87 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NC. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
11/ 3/87

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-720)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	72	M	04	27	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

OCCLUSION OF CORONARY ARTERY, HYPERTENSION, Death

This 72 y.o. man had a history of ischemic heart disease, left ventricular failure, and sustained ventricular tachycardia since 1980. He experienced episodes of palpitations and angina, approximately once per month, with each lasting more than 30 minutes. He had no history of myocardial infarction. Flecainide 200 mg daily was started on 6/17/85. Plasma flecainide levels remained at about 0.3 mcg/ml throughout therapy On 4/27/87, the man died suddenly at home. Results at autopsy show cause of death to be atheromatous occlusion of the right coronary artery.
9/10/87 Added blood pressure readings to lab data.

13. RELEVANT TESTS LABORATORY DATA

Plasma flecainide levels throughout two years of therapy: 0.3 mcg/ml

Date	Blood Pressure
23DEC85	170/80
27MAR86	190/90
03JUN86	240/80

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*: 06/17/85 - 04/27/87

19. THERAPY DURATION: 22 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

TRIAMTERENE/CYCLOTHIAZIDE	>2 YEARS	ISOSORBIDE DINITRATE	>2 YEARS
NITROGLYCERIN	>2 YEARS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See 87 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 9/10/87

24d. REPORT SOURCE *(Check one)*: ☒ FOREIGN ☒ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT: ☒ YES ☐ NO

25a. REPORT TYPE: ☐ INITIAL ☒ FOLLOW-UP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

13.1

ORIGINAL

3M

REPORTS
D

October 27, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are five (5) Follow-up Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Attachments: Follow-up Report
- [redacted] (initial sent 2/25/86)
- [redacted] (initial sent 6/20/86)
- [redacted] (initial sent 7/15/87)
- [redacted] (initial sent 8/21/87)
- [redacted] (initial sent 9/22/87)

Certified Mail P 504 523 733

CENTER FOR
REC'D
NOV 05 1987
HFN-116
DRUGS AND BIOLOGICS

11/6

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	77	M	01	24	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

MYOCARDIAL INFARCTION, HEART BLOCK, CARDIAC ARREST
PT. IS BELIEVED TO HAVE SUFFERED A MYCARDIAL INFARCTION ON 24JAN86 WHEN HE WAS ADMITTED WITH RECURRENT VENTRICULAR TACHYCARDIA. THE LATTER CONVERTED SPONTANEOUSLY FOLLOWING ATTEMPTS AT CARDIOVERSION. DURING HOSPITALIZATION HE WAS SAID TO HAVE DEVELOPED EPISODES OF NON-SPECIFIED HEART BLOCK. DEATH WAS DUE TO CARDIAC ARREST.
10/16/87 This case was subsequently reported in the literature in "Flecainide in the Treatment of Nonsustained Ventricular Tachycardia"; Annals of Internal Medicine 1986; 105:493-498.

13. RELEVANT TESTS LABORATORY DATA
NO AUTOPSY PERFORMED

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
100 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*
12APR85 - 25JAN86

19. THERAPY DURATION
9 MOS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ALLOPURINOL	10 MOS	DIGOXIN	9 MOS
NITROGLYCERIN	9 MOS	PREDNISONE	9 MOS
PSYLLIUM HYDROPHILIC MUCILLOID	9 MOS	FUROSEMIDE	6 MOS
DIOCYTL SODIUM SULFOSUCCINATE	9 MOS	POTASSIUM	6 MOS
IRON	9 MOS	NITROGLYCERIN	

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
ARTERIOSCLEROTIC HEART DISEASE, CORONARY ARTERY DISEASE, ATRIAL FLUTTER, NONSUSTAINED VENTRICULAR TACHYCARDIA.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
10/16/87

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [X] STUDY [X] LITERATURE
- [ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

Flecainide in the Treatment of Nonsustained Ventricular Tachycardia

ROOP LAL, M.D.; PETER D. CHAPMAN, M.D.; GERALD V. NACCARELLI, M.D.; KENNETH B. SCHECHTMAN, Ph.D.; ROBERT L. RINKENBERGER, M.D.; PAUL J. TROUP, M.D.; SUNG SOON KIM, M.D.; ANNE H. DOUGHERTY, M.D.; and RODOLPHE RUFFY, M.D.; St. Louis, Missouri; Milwaukee, Wisconsin; and Houston, Texas

Thirty-two patients received flecainide acetate for nonsustained ventricular tachycardia after having had unsuccessful treatment with a mean of four antiarrhythmic drugs. The mean left ventricular ejection fraction was 41% in 27. Thirty-one patients had organic heart disease, and 22 patients had arrhythmia-related symptoms. Total suppression of ventricular tachycardia occurred in 22 patients. Thirty patients were discharged from the hospital receiving flecainide at a mean (± SD) dosage of 315 ± 76 mg/d and 26 of these patients attained a mean trough plasma drug level of 567 ± 254 ng/mL. One patient had proarrhythmia and 3 had worsening of heart failure. Twenty-two patients remained in the trial for a mean follow-up of 13 ± 7 months. Five patients died (1 suddenly) during the follow-up period. Our data indicate that flecainide suppresses refractory nonsustained ventricular tachycardia in 69% of patients who have organic heart disease. Serious adverse effects were minimized by initiation of treatment in the hospital and careful surveillance of electrocardiograms and plasma drug levels.

FLECAINIDE ACETATE is a new drug classified generally as a Ic antiarrhythmic agent because of its pronounced negative dromotropic effect on cardiac tissues in the absence of marked alterations in repolarization (1). A few cases of its use in treating recurrent sustained and nonsustained ventricular tachycardia have been reported, but clinical experience with this drug in the United States remains limited (2-7). We describe the combined experience of three arrhythmia centers that have used flecainide to treat patients with nonsustained ventricular tachycardia who had had previous unsuccessful treatment with other antiarrhythmic drugs.

We examined 32 patients who were part of a larger group enrolled in a trial of flecainide for the treatment of ventricular tachyarrhythmias. The results of this trial in patients who had recurrent, sustained ventricular tachycardia or out-of-hospital cardiac arrest have been presented in a separate report (3).

Patients and Methods

Seventeen men and 15 women aged 32 to 76 years (mean ± SD, 56 ± 14) who had recurrent, nonsustained ventricular tachycardia participated in the study between 1 January 1982 and 31 December 1984 at the Jewish Hospital at Washington University in St. Louis, the Medical College of Wisconsin Hospitals in Milwaukee, and Hermann Hospital at the University of Texas Medical School in Houston.

Nonsustained ventricular tachycardia was defined as six or more consecutive ventricular complexes occurring at a rate of more than 100 beats/min, lasting less than 30 seconds, and not requiring artificial termination because of hemodynamic instability. Twenty patients had coronary artery disease that was diagnosed by electrocardiographic findings of infarction in 6 and by angiographic documentation of coronary stenoses in 14. Fifteen patients had sustained myocardial infarctions lasting from 1 to 180 months (mean, 48 ± 55) before entry into trial and 5 patients had stable angina pectoris. Seven patients had mitral valve prolapse, 3 had congestive cardiomyopathy, 1 had rheumatic valvular disease, and 1 had no structural heart disease. Twenty-two of these patients had symptoms believed to be arrhythmia related. The commonest symptom, palpitation, occurred in 18 patients. Other presenting symptoms of syncope, near syncope, and shortness of breath correlated with recorded arrhythmias in 4 patients. Previous unsuccessful antiarrhythmic therapy included the use of one to eight drugs (mean, four). Failure of previous antiarrhythmic therapy was due to intolerance or ineffectiveness as determined by clinical criteria that included the use of telemetry monitoring and ambulatory electrocardiograms. When patients were referred after several unsuccessful drug trials, attempts by the investigators to confirm intolerance or inefficacy of previously administered drugs generally were not made unless they thought inappropriate doses had been given before referral. Left ventricular ejection fraction measured in 27 patients ranged from 18% to 60% (mean, 41% ± 13%).

Patients who had PR intervals of more than 0.28 seconds, second or higher degree atrioventricular blocks, creatinine clearances of less than 20 mL/min, or digitalis-induced arrhythmias, and patients who were pregnant or of childbearing potential were excluded from study participation. Efforts were made to avoid the concomitant use of calcium channel blockers or the enrollment of patients totally dependent on artificial pacing. In all patients, flecainide was the only antiarrhythmic drug used.

STUDY PROTOCOL

The patients were admitted to a telemetry unit after having had electrocardiographic determination of nonsustained ventricular tachycardia, and were continuously monitored throughout the hospital phase of the trial. After granting informed consent, they had pretreatment evaluations, during which all antiarrhythmic drug treatment was discontinued. This evaluation included a patient history, physical examination, 12-lead electrocardiogram, roentgenogram of the chest, ophthalmologic examination, and measurement of left ventricular function by radionuclide ventriculography or, when indicated, contrast angiography. Twenty-four hour ambulatory electrocardiographic recordings, taken after a clearance from previous antiarrhythmic treatment involving at least five drug half-lives, were repeated during treatment with the highest tolerated dose of flecainide. All tapes were analyzed at a central computerized facility (Cardio Data Systems, Haddonfield, New Jersey).

Flecainide treatment was then begun orally at an initial dosage of 100 mg every 12 hours. If the drug was well tolerated but ventricular ectopy persisted, the dosage was increased in 100-mg/d increments every 2 to 4 days. For the patients enrolled in the study during the first year, the maximum daily dose was limited to 600 mg. The administrators of the drug decreased this limit to 400 mg for all patients enrolled in 1983 and 1984 because of proarrhythmic effects that occurred during treat-

▶ From Jewish Hospital at Washington University Medical Center, St. Louis, Missouri, Medical College of Wisconsin Hospitals, Milwaukee, Wisconsin, and Hermann Hospital at the University of Texas Medical School, Houston, Texas.

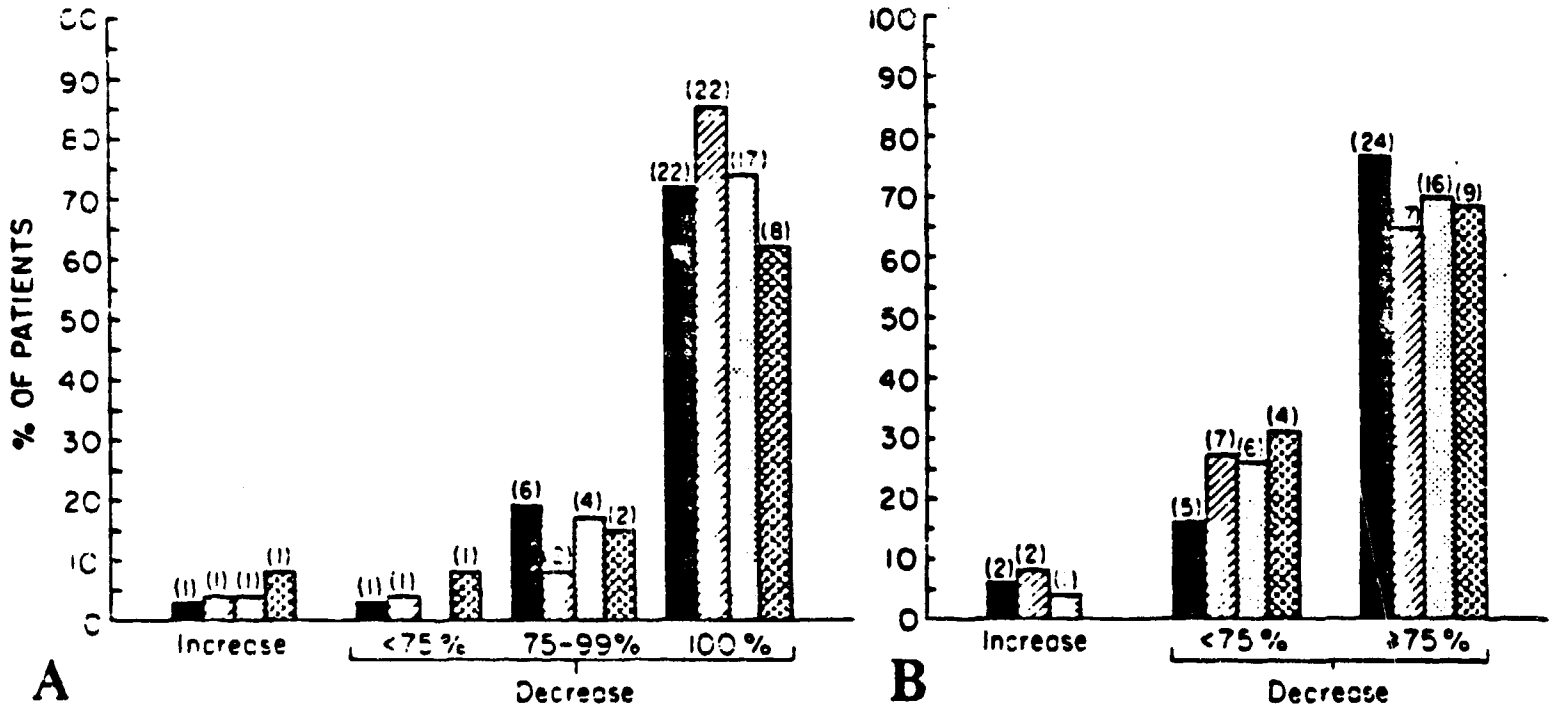

Figure 1. Percentage of patients compared with baseline, who showed reductions in ventricular tachycardia events (*panel A*) and premature ventricular complexes (*panel B*) on 24-hour ambulatory electrocardiographic recordings. Values given for 31 patients at discharge (*solic bars*), 26 patients at 3 months (*hatched bars*), 23 patients at 6 months (*dotted bars*), and 13 patients at 12 months (*cross-hatched bars*)

ment with higher doses. In addition, an interval of 4 days was required between each dose increment. On long-term treatment, only one of the patients reported here received dosages of higher than 400 mg/d. Twelve-lead electrocardiograms were recorded on 25-mm/s paper speed and the PR, QRS, and QTc intervals were measured using calipers before each increase in dosage. Trough plasma flecainide levels were determined in 26 patients before each dosage increment and at the maximum tolerated dose before discharge from the hospital by the laboratory of S. F. Chang (Riker Laboratories, Inc., St. Paul, Minnesota). Details of this liquid chromatographic method have been published (8-10). If patients had had histories of exercise-induced or exercise-exacerbated arrhythmia, they were given symptom-limited treadmill tests before discharge from the hospital to confirm the effectiveness of treatment during exercise.

Long-term treatment with flecainide was offered after a 75% or greater suppression of episodes of nonsustained ventricular tachycardia as determined by predischarge ambulatory electrocardiographic recordings (note that for 24-hour ambulatory electrocardiographic monitoring, ventricular tachycardia was defined as more than three consecutive ventricular complexes); a 75% or greater measured reduction in premature ventricular complexes; and good subjective tolerance of the drug in doses found effective according to these criteria.

Patients discharged on flecainide were seen regularly in outpatient clinics for long-term monitoring of drug safety and efficacy and for verification of compliance. Efficacy was verified by patient questioning and repeating 24-hour ambulatory electrocardiographic monitoring 1 month after discharge and thereafter at 3-month intervals (Figure 1). A 12-lead electrocardiogram and blood specimens were obtained at each visit for determination of hematologic and biochemical profiles. Compliance was verified by measurement of plasma drug levels. Follow-up radionuclide angiograms were ordered for patients who were in New York Heart Association class III or IV or for patients who developed signs or symptoms of congestive heart failure.

DATA ANALYSIS

We stored data in a statistical analysis system database using the Washington University mainframe computer system (IBM, Poughkeepsie, New York) and analyzed data using *t*-tests. Pooled values are reported as mean ± SD.

Results

Of the 32 patients in the study, 30 completed the in-hospital phase of the trial and received flecainide after discharge from the hospital. Flecainide treatment was discontinued for early ineffectiveness in 1 patient and because of a proarrhythmic effect in 1 (*see* below). The dosage at discharge ranged from 200 to 500 mg/d (mean, 315 ± 76). Trough plasma flecainide levels, measured in 26 patients, ranged from 203 to 1121 ng/mL (mean, 567 ± 254).

CHANGES ON ELECTROCARDIOGRAMS

Comparison of 12-lead electrocardiographic recordings before and during flecainide treatment showed a statistically significant increase in the mean PR interval from 172 ± 5 ms to 203 ± 6 ms ($p = 0.0001$), and in QRS duration from 98 ± 3 ms to 118 ± 6 ms ($p = 0.0003$). No statistically significant change in heart rate or corrected QT interval occurred during flecainide treatment. These electrocardiographic changes are summarized in Table 1.

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

We analyzed baseline and predischarge 24-hour ambulatory electrocardiograms in 31 patients (Table 2). Total suppression of ventricular tachycardia (more than three consecutive ventricular complexes) was achieved in 22 patients, and a greater than 75% suppression was achieved in 6 patients. One patient had a marked reduction in premature ventricular complexes and a less than 75% suppression of episodes of ventricular tachycardia, but remained in the trial because of the marked shortening and slowing of the runs. One patient left the trial

because of a marked increase both in premature ventricular complexes and in the number of episodes of ventricular tachycardia that occurred during treatment. One patient who had had previous electrocardiographic documentation of ventricular tachycardia, but no episodes of ventricular tachycardia recorded on the baseline or predischarge study ambulatory electrocardiograms, had a more than 85% reduction in premature ventricular complexes. Flecainide decreased the number of premature ventricular complexes by 75% or more in 24 patients, and by less than 75% in 5 additional patients. These findings and a comparison of the observations on ambulatory electrocardiograms obtained during long-term treatment are shown in Figure 1.

ADVERSE EFFECTS

Twenty-three patients had cardiac or noncardiac adverse effects during the in-hospital phase of the trial (Table 3). The commonest cardiac adverse effect was worsening of preexisting congestive heart failure, which occurred in three patients. This effect was controlled in each patient by an adjustment in dose of diuretics. These patients had left ventricular ejection fractions before treatment of 23%, 23%, and 36%, respectively. New rate-related left bundle branch block was seen in three patients during flecainide treatment. One patient had a proarrhythmic response consisting of an eightfold increase in the number of ventricular tachycardia episodes, a sixfold increase in the number of premature ventricular complexes over 24 hours, and the development of nonsustained ventricular tachycardia during an exercise test, which had not been seen before treatment with flecainide.

The commonest noncardiac side effect, blurring of vision, occurred in 14 patients and was associated with dizziness or headache in 5 patients. Other less frequent side

Table 1. Changes in Electrocardiographic Recordings in 32 Patients Given Flecainide for Nonsustained Ventricular Tachycardia*

	Baseline*	After Treatment*	*p* Value
Heart rate, *beats/min*	72 ± 3	69 ± 2	NS
PR interval, *ms*	172 ± 5	203 ± 6	0.0001
QRS duration, *ms*	98 ± 3	118 ± 6	0.0003
QTc interval, *ms*	456 ± 9	449 ± 7	NS

* Values expressed as mean ± SD. NS = not significant.

Table 2. Results of 24-Hour Ambulatory Electrocardiographic Monitoring in 32 Patients Given Flecainide for Nonsustained Ventricular Tachycardia

Patient Number	Diagnosis	Before Treatment			After Treatment			Dose	Plasma Level
		Premature Ventricular Complexes	Couplets	Runs*	Premature Ventricular Complexes	Couplets	Runs		
		n			*n*			*mg*	*ng/mL*
1	Coronary artery disease	4364	8	0	558	2	0	200	598
2	Mitral valve prolapse	3041	146	50	1468	0	0	500	986
3	Mitral valve prolapse	7309	283	4	1256	1	0	200	927
4	Coronary artery disease	2555	60	5	10	0	0	300	379
5	Mitral valve prolapse	31 552	5630	71	2486	62	0	300	527
6	Coronary artery disease	9804	5	1	13 225	6	0	200	465
7	Cardiomyopathy	11 602	429	34	2398	56	5	300	279
8	Mitral valve prolapse	28 258	629	29	20 427	5	0	300	883
9	Primary electrical disorder	11 521	108	2	1520	0	0	400	ND†
10	Coronary artery disease	12 966	74	9	2837	8	1	200	203
11	Coronary artery disease	11 121	676	95	964	205	4	300	463
12	Mitral valve prolapse	1909	15	2	119	0	0	300	515
13	Coronary artery disease	20 759	1941	356	885	4	1	300	1121
14	Coronary artery disease	15 647	0	5	6	0	0	400	ND
15	Coronary artery disease	1811	68	2	43	0	0	400	ND
16	Coronary artery disease	33 303	2452	291	15	0	0	400	ND
17	Coronary artery disease	4444	612	366	550	0	0	300	478
18	Coronary artery disease	2701	208	3	303	10	0	200	851
19	Coronary artery disease	49 269	3136	3280	8689	94	1	300	333
20	Coronary artery disease	35 403	5034	109	1642	30	0	300	369
21	Coronary artery disease	51 137	3040	434	126	0	0	200	ND
22	Coronary artery disease	13 746	2028	190	43	0	0	300	400
23	Coronary artery disease	31 476	1938	197	23 428	144	16	400	494
24	Cardiomyopathy	3600	100	16	97	14	11	300	747
25	Cardiomyopathy	6865	194	12	37 274	690	94	300	273
26	Coronary artery disease	2566	252	22	139	0	0	400	426
27	Coronary artery disease	8496	224	2	12	2	0	400	ND
28	Coronary artery disease	11 112	366	7	51	0	0	300	490
29	Rheumatic valvular disease	13 420	1160	64	1070	112	0	400	1052
30	Mitral valve prolapse	2666	1028	40	...	...	...	400	416
31	Mitral valve prolapse	4827	208	3	14	0	0	300	458
32	Coronary artery disease	28 864	2518	22	14 165	16	0	300	622

* Three consecutive ventricular complexes.
† ND = not determined.

Table 3. Adverse Effects of Flecainide in 32 Patients with Nonsustained Ventricular Tachycardia

	Patients*
	n
Proarrhythmia	1
Congestive heart failure	3
Rate-related left bundle branch block	3
Blurring of vision	14
Headache	4
Dizziness	5
Weakness	1
Fatigue	1
Nausea	2
Insomnia	1
Vertigo	1
Tinnitus	1

* Of the 32 patients, 23 had adverse effects and treatment was discontinued because of adverse effects in 1. Note that the same patient may have had more than one side effect

effects were nausea, insomnia, weakness, fatigue, vertigo, and tinnitus. None of these noncardiac side effects were severe enough to warrant discontinuation of treatment and they responded to either a decrease in dose of flecainide or a change in drug dispensation from twice to three times a day.

LONG-TERM TREATMENT

Thirty patients completed the in-hospital phase of the trial and received long-term treatment. Of the 30 patients who entered the outpatient phase of the study, 22 remained in the trial at follow-ups ranging from 4 to 28 months (mean, 13 ± 7). The courses of patients during the in-hospital and long-term phases of the treatment are shown in Figure 2. Dosages of flecainide were decreased during follow-up in 5 patients because of recurrent noncardiac side effects. Two of these five patients had undesirably high plasma levels of flecainide (1121 and 1752 ng/mL). Three patients required dosage increases to maintain total suppression of complex forms of ventricular ectopy during ambulatory monitoring. Mean plasma flecainide levels increased from 604 ng/mL to 714 ng/mL in 8 patients who had measurements at discharge from the hospital and 6 months afterwards with no intercurrent change in drug dosage: the change is not statistically significant.

Flecainide treatment was discontinued in one patient at his request after 11 months of successful therapy. Treatment also was discontinued in one patient after 4 months because of persistent chest wall paresthesia, constipation, and impotence. The relationship of these symptoms to the use of flecainide is unclear because some symptoms have persisted after withdrawal of the drug. In one patient, treatment had to be discontinued for late ineffectiveness at 12 months.

Five patients died during the follow-up period. One patient died suddenly after 7 months of treatment, 4 weeks after a 24-hour ambulatory electrocardiogram had shown total suppression of ventricular tachycardia and complex ectopy. Two patients died of acute myocardial infarctions and one patient died on the way to the hospital after an episode of prolonged chest pain. Among the three patients who died after ischemic events, two had histories of recurrent angina pectoris, and one died of hemodynamic consequences of the infarction. The fifth patient who died during flecainide treatment had become critically ill from intractable respiratory insufficiency. The flecainide plasma level had increased from 875 ng/mL 2 weeks earlier to 2306 ng/mL at the time of death, during which time the patient had been receiving a stable dosage of flecainide. The patient died of a combination of intractable respiratory insufficiency and hypotensive ventricular rhythm of 110 beats/min that probably had been caused by toxic amounts of flecainide. None of the patients had any biochemical or hematologic adverse effects during follow-up.

LEFT VENTRICULAR FUNCTION

Of the 32 patients enrolled in the trial, 27 had measurements of left ventricular ejection fraction done before initiation of therapy. Fifteen had left ventricular ejection fractions of 40% or greater, and 12 had fractions of less than 40%. All 12 patients who had ejection fractions of less than 40% were discharged on flecainide, and 4 died during follow-up. One died suddenly, 1 died after a prolonged ischemic episode, 1 died during an acute myocardial infarction, and 1 died of respiratory failure. At a mean follow-up of 12 months, 8 of the patients who had marked left ventricular dysfunction were still receiving flecainide and had significant suppression of ventricular

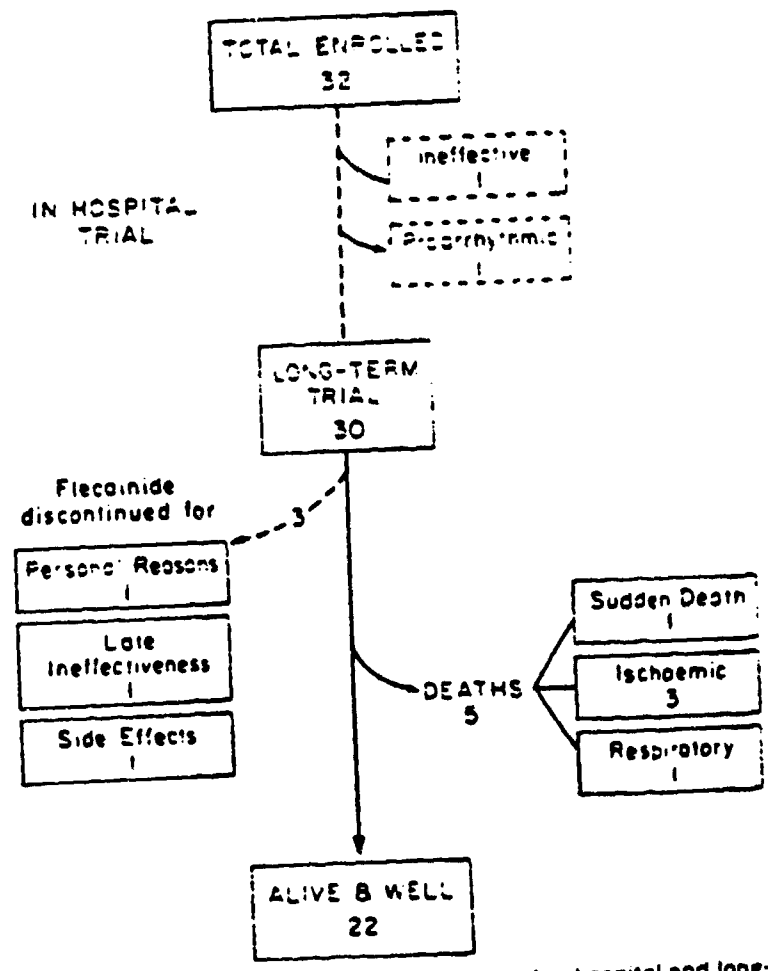

Figure 2. Flow diagram showing the results of in-hospital and long-term trials using flecainide to treat nonsustained ventricular tachycardia (mean follow-up, 13 months; range, 4 to 28).

Table 4. Analysis of Flecainide Treatment in 32 Patients by Diagnosis and Ventricular Function

	Patients		Results of Treatment		
	Total	Discharged on Flecainide	Treatment Discontinued	Eventual Death	Sudden Death
			n		
Diagnosis					
Coronary artery disease	20	20	2	3	1
Other	12	10	1	1	0
Left ventricular ejection fraction					
< 40%	12	12	0	3	1
≥ 40%	15	13	1	0	0
Not measured	5	5	2	1	0

tachycardia. Of the 15 patients who did not have marked left ventricular dysfunction (ejection fraction of 40% or greater), 13 were discharged from the hospital receiving flecainide. One patient from this group had flecainide treatment discontinued during long-term follow-up because of late ineffectiveness, and 12 have remained on treatment with adequate suppression of ventricular tachycardia. None of the patients from this group died. The outcome in relation to left ventricular function is shown in Table 4.

CORONARY ARTERY DISEASE

Of the 32 patients, 20 had coronary artery disease and all were discharged from the hospital receiving flecainide. Four of these patients died (1 suddenly) and the others remained on flecainide, achieving adequate suppression of ventricular tachycardia throughout follow-up. Of the 12 patients who had other diagnoses, 10 were discharged from the hospital receiving flecainide. Treatment was later discontinued in 1 of these patients due to subjective intolerance. One patient who had no coronary artery disease died of intractable respiratory insufficiency and 9 remained on flecainide with adequate suppression of ventricular tachycardia. Results are summarized in Table 4.

Discussion

The limited clinical experience accumulated thus far in the United States with the use of flecainide has shown the drug to be safe and highly effective in suppressing chronic, stable ventricular ectopy in patients who have no advanced organic heart disease (11, 12). The true efficacy and safety of an antiarrhythmic drug, however, can only be measured when it is given to patients at risk who, in general, have overt structural or ischemic heart disease associated with high-grade ventricular ectopy or sustained tachyarrhythmias. The proarrhythmic and myocardial depressant potentials of an antiarrhythmic drug will be reflected best in these patients. Reports from earlier trials of flecainide in high-risk patients raised concerns of an unacceptably high incidence of major proarrhythmic complications (7). Our observations in this group of patients indicate that flecainide can achieve long-term suppression of nonsustained ventricular tachycardia in a high percentage of patients with ischemic or structural heart disease even after several previous unsuccessful antiarrhythmic trials, and even in the presence of significant left ventricular dysfunction. Furthermore, proarrhythmic or other limiting adverse effects occurred infrequently. We believe that the low rate of serious complications in our trial, similar to that seen by others (13), is attributable to our strict adherence to the following rules: treatment was initiated in the hospital; dosage began with no more than 200 mg/d and loading doses were not used; increases in dosage were not made more often than every 4 days; dosages higher than 400 mg/d were not given; and plasma levels higher than 1 μg/mL were avoided. We therefore recommend following these rules when flecainide therapy is initiated in patients who have ventricular arrhythmias associated with advanced organic heart disease.

A negative inotropic effect with worsening of signs and symptoms of congestive heart failure can be an adverse effect from antiarrhythmic therapy and was seen in 3 of our patients. This side effect, which was anticipated on the basis of studies done by Legrand and colleagues (14) and Josephson and colleagues (15), occurred only in the presence of preexisting left ventricular dysfunction and was alleviated after adjustment of standard therapy for congestive heart failure. Flecainide must be used with caution in the treatment of patients who have severely depressed left ventricular function and an unstable cardiac output that causes variations in renal elimination of the drug. This mechanism may have resulted in flecainide accumulating to toxic levels in our patient who died of respiratory insufficiency.

Unlike serious adverse effects, nonlimiting side effects (visual ones, in particular) occurred frequently and required rearrangement of therapy for several patients. Overall, however, the drug was well tolerated on a long-term basis and few patients abandoned the trial because of side effects. Recently, Meinertz and associates (16) reported a long-term increase in plasma concentration of flecainide with no change in total daily dosage. In our study, a small rise in plasma flecainide level was measured in eight patients between discharge from the hospital and 6 months of follow-up, which suggests that even after 4 days of treatment, stable levels may not have been reached in some patients.

LIMITATION OF THE STUDY

Our trial was not controlled because strict comparisons with the effects of other antiarrhythmic agents were not its intent. Thus, our results should not be interpreted as demonstrative of the superior antiarrhythmic activity of

flecainide over other agents. Earlier randomized comparative trials in a low-risk population did, however, show a greater efficacy of flecainide in suppressing ventricular ectopy compared with that derived from both quinidine and disopyramide (12, 17).

A few patients included in this report had three or fewer episodes of ventricular tachycardia during baseline electrocardiographic monitoring. The short- and long-term elimination of nonsustained ventricular tachycardia in such patients thus may have been a reflection of mere spontaneous variability of the arrhythmia. In general, however, these patients had been selected for entry into the study because of frequently recurrent ventricular tachycardia as well as refractoriness to antiarrhythmic treatment. The absence of complex and high-grade ventricular ectopy on ambulatory electrocardiographic recordings during long-term treatment therefore was most likely a reflection of drug effect.

Although we tried to enroll patients who had symptoms, we recognize that suppression of symptoms as an endpoint of treatment in patients who have nonsustained tachyarrhythmias is unreliable and highly subjective, particularly when the trial does not involve controls. Therefore, we preferred to base our assessment of drug effect on 24-hour electrocardiographic measurements. In many of our patients, however, the effective control of arrhythmia was associated with the disappearance of symptoms, particularly palpitations, and these results contributed to the high compliance to, and acceptance of, long-term treatment.

Although one patient who received long-term treatment with flecainide died suddenly, this trial does not contribute information on the value of antiarrhythmic therapy in patients who have organic heart disease and a history of nonsustained ventricular tachyarrhythmias; only a large-scale placebo-controlled study could resolve this issue. In the meantime, if treatment is indicated for a patient who has nonsustained ventricular tachycardia, flecainide represents one of six choices available to the clinician. Because of its potentially serious side effects, we urge caution in its use, particularly in the early phase of treatment in patients who have underlying myocardial disease.

CONCLUSIONS

Results of this study indicate that flecainide can provide effective long-term suppression of nonsustained ventricular tachycardia in almost 70% of patients with organic heart disease. Adverse effects occurred in several patients initially, but tended to be nonlimiting. Aggravation of heart failure occurred in 9% of patients. Although proarrhythmic complications occurred infrequently, we recommend the initiation of treatment with flecainide in the hospital where the rhythm can be monitored. In addition, plasma drug levels should be surveyed closely both during the initial phase of treatment and during long-term follow-up.

▶ Requests for reprints should be addressed to Rodolphe Ruffy, M.D., Arrhythmia Service, Jewish Hospital at Washington University Medical Center, 216 S. Kingshighway, St. Louis, MO 63110.

References

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DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	77	M	1	24	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Myocardial infarction, heart block, cardiac arrest
Pt. is believed to have suffered a myocardial infarction on 24 Jan. 86 when he was admitted with recurrent ventricular tachycardia. The latter converted spontaneously following attempts at cardioversion. During hospitalization he was said to have developed episodes of non-specified heart block. Death was due to cardiac arrest.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

No autopsy performed.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

Tambocor®/flecainide acetate

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

15. DAILY DOSE: 100 mg

16. ROUTE OF ADMINISTRATION: Oral

17. INDICATION(S) FOR USE: Ventricular tachycardia, atrial flutter

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

18. THERAPY DATES *(From/To)*: 12 Apr. 85 to 25 Jan. 86

19. THERAPY DURATION: 9 months

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

allopurinol/ -	10 months	psyllium hydrophilic mucilloid/Metamucil	9 months
digoxin/ -	9 months	furosemide/Lasix	6 months
nitroglycerin/Nitrobid	9 months	diocytl sodium sulfosuccinate/Colace	9 months
prednisone/ -	9 months	potassium/ -	6 months

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Arteriosclerotic heart disease, coronary artery disease, atrial flutter, nonsustained ventricular tachycardia.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

Riker Laboratories, Inc.
225-1S-07/3M Center
St. Paul, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: NDA 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 1/27/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO N/A

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	62	M	02	21	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
MYOCARDIAL INFARCTION Death
Acute myocardial infarction resulted in secondary cardiogenic shock and death.
10/16/87 This case was subsequently reported in the literature in "Flecainide in the Treatment of Nonsustained Ventricular Tachycardia"; Annals of Internal Medicine 1986;105:493-498.

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
2/21/86; BUN 19; Glucose 155; pH 7.43; Na 134; CPK 22; PCO2 29; K 4.1; LDH 142; Hgb 17.3; PO2 137; WBC 15,000; CO2 18.
Serial EKGs showed complete left bundle branch block and an idioventricular rhythm. Serial cardiac enzymes didn't show significant elevation. Chest X-ray showed massive cardiomegaly and changes consistent with CHF.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*
03/21/85 - 02/21/86

19. THERAPY DURATION
11 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN	11 MONTHS	NITROGLYCERIN	11 MONTHS
POTASSIUM CHLORIDE	11 MONTHS	DIOCTYL SODIUM SULFOSUCCINATE	10 MONTHS
AMIODARONE	10 MONTHS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Severe ischemic and congestive cardiomyopathy, history of malignant ventricular arrhythmias, severe diffuse multivessel disease.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
10/16/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [X] LITERATURE
[ ] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Flecainide in the Treatment of Nonsustained Ventricular Tachycardia

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Thirty-two patients received flecainide acetate for nonsustained ventricular tachycardia after having had unsuccessful treatment with a mean of four antiarrhythmic drugs. The mean left ventricular ejection fraction was 41% in 27. Thirty-one patients had organic heart disease, and 22 patients had arrhythmia-related symptoms. Total suppression of ventricular tachycardia occurred in 22 patients. Thirty patients were discharged from the hospital receiving flecainide at a mean (± SD) dosage of 325 ± 76 mg/d and 26 of these patients attained a mean trough plasma drug level of 567 ± 254 ng/mL. One patient had proarrhythmia and 3 had worsening of heart failure. Twenty-two patients remained in the trial for a mean follow-up of 13 ± 7 months. Five patients died (1 suddenly) during the follow-up period. Our data indicate that flecainide suppresses refractory nonsustained ventricular tachycardia in 69% of patients who have organic heart disease. Serious adverse effects were minimized by initiation of treatment in the hospital and careful surveillance of electrocardiograms and plasma drug levels.

FLECAINIDE ACETATE is a new drug classified generally as a Ic antiarrhythmic agent because of its pronounced negative dromotropic effect on cardiac tissues in the absence of marked alterations in repolarization (1). A few cases of its use in treating recurrent sustained and nonsustained ventricular tachycardia have been reported, but clinical experience with this drug in the United States remains limited (2–5). We describe the combined experience of three arrhythmia centers that have used flecainide to treat patients with nonsustained ventricular tachycardia who had had previous unsuccessful treatment with other antiarrhythmic drugs.

We examined 32 patients who were part of a larger group enrolled in a trial of flecainide for the treatment of ventricular tachyarrhythmias. The results of this trial in patients who had recurrent, sustained ventricular tachycardia or out-of-hospital cardiac arrest have been presented in a separate report (3).

Patients and Methods

Seventeen men and 15 women aged 32 to 76 years (mean ± SD, 56 ± 14) who had recurrent, nonsustained ventricular tachycardia participated in the study between 1 January 1982 and 31 December 1984 at the Jewish Hospital at Washington University in St. Louis, the Medical College of Wisconsin Hospitals in Milwaukee, and Hermann Hospital at the University of Texas Medical School in Houston.

Nonsustained ventricular tachycardia was defined as six or more consecutive ventricular complexes occurring at a rate of more than 100 beats/min, lasting less than 30 seconds, and not requiring artificial termination because of hemodynamic instability. Twenty patients had coronary artery disease that was diagnosed by electrocardiographic findings of infarction in 6 and by angiographic documentation of coronary stenoses in 14. Fifteen patients had sustained myocardial infarctions lasting from 1 to 180 months (mean, 48 ± 55) before entry into trial and 5 patients had stable angina pectoris. Seven patients had mitral valve prolapse, 3 had congestive cardiomyopathy, 1 had rheumatic valvular disease, and 1 had no structural heart disease. Twenty-two of these patients had symptoms believed to be arrhythmia related. The commonest symptom, palpitation, occurred in 18 patients. Other presenting symptoms of syncope, near syncope, and shortness of breath correlated with recorded arrhythmias in 4 patients. Previous unsuccessful antiarrhythmic therapy included the use of one to eight drugs (mean, four). Failure of previous antiarrhythmic therapy was due to intolerance or ineffectiveness as determined by clinical criteria that included the use of telemetry monitoring and ambulatory electrocardiograms. When patients were referred after several unsuccessful drug trials, attempts by the investigators to confirm intolerance or inefficacy of previously administered drugs generally were not made unless they thought inappropriate doses had been given before referral. Left ventricular ejection fraction measured in 27 patients ranged from 18% to 60% (mean, 41% ± 13%).

Patients who had PR intervals of more than 0.25 second, second or higher degree atrioventricular blocks, creatinine clearances of less than 20 mL/min, or digitalis-induced arrhythmias, and patients who were pregnant or of childbearing potential were excluded from study participation. Efforts were made to avoid the concomitant use of calcium channel blockers or the enrollment of patients totally dependent on artificial pacing. In all patients, flecainide was the only antiarrhythmic drug used.

STUDY PROTOCOL

The patients were admitted to a telemetry unit after having had electrocardiographic determination of nonsustained ventricular tachycardia, and were continuously monitored throughout the hospital phase of the trial. After granting informed consent, they had pretreatment evaluations, during which all antiarrhythmic drug treatment was discontinued. This evaluation included a patient history, physical examination, 12-lead electrocardiogram, roentgenogram of the chest, ophthalmologic examination, and measurement of left ventricular function by radionuclide ventriculography or, when indicated, contrast angiography. Twenty-four hour ambulatory electrocardiographic recordings, taken after a clearance from previous antiarrhythmic treatment involving at least five drug half-lives, were repeated during treatment with the highest tolerated dose of flecainide. All tapes were analyzed at a central computerized facility (Cardio Data Systems, Haddonfield, New Jersey).

Flecainide treatment was then begun orally at an initial dosage of 100 mg every 12 hours. If the drug was well tolerated but ventricular ectopy persisted, the dosage was increased in 100-mg/d increments every 2 to 4 days. For the patients enrolled in the study during the first year, the maximum daily dose was limited to 600 mg. The administrators of the drug decreased this limit to 400 mg for all patients enrolled in 1983 and 1984 because of proarrhythmic effects that occurred during at-

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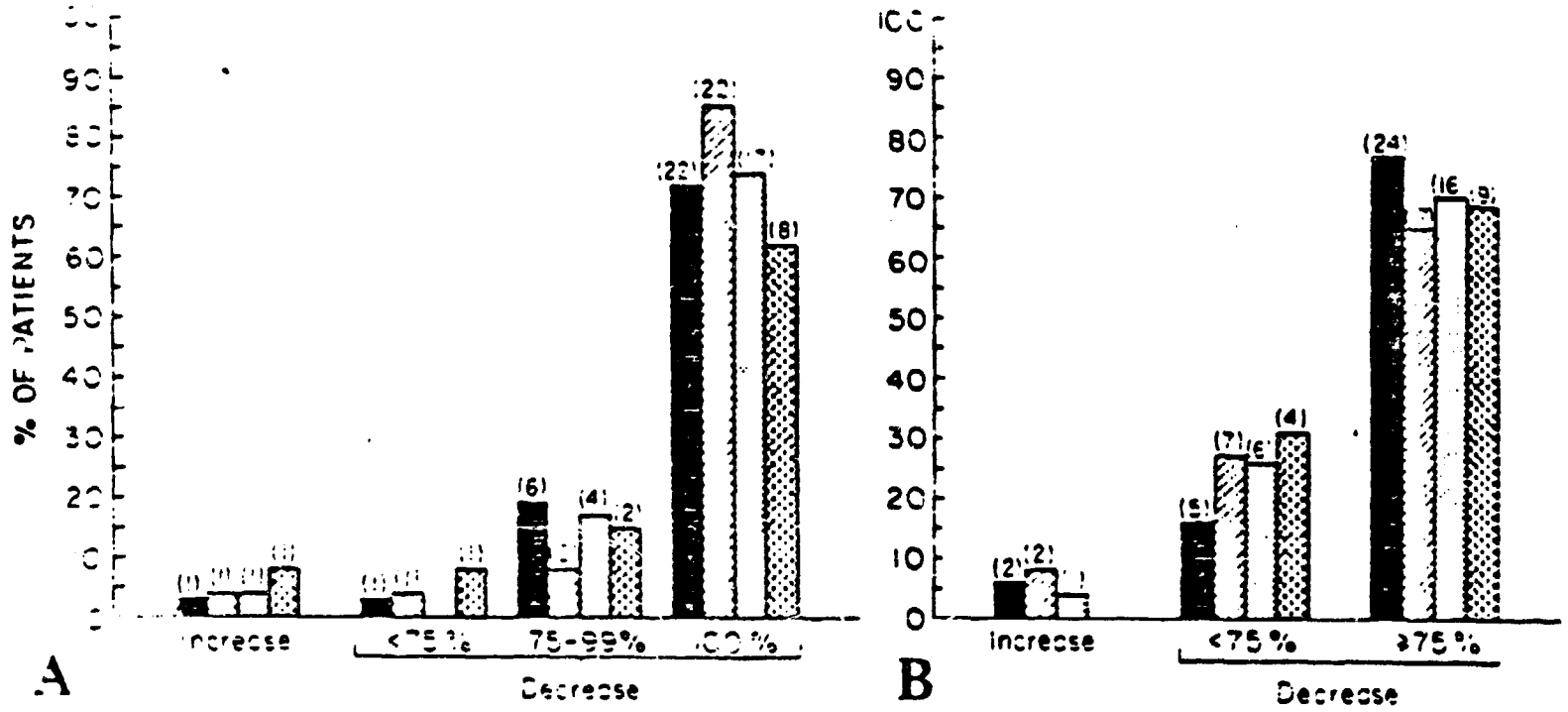

Figure 1. Percentage of patients compared with baseline who showed reductions in ventricular tachycardia events (*panel A*) and premature ventricular complexes (*panel B*) on 24-hour ambulatory electrocardiographic recordings. Values given for 31 patients at discharge (*solid bars*), 26 patients at 3 months (*hatched bars*), 23 patients at 6 months (*dotted bars*), and 13 patients at 12 months (*cross-hatched bars*).

ment with higher doses. In addition, an interval of 4 days was required between each dose increment. On long-term treatment, only one of the patients reported here received dosages of higher than 400 mg/d. Twelve-lead electrocardiograms were recorded on 25-mm/s paper speed and the PR, QRS, and QT intervals were measured using calipers before each increase in dosage. Trough plasma flecainide levels were determined in 26 patients before each dosage increment and at the maximum tolerated dose before discharge from the hospital by the laboratory of S. F. Chang (Riker Laboratories, Inc., St. Paul, Minnesota). Details of this liquid chromatographic method have been published (9-10). If patients had had histories of exercise-induced or exercise-exacerbated arrhythmia, they were given symptom-limited treadmill tests before discharge from the hospital to monitor the effectiveness of treatment during exercise.

Long-term treatment with flecainide was offered after a 75% or greater suppression of episodes of nonsustained ventricular tachycardia as determined by predischarge ambulatory electrocardiographic recordings (note that for 24-hour ambulatory electrocardiographic monitoring, ventricular tachycardia was defined as more than three consecutive ventricular complexes), a 75% or greater measured reduction in premature ventricular complexes, and good subjective tolerance of the drug in doses found effective according to these criteria.

Patients discharged on flecainide were seen regularly in outpatient clinics for long-term monitoring of drug safety and efficacy and for verification of compliance. Efficacy was verified by patient questioning and repeating 24-hour ambulatory electrocardiographic monitoring 1 month after discharge and thereafter at 3-month intervals (Figure 1). A 12-lead electrocardiogram and blood specimens were obtained at each visit for determination of hematologic and biochemical profiles. Compliance was verified by measurement of plasma drug levels. Follow-up radionuclide angiograms were ordered for patients who were in New York Heart Association class III or IV or for patients who developed signs or symptoms of congestive heart failure.

DATA ANALYSIS

We stored data in a statistical analysis system database using the Washington University mainframe computer system (IBM, Poughkeepsie, New York) and analyzed data using *t*-tests. Pooled values are reported as mean ± SD.

Results

Of the 32 patients in the study, 30 completed the in-hospital phase of the trial and received flecainide after discharge from the hospital. Flecainide treatment was discontinued for early ineffectiveness in 1 patient and because of a proarrhythmic effect in 1 (*see* below). The dosage at discharge ranged from 200 to 500 mg/d (mean, 315 ± 76). Trough plasma flecainide levels, measured in 26 patients, ranged from 203 to 1121 ng/mL (mean, 560 ± 254).

CHANGES ON ELECTROCARDIOGRAMS

Comparison of 12-lead electrocardiographic recordings before and during flecainide treatment showed a statistically significant increase in the mean PR interval from 172 ± 5 ms to 203 ± 6 ms ($p = 0.0001$), and in QRS duration from 98 ± 3 ms to 118 ± 6 ms ($p = 0.0003$). No statistically significant change in heart rate or corrected QT interval occurred during flecainide treatment. These electrocardiographic changes are summarized in Table 1.

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

We analyzed baseline and predischarge 24-hour ambulatory electrocardiograms in 31 patients (Table 2). Total suppression of ventricular tachycardia (more than three consecutive ventricular complexes) was achieved in 22 patients, and a greater than 75% suppression was achieved in 6 patients. One patient had a marked reduction in premature ventricular complexes and a less than 75% suppression of episodes of ventricular tachycardia, but remained in the trial because of the marked shortening and slowing of the runs. One patient left the trial

because [illegible] premature ventricular complexes and the number of episodes of ventricular tachycardia that occurred during treatment. One patient who had had previous electrocardiographic documentation of ventricular tachycardia, but no episodes of ventricular tachycardia recorded on the baseline or predischarge study ambulatory electrocardiograms, had a more than 85% reduction in premature ventricular complexes. Flecainide decreased the number of premature ventricular complexes by 75% or more in 24 patients, and by less than 75% in 5 additional patients. These findings and a comparison of the observations on ambulatory electrocardiograms obtained during long-term treatment are shown in Figure 1.

ADVERSE EFFECTS

Twenty-three patients had cardiac or noncardiac adverse effects during the in-hospital phase of the trial (Table 3). The commonest cardiac adverse effect was worsening of preexisting congestive heart failure, which occurred in three patients. This effect was controlled in each patient by an adjustment in dose of diuretics. These patients had left ventricular ejection fractions before treatment of 23%, 23%, and 36%, respectively. New rate-related left bundle branch block was seen in three patients during flecainide treatment. One patient had a proarrhythmic response consisting of an eightfold increase in the number of ventricular tachycardia episodes, a sixfold increase in the number of premature ventricular complexes over 24 hours, and the development of nonsustained ventricular tachycardia during an exercise test, which had not been seen before treatment with flecainide.

The commonest noncardiac side effect, blurring of vision, occurred in 14 patients and was associated with dizziness or headache in 5 patients. Other less frequent side

Table 1. Changes in Electrocardiographic Recordings in 32 Patients Given Flecainide for Nonsustained Ventricular Tachycardia*

	Baseline*	After Treatment*	*p* Value
Heart rate, *beats/min*	72 ± 3	69 ± 2	NS
PR interval, *ms*	172 ± 5	203 ± 6	0.0001
QRS duration, *ms*	98 ± 3	118 ± 6	0.0003
QTc interval, *ms*	456 ± 9	449 ± 7	NS

* Values expressed as mean ± SD. NS = not significant.

Table 2. Results of 24-Hour Ambulatory Electrocardiographic Monitoring in 32 Patients Given Flecainide for Nonsustained Ventricular Tachycardia

Patient Number	Diagnosis	Before Treatment			After Treatment			Dose	Plasma Level
		Premature Ventricular Complexes	Couplets	Runs*	Premature Ventricular Complexes	Couplets	Runs		
		n			*n*			*mg*	*ng/mL*
1	Coronary artery disease	4364	8	0	556	2	0	200	595
2	Mitral valve prolapse	3041	146	50	1403	0	0	500	956
3	Mitral valve prolapse	7309	283	4	1256	1	0	200	927
4	Coronary artery disease	2555	60	5	10	0	0	300	378
5	Mitral valve prolapse	31 552	5630	71	2456	62	0	300	527
6	Coronary artery disease	3524	5	1	13 224	6	0	200	465
7	Cardiomyopathy	11 612	420	34	2366	16	5	300	270
8	Mitral valve prolapse	28 256	620	26	23 427	5	0	300	883
9	Primary electrical disorder	11 521	108	2	1522	2	0	400	ND†
10	Coronary artery disease	12 956	74	6	2837	6	1	200	203
11	Coronary artery disease	11 121	676	95	964	205	4	300	463
12	Mitral valve prolapse	1909	15	2	119	0	0	300	515
13	Coronary artery disease	20 759	1941	356	855	4	1	300	1121
14	Coronary artery disease	15 647	0	5	6	0	0	400	ND
15	Coronary artery disease	1811	68	2	43	0	0	400	ND
16	Coronary artery disease	33 303	2452	291	15	0	0	400	ND
17	Coronary artery disease	4444	612	366	550	0	0	300	478
18	Coronary artery disease	2701	208	3	303	10	0	200	851
19	Coronary artery disease	49 269	3136	3280	8089	94	1	300	333
20	Coronary artery disease	35 403	5034	109	1642	30	0	300	369
21	Coronary artery disease	51 137	3040	434	126	0	0	200	ND
22	Coronary artery disease	13 746	2028	190	43	0	0	300	400
23	Coronary artery disease	31 476	1938	197	23 428	144	16	400	494
24	Cardiomyopathy	3600	100	16	97	14	11	300	747
25	Cardiomyopathy	6865	194	12	37 274	690	94	300	273
26	Coronary artery disease	2566	252	22	139	0	0	400	426
27	Coronary artery disease	5496	224	2	12	2	0	400	ND
28	Coronary artery disease	11 112	366	7	51	0	0	300	490
29	Rheumatic valvular disease	13 420	1160	64	1070	112	0	400	1052
30	Mitral valve prolapse	2666	1028	40	...	...	...	400	416
31	Mitral valve prolapse	4827	208	3	14	0	0	300	458
32	Coronary artery disease	28 864	2518	22	14 165	16	0	300	622

* Three consecutive ventricular complexes.
† ND = not determined

Table 3. Adverse Effects of Flecainide in 32 Patients with Nonsustained Ventricular Tachycardia

	Patients*
	n
Proarrhythmia	1
Congestive heart failure	3
Rate-related left bundle branch block	3
Blurring of vision	14
Headache	4
Dizziness	5
Weakness	1
Fatigue	1
Nausea	2
Insomnia	1
Vertigo	1
Tinnitus	1

* Of the 32 patients, 23 had adverse effects and treatment was discontinued because of adverse effects in 1. Note that the same patient may have had more than one side effect.

effects were nausea, insomnia, weakness, fatigue, vertigo, and tinnitus. None of these noncardiac side effects were severe enough to warrant discontinuation of treatment and they responded to either a decrease in dose of flecainide or a change in drug dispensation from twice to three times a day.

LONG-TERM TREATMENT

Thirty patients completed the in-hospital phase of the trial and received long-term treatment. Of the 30 patients who entered the outpatient phase of the study, 22 remained in the trial at follow-ups ranging from 4 to 28 months (mean, 13 ± 7). The courses of patients during the in-hospital and long-term phases of the treatment are shown in Figure 2. Dosages of flecainide were decreased during follow-up in 5 patients because of recurrent noncardiac side effects. Two of these five patients had undesirably high plasma levels of flecainide (1121 and 1752 ng/mL). Three patients required dosage increases to maintain total suppression of complex forms of ventricular ectopy during ambulatory monitoring. Mean plasma flecainide levels increased from 604 ng/mL to 714 ng/mL in 5 patients who had measurements at discharge from the hospital and 6 months afterwards with no intercurrent change in drug dosage; the change is not statistically significant.

Flecainide treatment was discontinued in one patient at his request after 11 months of successful therapy. Treatment also was discontinued in one patient after 4 months because of persistent chest wall paresthesia, constipation, and impotence. The relationship of these symptoms to the use of flecainide is unclear because some symptoms have persisted after withdrawal of the drug. In one patient, treatment had to be discontinued for late ineffectiveness at 12 months.

Five patients died during the follow-up period. One patient died suddenly after 7 months of treatment, 4 weeks after a 24-hour ambulatory electrocardiogram had shown total suppression of ventricular tachycardia and complex ectopy. Two patients died of acute myocardial infarctions and one patient died on the way to the hospital after an episode of prolonged chest pain. Among the three patients who died after ischemic events, two had histories of recurrent angina pectoris, and one died of hemodynamic consequences of the infarction. The fifth patient who died during flecainide treatment had become critically ill from intractable respiratory insufficiency. The flecainide plasma level had increased from 875 ng/mL 2 weeks earlier to 2306 ng/mL at the time of death, during which time the patient had been receiving a stable dosage of flecainide. The patient died of a combination of intractable respiratory insufficiency and hypotensive ventricular rhythm of 110 beats/min that probably had been caused by toxic amounts of flecainide. None of the patients had any biochemical or hematologic adverse effects during follow-up.

LEFT VENTRICULAR FUNCTION

Of the 32 patients enrolled in the trial, 27 had measurements of left ventricular ejection fraction done before initiation of therapy. Fifteen had left ventricular ejection fractions of 40% or greater, and 12 had fractions of less than 40%. All 12 patients who had ejection fractions of less than 40% were discharged on flecainide, and 4 died during follow-up. One died suddenly, 1 died after a prolonged ischemic episode, 1 died during an acute myocardial infarction, and 1 died of respiratory failure. At a mean follow-up of 12 months, 8 of the patients who had marked left ventricular dysfunction were still receiving flecainide and had significant suppression of ventricular

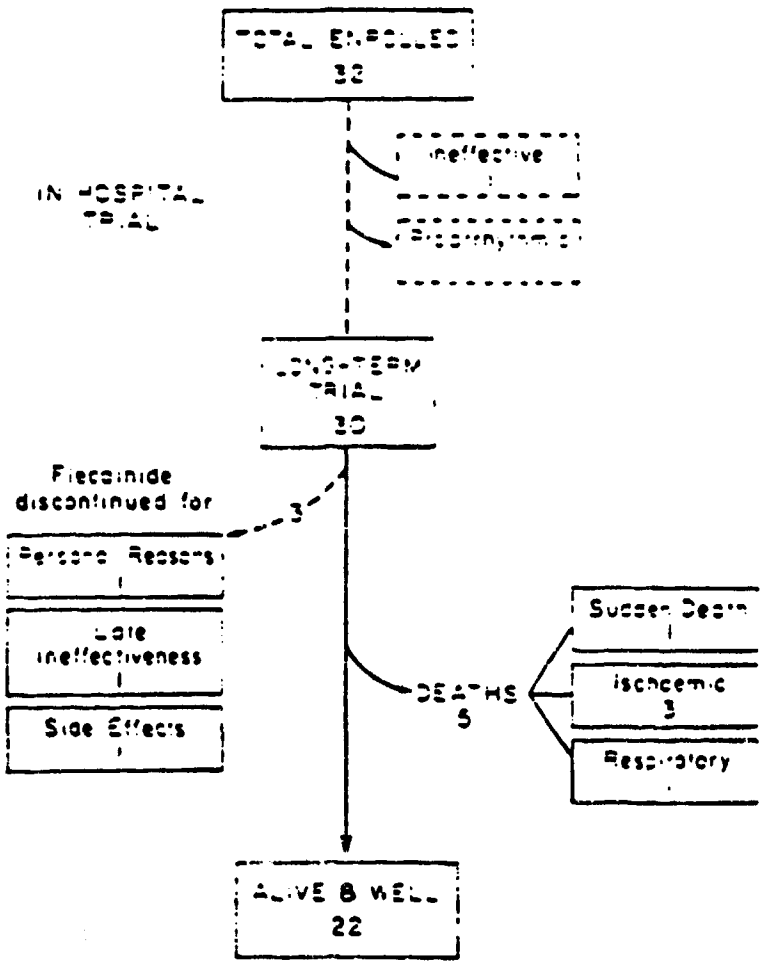

Figure 2. Flow diagram showing the results of in-hospital and long-term trials using flecainide to treat nonsustained ventricular tachycardia (mean follow-up, 13 months; range, 4 to 28).

Table 4. Analysis of Flecainide Treatment in 32 Patients by Diagnosis and Ventricular Function

	Patients		Results of Treatment		
	Total	Discharged on Flecainide	Treatment Discontinued	Eventual Death	Sudden Death
	n				
Diagnosis					
Coronary artery disease	20	20	2	3	1
Other	12	10	1	1	0
Left ventricular ejection fraction					
< 40%	12	12	0	3	1
≥ 40%	15	13	1	0	0
Not measured	5	5	2	1	0

tachycardia. Of the 15 patients who did not have marked left ventricular dysfunction (ejection fraction of 40% or greater), 13 were discharged from the hospital receiving flecainide. One patient from this group had flecainide treatment discontinued during long-term follow-up because of late ineffectiveness, and 12 have remained on treatment with adequate suppression of ventricular tachycardia. None of the patients from this group died. The outcome in relation to left ventricular function is shown in Table 4.

CORONARY ARTERY DISEASE

Of the 32 patients, 20 had coronary artery disease and all were discharged from the hospital receiving flecainide. Four of these patients died (1 suddenly) and the others remained on flecainide, achieving adequate suppression of ventricular tachycardia throughout follow-up. Of the 12 patients who had other diagnoses, 10 were discharged from the hospital receiving flecainide. Treatment was later discontinued in 1 of these patients due to subjective intolerance. One patient who had no coronary artery disease died of intractable respiratory insufficiency and 9 remained on flecainide with adequate suppression of ventricular tachycardia. Results are summarized in Table 4.

Discussion

The limited clinical experience accumulated thus far in the United States with the use of flecainide has shown the drug to be safe and highly effective in suppressing chronic, stable ventricular ectopy in patients who have no advanced organic heart disease (11, 12). The true efficacy and safety of an antiarrhythmic drug, however, can only be measured when it is given to patients at risk who, in general, have overt structural or ischemic heart disease associated with high-grade ventricular ectopy or sustained tachyarrhythmias. The proarrhythmic and myocardial depressant potentials of an antiarrhythmic drug will be reflected best in these patients. Reports from earlier trials of flecainide in high-risk patients raised concerns of an unacceptably high incidence of major proarrhythmic complications (7). Our observations in this group of patients indicate that flecainide can achieve long-term suppression of nonsustained ventricular tachycardia in a high percentage of patients with ischemic or structural heart disease even after several previous unsuccessful antiarrhythmic trials, and even in the presence of significant left ventricular dysfunction. Furthermore, proarrhythmic or other limiting adverse effects occurred infrequently. We believe that the low rate of serious complications in our trial, similar to that seen by others (13), is attributable to our strict adherence to the following rules: treatment was initiated in the hospital; dosage began with no more than 200 mg/d and loading doses were not used; increases in dosage were not made more often than every 4 days; dosages higher than 400 mg/d were not given, and plasma levels higher than 1 μg/mL were avoided. We therefore recommend following these rules when flecainide therapy is initiated in patients who have ventricular arrhythmias associated with advanced organic heart disease.

A negative inotropic effect with worsening of signs and symptoms of congestive heart failure can be an adverse effect from antiarrhythmic therapy and was seen in 3 of our patients. This side effect, which was anticipated on the basis of studies done by Legrand and colleagues (14) and Josephson and colleagues (15), occurred only in the presence of preexisting left ventricular dysfunction and was alleviated after adjustment of standard therapy for congestive heart failure. Flecainide must be used with caution in the treatment of patients who have severely depressed left ventricular function and an unstable cardiac output that causes variations in renal elimination of the drug. This mechanism may have resulted in flecainide accumulating to toxic levels in our patient who died of respiratory insufficiency.

Unlike serious adverse effects, nonlimiting side effects (visual ones, in particular) occurred frequently and required rearrangement of therapy for several patients. Overall, however, the drug was well tolerated on a long-term basis and few patients abandoned the trial because of side effects. Recently, Meinertz and associates (16) reported a long-term increase in plasma concentration of flecainide with no change in total daily dosage. In our study, a small rise in plasma flecainide level was measured in eight patients between discharge from the hospital and 6 months of follow-up, which suggests that even after 4 days of treatment, stable levels may not have been reached in some patients.

LIMITATION OF THE STUDY

Our trial was not controlled because strict comparisons with the effects of other antiarrhythmic agents were not its intent. Thus, our results should not be interpreted as demonstrative of the superior antiarrhythmic activity of

flecainide over other agents. Earlier randomized comparative trials in a low-risk population did, however, show a greater efficacy of flecainide in suppressing ventricular ectopy compared with that derived from both quinidine and disopyramide (12, 17).

A few patients included in this report had three or fewer episodes of ventricular tachycardia during baseline electrocardiographic monitoring. The short- and long-term elimination of nonsustained ventricular tachycardia in such patients thus may have been a reflection of mere spontaneous variability of the arrhythmia. In general, however, these patients had been selected for entry into the study because of frequently recurrent ventricular tachycardia as well as refractoriness to antiarrhythmic treatment. The absence of complex and high-grade ventricular ectopy on ambulatory electrocardiographic recordings during long-term treatment therefore was most likely a reflection of drug effect.

Although we tried to enroll patients who had symptoms, we recognize that suppression of symptoms as an endpoint of treatment in patients who have nonsustained tachyarrhythmias is unreliable and highly subjective, particularly when the trial does not involve controls. Therefore, we preferred to base our assessment of drug effect on 24-hour electrocardiographic measurements. In many of our patients, however, the effective control of arrhythmia was associated with the disappearance of symptoms, particularly palpitations, and these results contributed to the high compliance to, and acceptance of, long-term treatment.

Although one patient who received long-term treatment with flecainide died suddenly, this trial does not contribute information on the value of antiarrhythmic therapy in patients who have organic heart disease and a history of nonsustained ventricular tachyarrhythmias; only a large-scale placebo-controlled study could resolve this issue. In the meantime, if treatment is indicated for a patient who has nonsustained ventricular tachycardia, flecainide represents one of six choices available to the clinician. Because of its potentially serious side effects, we urge caution in its use, particularly in the early phase of treatment in patients who have underlying myocardial disease.

CONCLUSIONS

Results of this study indicate that flecainide can provide effective long-term suppression of nonsustained ventricular tachycardia in almost 70% of patients with organic heart disease. Adverse effects occurred in several patients initially, but tended to be nonlimiting. Aggravation of heart failure occurred in 9% of patients. Although proarrhythmic complications occurred infrequently, we recommend the initiation of treatment with flecainide in the hospital where the rhythm can be monitored. In addition, plasma drug levels should be surveyed closely both during the initial phase of treatment and during long-term follow-up.

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DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)* [redacted]

2. AGE YRS. 62

3. SEX M

4.-6. REACTION ONSET: MO. 02 | DA. 21 | YR. 86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
Death, myocardial infarction
Acute myocardial infarction resulted in secondary cardiogenic shock and death.

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
2/21/86: BUN 19; Glucose 155; pH 7.43; Na 134; CPK 22; PCO2 29; K 4.1; LDH 162; Hgb 17.3; PO2 137; WBC 15,000; CO2 18.
Serial EKGs showed complete left bundle branch block and an idioventricular rhythm. Serial cardiac enzymes didn't show significant elevation. Chest X-ray showed massive cardiomegaly and changes consistent with CHF.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
03/21/85 - 02/21/86

19. THERAPY DURATION
11 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN	11 MONTHS	NITROGLYCERIN	11 MONTHS
POTASSIUM CHLORIDE	11 MONTHS	DIOCYTL SODIUM SULFOSUCCINATE	10 MONTHS
AMIODARONE	10 MONTHS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Severe ischemic and congestive cardiomyopathy, history of malignant ventricular arrhythmias, severe diffuse multivessel disease.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO. [redacted]

24c. DATE RECEIVED BY MANUFACTURER
5/ 5/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [X] STUDY
- [ ] LITERATURE
- [ ] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)* [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612) 736-5016

ORIGINAL

REPORTS

3M

June 16, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are seven (7) Adverse Reaction Reports (Form FDA 1639) pertinent to adverse experiences which occurred in association with the use of the subject product.

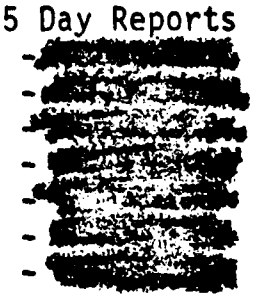
Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Enclosure: 15 Day Reports



Certified Mail P 504 523 659

7/7

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	72	M	04	27	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***OCCLUSION OF CORONARY ARTERY, HYPERTENSION* Death**
This 72 y.o. man had a history of ischemic heart disease, left ventricular failure, and sustained ventricular tachycardia since 1980. He experienced episodes of palpitations and angina, approximately once per month, with each lasting more than 30 minutes. He had no history of myocardial infarction. Flecainide 200 mg daily was started on 6/17/85. Plasma flecainide levels remained at about 0.3 mcg/ml throughout therapy On 4/27/87, the man died suddenly at home. Results at autopsy show cause of death to be atheromatous occlusion of the right coronary artery and hypertension.

13 RELEVANT TESTS LABORATORY DATA

Plasma flecainide levels throughout two years of therapy: 0.3 mcg/ml

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15 DAILY DOSE: 200 MG

16 ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

HERAPY DATES *(From To)*: 06/17/85 - 04/27/87

19 THERAPY DURATION: 22 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

BUMETANIDE/KCL	>2 YEARS	ISOSORBIDE DINITRATE	>2 YEARS
NITROGLYCERIN	>2 YEARS		

23 OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

DATE RECEIVED BY MANUFACTURER: 5/26/87

24d. REPORT SOURCE *(Check one)*

[X] FOREIGN ☐ STUDY ☐ LITERATURE
[X] HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT

[X] YES ☐ NO

25a. REPORT TYPE

[X] INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?

☐ YES ☐ NO

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

11-1

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000
(612)733-0633

ORIGINAL

3M

REPORTS

April 24, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Reports
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are three Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

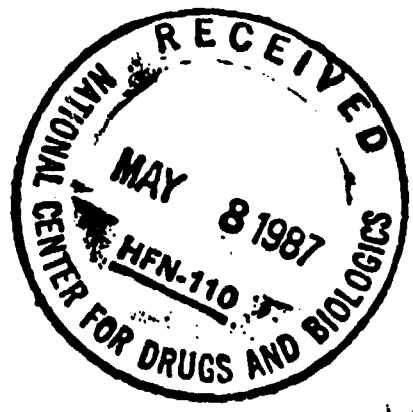
Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/dls

Enclosure - [redacted]

Certified Mail P 504 523 615



5/12

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

ENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	57	M	01	29	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ACUTE CARDIO-RESPIRATORY FAILURE, CORONARY ARTERY THROMBOSIS Death
This 57 y.o. man was started on flecainide 300 mg daily on 10/30/86 for atrial fibrillation. He had a medical history of ischemic heart disease since 1970 with angina and myocardial infarction, also in 1970. He was diagnosed with intermittent claudication and cardiomegaly, and underwent coronary artery bypass graft in 1986. While receiving flecainide, his EKG showed PR 0.248 sec. and QRS 0.156 sec. He was considered a high risk patient. On 1/29/87 he collapsed and died while dancing. Post-mortem report states death due to acute cardio-respiratory failure and coronary artery thrombosis.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☒ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
EKG (while receiving flecainide): PR=0.248 sec, QRS=0.156 sec.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
ATRIAL FIBRILLATION

18. THERAPY DATES *(From To)*
10/30/86 - 01/29/87

19. THERAPY DURATION
3 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
DIGOXIN 13 MONTHS DISOPYRAMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/17/87

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

5 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

11.1

JUN 17

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FROM REVIEW

NDA #18-830

Name of Drug: Tombocor (flecainide acetate) Tablets

Sponsor: Riker

Type of Submission: ADR

Date of Submission: April 16, 1987

Date of Review: May 11, 1987

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

*[redacted]**THROMBOCYTOPENIA, GRANULOCYTOPENIA**

72 y/M with history of HTN, arthritis, COPD, pemphigous, resected abdominal aneurysm and VT flatter attempted to be treated with procainamide and Norpace but intolerant to them was admitted to hospital on 19FEB86 for right chest pain. He was on multiple medications. Ventricular fibrillation and cardiac arrest occurred on 2/19/86 and he was resuscitated. Respitatory arrest occurred 3x. Flecainide was on from 2/28 to 3/11/86. Thrombocytopenia Granulocytopenia was noted. F was d/ced. A bone marrow on 3/13 showed left shifted granulocytic maturation with toxic changes. The patient died on 3/17/86 of nerpatic pneumonia.

*[redacted]*GRANULOCYTOPENIA, HERPES LABIALIS, URTICARIA*

Tnis 53 y/F has a Hx of diltatative cardiomyopathy and life-threatening arrythmias which required hospitalization on 6/10/86. On 7/1/86 she was started on flecainide 200 mg daily but the drug was discontinued on 7/4/86 for unknown reasons. On 7/6/86 the woman developed leukopenia which required hospitalization. Initially the physician believed this to be an immunoallergic reaction, but later felt it was due to "pharmocologic action". Following this, the woman developed severe herpes labialis with urticaria. This was believed due to immunodeficiency. The woman was discharged from the hospital in good condition in August 1986.

Discharge medications included amiodarone.

Lab Data:

	7/7/86	7/8/86	7/9/86	7/16/86	7/25/86
Leukocytes	800	1340	420	2330	18,111
Lymphocytes	82	89	82.7	74.2	69.7
Neutrophils	7	9.9	13.9	13.9	24.5
Eosinophils	---	0.2	0.6	0	0.2

[redacted]

GRANULOCYTOPENIA, THROMBOCYTOPENIA

This 66 y.o. man was started on low-dose flecainide on 4/11/85 (later increased to 300 mg daily). His cardiac arrnythmias stated following an inferior-wall myocardial infarction on 3/28/85. History includes psoriatic arthritis and essential hypertension. Hematologic, renal, and hepatic function were normal. At initiation of flecainide therapy, the leukocyte count was 7800/mm3. After three months of flecainide therapy, his leukocyte count was 1400. He was admitted to the hospital on 7/5/85 for hematologic evaluation. All medications were discontinued. Platelet count was 1400. He was admitted to the hospital on 7/5/85 for hematologic evaluation. All medications were discontinued. Platelet count was moderately depressed on admission, but improved steadily thereafter. By the 7th hospital day, the man showed improvement in peripheral blood leukocyte and absolute neutrophil counts. He was discharged on the tenth hospital day with a neutrophil count of 4250/mm3. Eleven days later peripheral blood picture was normal.

Immunologic investigation demonstrated circulating granulocyte-binding anti-flecainide IgG. No such immunoglobulin was detected for the other medications concomitantly used by the patient: hydrochlorothiazide, indomethacin, metnotrexate, and metoprolol.

Peripheral blood count:

	Platelets	PMN	WBC	[segs	lymphocytes	eosinophils	bands]
4/11/85	411,000/mm3		7300	74%	17%		
7/05/85	161,000	350					
7/08/85	220,000						
7/10/85	250,000						
7/12/85	280,000	2000					
7/16/85	363,000		7000	57%	37%	6%	
7/26/85	300,000	7500					
10/8/85	301,000		9100	76%	17%	2%	5%

[redacted]

PULMONARY EDEMA Man 76 years old with history of myocardial infarct and longstanding cardiomyopathy developed cardiac dysrhythmia with bigeminy was treated with flecainide, rhythm was well-controlled, with digoxin continued. Within 5 days he was showing signs of pulmonary edema. Admitted to hospital, flecainide was discontined, lidocaine was administered followed by procainamide, and furosemide infused. He began to improve promptly. Reporting physician believed flecainide was accountable for development of the pulmonary edema.

[redacted] CARDIAC ARREST* Death
This man was being treated with flecainide (dose and duration unknown) for the control of intermittent atrial fibrillation. He had been in normal sinus rhythm at his last check-up. Three weeks later he was admitted to the hospital in cardiac arrest and was successfully resuscitated. However, he suffered irreversible brain death during the CPR attempt and died.

S K Chun 6/17/87
Sughok K. Chun, M.D.

cc:
Orig.
HFN-110
HFN-110/CSO
HFN-110/SChun
klb/5/28/87/08691

11.1

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St Paul, Minnesota 55144-1000
(612)733-0633

ORIGINAL

REPORTS

3M

April 16, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-day Adverse Reaction Reports
NDA 18-830 Tambocor®, flecainide acetate

Dear Sir/Madam,

Enclosed are five Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject drug product.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/dls

Enclosure - [redacted]

Certified Mail P 504 523 613

RECEIVED
APR 27 1987
HFN-110
NATIONAL CENTER FOR DRUGS AND BIOLOGICS

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

PATIENT ID. INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	72	M	03	08	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

****THROMBOCYTOPENIA, GRANULOCYTOPENIA****
72 y.o. man with history of hypertension, arthritis, pemphigous, resected abdominal aneurysm and ventricular tachycardia (latter attempted to be treated with procainamide and Norpace but intolerant to them) was admitted to hospital on 19FEB86 for right chest pain. He was on multiple medications. Ventricular fibrillation and cardiac arrest occurred 21FEB86 resuscitated with lidocaine after which TONOCARD was begun. He also had chronic obstructive pulmonary disease which now became prominent requiring addition of aminophylline and SoluMedrol. He now had multifocal atrial?tachycardia for which verapamil was begun. On 22FEB86 respiratory arrest ensued and i.v. LOPRESSOR was added for multifocal

13. RELEVANT TESTS LABORATORY DATA

See #7, above for hematolotical and bacteriological information.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- [X] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
300MG	ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
28FEB86 - 11MAR86	11 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [x] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

CONCOMITANT DRUGS AND HISTORY

14. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

CIMETIDINE
FUROSEMIDE
VERAPAMIL HCL
ISOSORBIDE DINITRATE
POTASSIUM CHLORIDE
PREDNISONE
GENTAMICIN SULFATE
METOPROLOL TARTRATE
METHYLDOPA
DIGOXIN(LANOXIN)
FLUOCINONIDE
TOCAINIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

PREVIOUS ANTIARRHYTHMIC THERAPY INCLUDED PROCAINAMIDE AND TONACARD. PATIENT WAS REFRACTORY TO BOTH. CHRONIC OBSTRUCTIVE PULMONARY DISEASE. SEE ALSO #7, ABOVE, FOR ADDITIONAL HISTORY

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/14/87

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [x] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [x] YES [ ] NO

25a. REPORT TYPE
- [ ] INITIAL [x] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID/INITIALS (In Confidence)	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

atrial?tachycardia. On 27FEB ZINACEF was added for Citrobacter pulmonary infection. Flecainide (100mg tid) was begun on 28FEB86 which yielded complete control of ventricular ectopy. On 04MAR86 a second respiratory arrest developed (without ventricular arrhythmias). 06MAR84 Staph. conjunctivitis developed. That day a third respiratory arrest occurred. On 08MAR86 thrombocytopenia of 60,000 was noted. TAGAMET and heparin ware discontinued. On 11MAR86 a decrease in white count was noticed. On 11MAR86 sputum smear suggested herpetic pneumonia, flecainide D/C'ed acyclovir was begun. A bone marrow on 13MAR86 showed left sided granulocytic maturation with toxic change with differential etiology of infectious vs drug-related basis. NORPACE was begun despite earlier

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
17. INDICATION(S) FOR USE	
18. THERAPY DATES *(From/To)*	19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

AMINOPHYLLINE
CEFAZOLIN SODIUM
ALPRAZOLAM
NIFEDIPINE
METHYLPREDNISOLONE
BITOLTEROL MESYLATE
TICARCILLIN DISODIUM
HEPARIN SODIUM

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)* ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER
15 DAY REPORT ☐ YES ☐ NO	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 3)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

intolerance and i.v. acyclovir was added to the oral regimen. on 15MAR Pseudomonas was grown from sputum and i.v. AMIKACIN was added to treatment. The patient died on 17MAR86. The multiple medications the patient was taking before thrombocytopenia was noted are listed in Section 22, below.
ORIGINALLY SUBMITTED AS 15-DAY,ADDITIONAL INFORMATION RECEIVED SHOWED IT TO BE A NON-15 DAY REPORT.
4/14/86: Review of the clinical pathology data leads to redefinition of the adverse experience: LEUKOPENIA changed to GRANULOCYTOPENIA. Technically, this change results in reclassification of the report to 15-DAY status, as GRANULOCYTOPENIA is not a labeled adverse experience.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT ☐ YES ☐ NO

25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	??		

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

CARDIAC ARREST Death
This man was being treated with flecainide (dose and duration unknown) for the control of intermittent atrial fibrillation. He had been in normal sinus rhythm at his last check-up. Three weeks later he was admitted to the hospital in cardiac arrest and was successfully resuscitated. However, he suffered irreversible brain death during the resuscitation attempt and died. The physician states that "it is difficult to implicate flecainide in the patient's death" because normal sinus rhythm was restored.

13. RELEVANT TESTS LABORATORY DATA
None.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
??

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
ATRIAL FIBRILLATION

18. THERAPY DATES *(From To)*
?? ??

19. THERAPY DURATION
??

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/ 3/87

24d. REPORT SOURCE *(Check one)*
- [x] FOREIGN [ ] STUDY [ ] LITERATURE
- [x] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT
- [x] YES [ ] NO

25a. REPORT TYPE
- [x] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	??		

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

CARDIAC ARREST Death
This man was being treated with flecainide (dose and duration unknown) for the control of intermittent atrial fibrillation. He had been in normal sinus rhythm at his last check-up. Three weeks later he was admitted to the hospital in cardiac arrest and was successfully resuscitated. However, he suffered irreversible brain death during the resuscitation attempt and died. The physician states that "it is difficult to implicate flecainide in the patient's death" because normal sinus rhythm was restored.

13. RELEVANT TESTS LABORATORY DATA
None.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
??

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
ATRIAL FIBRILLATION

18. THERAPY DATES *(From To)*
?? - ??

19. THERAPY DURATION
??

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
ASPIRIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/ 3/87

24d. REPORT SOURCE *(Check one)*
- [x] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [x] HEALTH PROFESSIONAL
- [ ] CONSUMER

15 DAY REPORT
- [x] YES
- [ ] NO

25a. REPORT TYPE
- [x] INITIAL
- [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES
- [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES
- [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	??		

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

CARDIAC ARREST Death

This man was being treated with flecainide (dose and duration unknown) for the control of intermittent atrial fibrillation. He had been in normal sinus rhythm at his last check-up. Three weeks later he was admitted to the hospital in cardiac arrest and was successfully resuscitated. However, he suffered irreversible brain death during the resuscitation attempt and died. The physician states that "it is difficult to implicate flecainide in the patient's death" because normal sinus rhythm was restored.

13. RELEVANT TESTS LABORATORY DATA
None.

9.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
??

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
ATRIAL FIBRILLATION

18. THERAPY DATES *(From/To)*
?? - ??

19. THERAPY DURATION
??

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-850

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
4/ 3/87

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

11.1

JUN 23

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA 18-830

NAME OF DRUG: Tombocor (flecainide acetase) Tablets

SPONSOR: Riker

TYPE OF SUBMISSION: Periodic ADR Report (12/11/80 to 3/10/87)

DATE OF SUBMISSION: April 16, 1987

DATE OF REVIEW: May 11, 1987

REVIEWER: Sughok K. Chun, M.D., HFN-110

A. Resume:

I. Initial Reports This Period

A. Serious Labeled

Manufactured Report No.	Reaction Term
[redacted]	Arrhythmia/ECG abnormal
	Rash Erythematous
	Death, cause unknown
	Thrombocytopenia
	Dizziness, nausea
	Depression, fatigue
	Hypotension

B. Non-serious

urticaria, angioedema/ANA elevation 1	fever 1
hepatic function abnormal 7	neuropathy 1
arrhythmia/tachycardia z	headache/vision abnormal 1
chest pain 1	confusion 1
hypotension 1	tinnitus, paresthesia 1
arthralgia 2	myalgia 1
flatulence 3	twitching, depression 1
menstrual disorder 1	impotense 1
hyperthroidism 1	Euphoria 1
increased amylase, alk phos 1	depression 1

S.K. Chun 6/24/87
Sughok K. Chun, M.D.

cc:
Orig. NDA #18-830
HFN-80/DDIR
HFN-110
HFN-110/CSO
HFN-110/SChun/4/27/87
klr/6/19/87/08791

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000

P-5

ORIGINAL

REPORTS

April 16, 1987

3M

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir or Madam:

Pursuant to 21 CRF 314.80, enclosed is the Periodic ADR Report in duplicate for Tambocor ®(flecainide acetate) NDA 18-830. There are 55 FDA-1639 forms in this submission, 49 of which are initial reports and six are follow-up reports.

The time period covered by this report is December 11, 1986 to March 10, 1987.

Sincerely,

Florence N. Wong

Florence N. Wong
Regulatory Specialist

FNW/ds/8f

Desk Copy: Dr. S. K. Chun
Division of Cardio-Renal Drug Products
HFN-110

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID: INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	10	05	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

WORSENING OF ARRHYTHMIA Death

This patient had a history of chronic renal failure requiring dialysis, congestive heart failure, and premature ventricular contractions when flecainide acetate was started at 100 mg bid. The week prior to flecainide, the patient experienced ventricular tachycardia while on dialysis which required cardioversion. Sustained V-tach started about 48 hours after flecainide was started and progressed to ventricular fibrillation and death after 10 days of flecainide therapy.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*: 09/26/86 - 10/05/86

19. THERAPY DURATION: 10 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Renal failure requiring dialysis.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST. PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 12/19/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	07	??	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

PACEMAKER EXIT BLOCK DEATH

This man was started on flecainide on 20FEB86 because his present medication (procainamide HCL) was not controlling his PVCs. A pacemaker had been installed in 1981 for sick sinus syndrome. About three weeks after flecainide was started his pacemaker function was normal and the serum digoxin level was 1.8 ng/ml. Other concomitant medication included cortisone and carbidopa-levodopa and his medical history included Parkinsonism, relative adrenal insufficancy and congestive heart failure After about 5 months of flecainide therapy his pacemaker threshold requirements apparently changed, but a new threshold level could not be established and he died.

13. RELEVANT TESTS LABORATORY DATA

13MAR86: pacemaker function normal
MAR86: serum digoxin level 1.8 ng/ml

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

THERAPY DATES *(From/To)*: 02/20/86 - 07/??/86

19. THERAPY DURATION: 5 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN(LANOXIN)
CORTISONE
LEVODOPA-CARBIDOPA

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Pacemaker installed 5/81 for sick sinus syndrome; congestive heart failure; chronic ventricular arrhythmia; Parkinsonism; relative adrenal insufficency.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 1/16/87

24d. REPORT SOURCE *(Check one)*

[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT

[ ] YES [X] NO

25a. REPORT TYPE

[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	37	M	09	12	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

*VENTRICULAR FIBRILLATION*Death

This 37 y.o. man with history of coronary artery bypass graft but good left ventricular function was admitted to hospital for premature ventricular complexes and sustained ventricular tachycardia. Flecainide was started at 200 mg/day which controlled the arrhythmias well. 27-72 hours after start of flecainide, while still in the intensive care unit, he developed ventricular fibrillation. He could not be resuscitated and expired. No autopsy was obtained and flecainide acetate plasma levels were not determined.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*: 09-09-86 - 09-12-86

19. THERAPY DURATION: 3 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Please see #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
1/23/87	[ ] FOREIGN [ ] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
[ ] YES [X] NO	[ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	9/	9/	6

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

QRS WIDENING Death

This patient was being treated for symptomatic, unifocal PVC's. He had received quinidine previously but could not tolerate it. He was started on flecainide 100 mg bid. After approximately two weeks of flecainide therapy, he was being tested on the treadmill when QRS widening occurred The treadmill was stopped but the patient's QRS continued to widen. The patient's EKG showed sine wave configuration. The patient became unresuscitable and died.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

THERAPY DATES *(From To)*: 9/23/86 - 9/29/86

19. THERAPY DURATION: 6 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIPYRIDAMOLE

23. OTHER RELEVANT HISTORY *(e g. diagnoses, allergies, pregnancy with LMP etc.)*

None.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 12/16/86

24d. REPORT SOURCE *(Check one)*

[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT

[ ] YES [X] NO

25a. REPORT TYPE

[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	67	M	12	08	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

HEPATIC FAILURE Death
This 67 y.o. man had long history of severe cardiac disease complicated by chronic obstructive pulmonary disease. He had history of coronary artery bypass surgery and failure controlled with digoxin and furosemide. At the time of the event he was in hospital taking a number of medications (see below) and verapamil had been used for a short period. While in hospital he received flecainide 100mg bid for ventricular arrhythmias, but about five days following start of dosing he developed nausea, anorexia and poor skin color. Flecainide was stopped and hepatic SGOT was found to be 1000 with normal bilirubin but HBD elevated. Cardiac enzymes were not obtained but EKG showed no changes indicative

13. RELEVANT TESTS LABORATORY DATA

Within 24 hours of death - SGOT > 1000; normal bilirubin; elevated HBD. No measurement of cardiac enzymes. No EKG changes were present to indicate myocardial infarction. No ammonia levels were obtained during shock and coma prior to death. No autopsy was performed.

8-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

THERAPY DATES *(From To)*: 12-02-86 - 12-07-86

19. THERAPY DURATION: 5 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN(LANOXIN)	>6 MONTHS	FUROSEMIDE	>4 YEARS
PHENYTOIN	>2 YEARS	DIPYRIDAMOLE	1 YEAR
PREDNISONE	>6 MONTHS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

This patient had a history of severe, chronic COPD with ventricular irritability secondary to cor pulmonale plus ASHD, status post-1 year post-PTCA with excellent artery patency at last coronary angiogram three months prior to death.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 1/27/87

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

of myocardial infarction. Within 24-48 hours following onset of symptoms the patient developed sudden shock, comatose state and died within a few hours. The impression was one of sudden, severe liver failure. As other drugs had been given chronically, they did not appear to be a likely cause of this problem.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26c. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR
[redacted]	62	M	??		

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
VENTRICULAR FIBRILLATION Death
This 62 y.o. male had advanced heart disease with a history of myocardial infarction 15 years ago and coronary bypass surgery 6 months following the MI. He had also experienced cardiac arrest 7 years ago. He was being treated with quinidine for an extensive time when side effects of diarrhea and gastritis appeared. The patient was switched to flecainide 100 mg bid with improvement. After six weeks of flecainide therapy, the patient died suddenly while hunting. The cause of death is believed to be ventricular fibrillation.

13. RELEVANT TESTS LABORATORY DATA
None.

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

18. THERAPY DATES *(From/To)*
?? - ??

19. THERAPY DURATION
6 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
12/18/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [X] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [X] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	F	??		

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

DEATH, CAUSE UNKNOWN
This 70 y.o woman had a history of advanced coronary artery disease and chronic congestive failure. Approximately 12-18 months ago, a Holter monitor showed multiple PVC's. The patient was being treated with quinidine until gastrointestinal symptoms necessitated discontinuance of the medication. Flecainide was started at 100 mg bid. Two to four weeks after initiation of flecainide, the patient died suddenly in bed.

13. RELEVANT TESTS/LABORATORY DATA
None.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*
?? - ??

19. THERAPY DURATION
2-4 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
12/18/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	75	M	10	30	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

VENTRICULAR TACHYCARDIA Death
This 75 y.o. male was hospitalized with an acute myocardial infarction on 10/20/86. He had a history of an extensive myocardial infarction in July 1985 complicated by cardiogenic shock and episodes of complete heart block with poor left ventricular performance. Chest x-ray showed large pleural effusions and congestive heart failure. Flecainide was started at 100 mg bid on 10/27/86 for the treatment of frequent PVC's and bursts of nonsustained ventricular tachycardia with triplets. Initial PR and QRS intervals were 0.18msec and 0.08msec; these intervals increased progressively to PR 0.24msec and QRS 0.10msec. On 10/30/86, the patient began having incessant ventricular tachycardia with cycle

13. RELEVANT TESTS/LABORATORY DATA
Lab results from 10/20/86 hospitalization: Ejection fraction: 25-29%.
Chest x-ray showed large pleural effusions and congestive heart failure.
Serial cardiac enzymes following admission: CPK 446 with peak MB of 65 IU.
Flecainide levels were not taken.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

THERAPY DATES *(From/To)*: 10/27/86 - 10/30/86

19. THERAPY DURATION: 4 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 12/23/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

length of approximately 400msec. Lidocaine was started with some initial response but subsequent incessant ventricular tachycardia. Continuation of iidocaine and addition of bretylium showed no response. The patient died following prolonged rescusitation efforts.

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*

☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT

☐ YES ☐ NO

25a. REPORT TYPE

☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?

☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	25	F	12	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ARRHYTHMIA DEATH FROM OVERDOSE
This 25 y/o woman with a history of depression deliberately administered an unknown number of flecainide acetate tablets to herself. When admitted to the emergency room she was treated with lidocaine for an apparent arrhythmia. She was pronounced dead minutes later. A post-mortem blood level for flecainide was 15000 ng/ml and for butalbital was 7.2 mg/liter. The reporter said the lack of sufficient documentation prevents reaching a dsfinite correlation between flecainide and her death.

13. RELEVANT TESTS/LABORATORY DATA
Flecainide blood level - 15000 ng/ml (postmortem)
Butalbital blood level - 7.2 mg/liter (postmortem)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X OVERDOSE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
?

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
POISON-MEDICINAL AGT NOS

THERAPY DATES *(From/To)*
? - ?

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Depression

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
1/16/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	55	M	11	14	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

DEATH, Cause Unknown.
This 55 y.o. male died under circumstances that made the matter a coroner's case. By history, medication was furosemide, propranolol, nifedipine, and flecainide. None of the first three drugs were identified in qualitative testing but 1.7 microgm/ml of flecainide was found in heart blood. An autopsy certified death was due to arteriosclerotic hypertensive cardiovascular disease.

13. RELEVANT TESTS LABORATORY DATA
See #7, above.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

THERAPY DATES *(From To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
FUROSEMIDE
PROPRANOLOL
NIFEDIPINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
1/22/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1985

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
DEATH
Letter sent to physician requesting additional information. Initial report received from a Riker representative.

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

18. THERAPY DATES *(From/To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
1/20/87

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [X] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [X] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. INITIALS (In Confidence)	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	??		

DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
VENTRICULAR ARRHYTHMIC EVENT* Death

This man was referred to a cardiologist, and spent one weekend in the hospital where he was started on flecainide. The initial reported dose was 600-800 mg daily (200mg tid or qid). The man had a low ejection fraction prior to flecainide initiation. He was discharged from the hospital but began to experience adverse events. He contacted his pharmacist who recommended dose reduction. The dose was decreased but the man died.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
UNKNOWN

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
UNKNOWN

18. THERAPY DATES *(From/To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
??

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
2/27/87

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [X] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	48	M	10	20	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

*PVCs, VENT.TACH, BUNDLE BRANCH BLOCK, UNRESUSC. VENT. FIB.-*DEATH
This 48 y/o man was admitted to the hospital with a history of hypertension, syncope, seizures(?), 2nd degree AV block and V. tachycardia. Enalapril maleate therapy was ongoing. While hospitalized, he experienced no dysrhythmias and all tests run (Stress, Echo, ECG, Carotid flow) were normal. On day 2 of hospitalization, flecainide acetate and diltiazem HCL were started and he was discharged later in the day. Two weeks later the patient was again admitted to the hospital with seizures, syncope, and ventricular tachycardia. Diltiazem was stopped the next day (flecainide and enalapril still ongoing). At 0045 hours on day 3 of this hospitalization he had sudden onset of CBBB with rare PVCs which

13. RELEVANT TESTS LABORATORY DATA
SEE #7, ABOVE

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [X] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*
10/04/86 - 10/20/86

19. THERAPY DURATION
16 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
ENALAPRIL
DILTIAZEM HCL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7, above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
2/19/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

converted to normal sinus rhythem at 0046 hours without intervention. The patient was alert and asymtomatic but 20 minutes later he developed ventricular tachycardia which did not respond to cardioversion. He went into ventricular fibrillation and expired at 0205 hours. Histopathology results are still needed to complete the autopsy report.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

12.1

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 4-14-87
FROM: Team Leader, HFN-730		OFFICE
TO: Division Director, HFN-[redacted]110		DIVISION
SUBJECT: Ended Monitored Adverse Reaction (see attached)		

SUMMARY

We have had Sudden Death associated with Flecainide on our monitor list for 1 year. Although a few more cases (9) have accumulated since last year, there is no evidence that the drug is associated with a high risk for this reaction because all cases were confounded based on previous history.

We will therefore end this monitoring unless you have some objections.

cc CSO

SIGNATURE Lynn Bosco

DOCUMENT NUMBER

FD FORM 2034 (2/72)

MAR

UPDATE OF MAR STATUS AT ONE YEAR
April, 1986 - April, 1987

APR 10 1987

DRUG: Tambocor (flecainide acetate) Tablets
MAR: Myocardial Infarction (MI)

HISTORY:
Tambocor Tablets (NDA #18-830/ Riker Labs.) was approved December 31, 1985.

A MAR for myocardial infarction has the following history:

1. March 10, 1986 - A MAR was presented at the Team Meeting,
2. April, 1986 - It was then presented at the Safety Conference, and
3. April, 1986 - It was put on an Annual Status.

There were three cases of MI at that time and all of the patients were male, between the ages of 61 and 87 years.
(See the attached sheet for the Summary of the March, 1986 presentation)

UPDATE:

Subsequently, since April, 1986, reports of 9 additional cases have been received for which MI has been a COSTART. Therefore, there are a total of 12 cases as of March, 1987.
The cases have the following parameters:

Age: 11 of the 12 case were between the ages 61 and 87.
1 case was 49 yo.
1 case failed to provide an age.
Sex: All were male.

Of the 12 cases, 7 had a history of a previous MI. Of the 12 cases, 7 reportedly expired secondary to the event reported.

Of the remaining 5 cases,
1 had a history of ASHD with cardiac disease
1 had a history of ischemia and cardiomyopathy
2 had a history of coronary artery obstruction and coronary artery disease
1 had no history of MI, and the case was confounded (

11.1

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA 18-830

Name of Drug: Tombocor (flecainide acetate)

Sponsor: Riker

Type of Submission: Analysis of ADR Reports

Date of Submission: April 15, 1987

Date of Review: April 27, 1987

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

This report is prepared in response to my request for search and analysis of all F adverse reaction reports of thrombocytopenia. The request was prompted by receipt of 15-Day report, [redacted] - a positive rechallenge event submitted 20 February 1987.

A search was conducted with Regulatory supplied related cases submitted as part of the original NDA which included worldwide experience prior to U.S. launch of the drug.

All reported events of the following are reviewed:

1) Platelet, Bleeding and Clotting Disorders
2) Red Blood Cell Disorders
3) White Cell and RES Disorders
4) Vascular and Extracardiac Disorders

There was 13 thrombocytopenia-relevant cases.

"Likely" causative relations to F:

[redacted] Observance of progressive thrombocytopenia during the initial month of F treatment with trend toward normal upon discontinuation and fall again with rechallenge is compelling evidence for a causative role of F in the thrombocytopenia observed in this patient. Concomitant medications reported are not recognized a prominent causes of such changes and, were continued throughout the testing.

[redacted]

After 3 months on F the patient was found to have profound neutropenia associated with moderate thrombocytopenia (161,000). When this drug was discontinued, the blood picture promptly improved.

This pt had chronic psoriatic dermatitis and arthritis and his chronic treatment with indomethacin and methotrexate among other drugs. To what degree these factors predisposed or contributed to the apparent effect of Flecainide in this patient remains unknown.

[redacted]:

The lack of reports of bone marrow hypoplasia with F and its recognition in association with use of valproic acid, which has been taken in substantial dose concomitantly, argues against a causative role of F.

[redacted]

Died of overwhelming infection and a bone marrow showing either infectious or drug-related toxic changes. At least 20 drugs in addition to F were in use prior to recognition of thrombocytopenia, some of them were recognized hematologic toxicity.

[redacted]: (Multiple Drug Rx)

[redacted]: Low platelets persisted unchanged for two months following discontinuation of F. The hematologist believes the causative factor likely to be acenocoumarol.

Other patients had associated with malignant disease, post surgery or prior Hx of thrombocytopenia that F was unlikely as a casusative agent rather possible contributing factor.

COMMENT: The present package insert stated as an adverse experence popssibly related to F therapy in less than 1% of patients. The possibility of blood dyscrasia in general is also discussed in the second paragraph of the Adverse Effects section, including an advice to discontinue Tambocor should it be observed.

A case [redacted] is dischallenged/rechallenged proven case of thrombocytopenia probably ideopathic hypersensitivity to F. We shall watch any further proven case report than have propose the change in the labeling. At present time no labeling revision is warrented.

Sughok K. Chun, M.D.

cc: Orig. NDA #18-830
HFN-110
HFN-110/CSO
HFN-110/SChun/4/27/87
klb/4/30/87/08481

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A, 3M Center
St. Paul, Minnesota 55144-1000

111 SUPPL ES N C

April 15, 1987

3M

CERTIFIED MAIL

Food and Drug Administration
Division of Cardio-Renal Products
HFN-110
Room 16B-45
5600 Fishers Lane
Rockville, MD 20857

Attn: Dr. S. K. Chun

Subject: NDA 18-830 Tambocor® (flecainide acetate, R-818)
Analysis of ADE Reports Re Thrombocytopenia
Supplement 008

Dear Dr. Chun:

In response to your request of March 24, we have researched our database for reports that may involve thrombocytopenia, covering all data both pre- and post- NDA approval to the best of our knowledge. The attached report includes a description of the method of search, analysis of the cases, classification of the cases vis-a-vis the relationship with flecainide and our recommendation regarding any labeling change.

Thrombocytopenia is listed in the current labeling as an adverse experience possibly related to flecainide therapy in less than 1% of patients. The possibility of blood dyscrasia in general is also discussed in the second paragraph of the ADVERSE EFFECTS section, including an advice to discontinue Tambocor should it be observed (see attached labeling, pertinent sections highlighted). The recent cases do not signal any increase in incidence nor suggest any change in our recommendation. Accordingly, we do not feel any labeling revision is warranted.

If you have any questions please do not hesitate to contact me at (612) 733-0633.

Sincerely,

Florence N. Wong
Regulatory Specialist

FNW/ds/8qq

Attachment

RECEIVED
APR 22 1987
HFD-110
BUREAU of DRUGS

Review of Cases Evidencing Low or Decreasing Circulating Platelets Amor.g Patients Taking Flecainide Acetate

This report is prepared in response to an FDA request for search and analysis of all flecainide adverse reaction reports of thrombocytopenia. The request was prompted by receipt of 15-Day report, TT-87-098 -- a positive rechallenge event submitted 20 February 1987.

A search on the broadest base was conducted. Regulatory supplied related cases submitted as part of the original NDA which included worldwide experience prior to U.S. launch of the drug. The computerized data base covering worldwide events received since initiating U.S. distribution on 11 December 1985 was searched for specific terms, such as thrombocytopenia, purpura, etc. Body systems searched were:

1) Platelet, Bleeding and Clotting Disorders
2) Red Blood Cell Disorders
3) White Cell and RES Disorders
4) Vascular and Extracardiac Disorders

Then, all texts describing the reactions and laboratory findings of all flecainide cases were examined for indications of low platelets which may not have been recorded in the coding systems searched above. All of these search procedures identified 13 cases in which abnormal values for platelets were mentioned. These are tabulated in Table I.

Each case was then examined in detail with the aim of categorizing each according to a causative relationship to flecainide of "unlikely", "uncertain", or "likely".

Because classification of causality is an intrepretive matter, full details are attached for each of the 13 thrombocytopenia-relevant cases so that the reviewer has full information readily available. Eleven are presented in FDA 1639 format for ease of review. (Case [redacted] does not meet FDA-submission requirements, but is also presented in 1639 format. German cases [redacted] and [redacted], which were part of the original NDA, are submitted in their original format.) Basic facts of each case and some comments are summarized in Table I.

Seven of the cases are from foreign sources (Germany [redacted], Germany [redacted], [redacted], [redacted], [redacted] and [redacted]). Of the U.S. cases, four were spontaneously reported [redacted], and [redacted]); one was from a clinical study [redacted], and one from the literature ([redacted]). As the latter literature case appears to have been from the NIH Multicentric Cardiac Arrhythmia Pilot Study, it is likely that it has been reported to FDA independently.

Because full details are attached, cases are not summarized again in this text but rather only the reasons for classifying them as they have been classified here.

"Unlikely" causative relationship to flecainide administration:

Germany [redacted] Platelets and other formed elements continued to deteriorate for months following discontinuation of flecainide, and bone marrow showed no improvement. The physician finally diagnosed peripheral pancytopenia with aplastic syndrome due to preleukemia and did not attribute the changes to flecainide.

Germany [redacted]: This patient had history of thrombocytopenic purpura on two occasions prior to that which was noted during treatment with flecainide. For two months following discontinuation of flecainide, platelets remained low and within the same order of magnitude as they had been during 1 1/2 years of flecainide treatment.

[redacted]: The only mention is, "decreased hematocrit, platelets, red blood cells", in this clinical study patient who was in his terminal three weeks of pulmonary malignancy and who received flecainide only in his final 6 weeks of life.

[redacted] This man died of overwhelming infection and a bone marrow showing either infectious or drug-related toxic changes. At least 20 drugs in addition to flecainide were in use prior to recognition of thrombocytopenia, among which were drugs with recognized hematologic toxicity.

[redacted] The patient was known to have acute myelogenous leukemia which had been treated with several anticancer drugs known to cause the picture observed. At time of the event he was taking 13 drugs.

[redacted]: This patient had pre-flecainide malignant lymphoreticulosis and developed an intravascular coagulopathy which his physician considered to be the cause of the thrombocytopenia observed.

[redacted] This patient was on multiple drug therapy, and his physician did not attribute the thrombocytopenia to flecainide.

[redacted] Low platelets persisted unchanged for two months following discontinuation of flecainide. The hematologist believes the causative factor likely to be acenocoumarol.

[redacted]: This case is considered "unlikely" on the basis that it would seem that thrombocytopenia appeared suddenly in less than one day following surgery and after three months of flecainide dosing. The patient was admitted to a U.S. hospital for surgery which is a compelling reason to believe that pre-operative laboratory tests showed platelets to be normal. The next day following the surgery, bleeding was noted and platelets were reported to be low. Some event associated with the surgery and or related care seems more likely to be the cause than flecainide.

[redacted]: The pre-flecainide platelet count (150,000) was already low and hepatic abnormalities subsequently developed to complicate the picture. Among concomitant drugs being taken at the time were agents recognized to be associate with hepatic charge, leukopenia and agranulocy is as well as thrombocytopenia.

"Uncertain" causative relationship to flecainide administration:

[redacted]: The lack of reports of bone marrow hypoplasia with flecainide and its recognition in association with use of valproic acid, which was being taken in substantial dose concomitantly, argues against a causative role of flecainide as does this patient's inclination to self-medicate. Nevertheless, absence of more complete information with respect to the time course of platelet concentrations in relationship to the drugs, absence of the treating physician's opinion, and other agents he may have been taking leaves this case in an "uncertain" state.

"Likely" causative relationship to flecainide administration:

[redacted] Observance of progressive thrombocytopenia during the initial month of flecainide treatment with trend toward normal upon discontinuation and fall again with rechallenge is compelling evidence for a causative role of flecainide treatment in the thrombocytopenia observed in this patient. Concomitant medications reported are not recognized as prominent causes of such changes and, in any event, were said to have been continued throughout the testing.

[redacted] While it is yet early in our investigation of this literature report, the initial impression is that it presents substantial cause-effect relationship between flecainide administration and thrombocytopenia. After 3 months on the drug the patient was found to have profound neutropenia associated with moderate thrombocytopenia (161,000). When this drug was discontinued, the blood picture promptly improved. Although studies in this case focused only on white cells, for which an immunologic cause was proposed, it is tempting to postulate that an immunologic basis may have underlain the drop in platelets as well.

Complicating factors underlying this case include the nature of the patient's disease (chronic psoriatic dermatitis and arthritis) and his chronic treatment with indomethacin and methotrexate among other drugs. To what degree these factors predisposed or contributed to the apparent effect of flecainide in this patient remains unknown.

Considerations for labeling: We are left with one case of thrombocytopenia of apparent causal relationship to flecainide which arose in the course of a U.S. clinical study prior to marketing ([redacted]) and another convincing rechallange case reported spontaneously from France.

Current prescribing information for flecainide acetate includes thrombocytopenia as "possibly related to [flecainide] therapy" in less than 1% of patients. It further advises "...to discontinue [flecainide] in patients who develop unexplained...blood dyscrasias in order to eliminate [flecainide] as the possible causative agent." In each of the cases identified, thrombocytopenia presented in association with alerting clinical signs, prompted confirming laboratory evaluation, drug discontinuation and was followed by recovery. Among the entire group of 13 flecainide-related thrombocytopenias, that condition did

not appear to be causally related to the 6 deaths that did occur.

It is concluded that the current prescribing information continues to alert physicians appropriately to the rare possibility of thrombocytopenia and to advise correctly on what should be done should it be encountered. That we have yet to receive our first spontaneous report of confirmed, causally-related thrombocytopenia from the U.S. marketing experience (now at 15 months) and that the European case comes from over 5 years marketing experience in more than 200,000 patients do not suggest a notable increase in such events.

Riker's adverse reaction reporting system proved sufficiently sensitive to have seen initial notices for both of these events on their way to FDA within 15 days of intital knowledge of them whether the information was first obtained in the U.S. or abroad. It is expected to be able to get future reports to the agency in a sufficiently timely manner to spot important changes in future thrombocytopenia data should such occur.

George B. Eagleton, M.D., M.P.H.
13 April '87

TABLE I
Cases Involving Thrombocytopenia

ADE #	HEMATOLOGIC CLASSIFICATION	AGE	SEX	TAMBOCOR DOSE MG/DAY	TAMBOCOR PRIOR TO ADE	RECOVERY	COMMENTS
Germany [redacted]	Preleukemic Pancytopenia	85	M	200	6 weeks	N(Died)	Death after one year due to acute bronchitis and heart failure (Germany)
Germany [redacted]	Thrombocytopenia	56	F	?	5 months	?	Prior Idiopathic Thrombocytopenic Purpura (Germany)
[redacted]	Decreased Platelets/RBC's	63	M	200	6 weeks	N(Died)	Carcinoma of Lung
[redacted]	Thrombocytopenia/ Leukopenia	72	M	300	8 days	N(Died)	Citrobacter/Herpetic pneumonia. Taking 21 drugs.
[redacted]	Myelogenous Leukemia/Aplastic Anemia/Pancytopenia	56	M	300	1 month	N(Died)	Prior Myelogenous Leukemia treated with cytotoxic drugs causing marrow ablation
[redacted]	Pancytopenia	73	M	300	Several mos	N(Died)	Aplastic bone marrow. On valproic acid (France)
[redacted]	Intravascular Coagulopathy/ Thrombocytopenia	72	M	100	3 days	N(Died)	Died of mycosis fungoides and intravascular coagulation (France)
[redacted]	Thrombocytopenia	?	?	?	?	Y	Physician indicates do to other cause.
[redacted]	Thrombocytopenia	?	?	100-300	?	?	No change 2 mos after stopping. Other drug suspected. (Belgium)

TABLE I
(Continued)
Cases Involving Thrombocytopenia

ADE #	HEMATOLOGIC CLASSIFICATION	AGE	SEX	TAMBOCOR DOSE MG/DAY	TAMBOCOR PRIOR TO ADE	RECOVERY	COMMENTS
[redacted]	Thrombocytopenia	68	M	200	3 months	?	Discovered 1 day post-op.
[redacted]	Thrombocytopenia	73	M	200	7 days	?	Prior GI bleed, surgery, infection
[redacted]	Thrombocytopenia	65	M	200	15 days	Y	Positive Rechallenge (France)
[redacted]	Granulocytopenia/ Thrombocytopenia	66	M	300	3 months	Y	Possible Immunologic basis (Literature report)

Riker Germany Case No. [redacted]

This 85 year-old male was admitted to the hospital with right sided congestive heart failure. At the time of admission, he had been receiving Tambocor, 200 mg per day for approximately six weeks with concomitant medications of digoxin, spironolactone, furosemide, xipamide, quaifenesin and possibly reserpine and aminophylline. While in the hospital he was maintained on digoxin and unknown diuretic. On that admission he was found to have a hemoglobin of 10.8 g/dl, erythrocyte count of 3.89 million/mm^3, a white blood cell count of 4400/mm^3 with 63% neutrophils, 14% monocytes and 23% lymphocytes. Platelets were 124,000/mm^3. There were minor elevations of bilirubin, alkaline phosphatase, gamma-GT and acid phosphatase. Flecainide was discontinued one week later and over the next two and one-half months the erythrocytes decreased to 2.7 million/mm^3, the blood count decreased to 1500/mm^3, and platelets decreased to 80,000/mm^3.

Bone marrow aspiration one month after admission showed "low cell content, slight left deviation of granulo- and erythropoiemis, and mild toxic granulation. Megakaryocytes also decreased. Plasma cells were within normal range. Increase of reticular cells. No foreign elements in the bone marrow." A bone marrow biopsy one week later showed "rich myelopoiesis with maturation disturbances of both the red and the white precursors and of the megakaryocytes. Foci of increased eosinophilia ...Because of these present findings it cannot be assessed whether regenerative changes following aplastic bone marrow damage are taking place or whether it is an early acute megakaryocytic myelosis in the early stages." Three months after admission to the hospital, a repeat bone marrow biopsy was done which showed "no significant changes except for increasing maturation disturbances also in the granulopoiesis and erythropoiesis. These findings are now more or less typical for pre-leukemia."

Riker Germany Case No. [redacted]

(Continued)

The patient was treated with a short course of steroids without improvement and required several blood transfusions over the next several months. At this time the physician, who had originally suspected flecainide as the cause of a drug-induced blood dyscrasia, concluded that the patient had "aplastic syndrome of undertermined origin (suspected pre-leukemia)."

One year after receiving flecainide (ten and one-half months after the blood dyscrasia was first noted) the patient died of "terminal cardiovascular failure" following an episode of acute bronchitis. The physician's final diagnosis for the blood dyscrasia was "peripheral pancytopenia with aplastic syndrome due to pre-leukemia."

* Submitted to NDA 18-830 ON 24 October 1984 in Safety Update, Vol. 14.1.

Riker Germany Case No. [redacted]

This 56 year-old female received Tambocor for five months when petechiae were noted on the lower legs. Platelet count was 186,000/mm^3 and other blood tests were normal. The clinician suspected Tambocor induced Thrombocytopenia. However, when the patient's previous records were reviewed, it was found that she had twice developed similar petechiae and had been previously given the diagnosis of "probable idiopathic thrombocytopenic diathesis." The patient was continued on Tambocor for approximately one additional year during which platelet counts varied between 104,00/mm^3 and 145,000/mm^3. During the two months after Tambocor was discontinued, platelet counts varied between 95,000/mm^3 and 123,000/mm^3. These changes appear not to be related to Tambocor therapy.

* Submitted to NDA 18-830 on 24 October 1984 in Safety Update, Vol. 14.1.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO

ACCESSION NO.

I. REACTION INFORMATION

ENT ID INITIALS *(In Confidence)*	2 AGE YRS	3 SEX	4-6 REACTION ONSET MO.	DA	YR.
[redacted]	63	M	01	15	86

7 DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

LUNG CANCER Death
PATIENT WAS DIAGNOSED AS HAVING LUNG CANCER 3 WEEKS FOLLOWING START OF FLECAINIDE ACETATE TREATMENT. ENTERED HOSPITAL, BECAME MORIBUND AND DIED ABOUT 3 WEEKS LATER. FLECAINIDE DOSING STARTED AT 150 MG BID AND WAS DECREASED TO 100 MG BID ON 12/29/85. MEDICATION USED DURING HOSPITALIZATION TO TREAT CARCINOMA-RELATED SYMPTOMS: SOLU-MEDROL, PREDNISONE, ALUPENT, MORPHINE SULFATE, COMPAZINE, AMPHOGEL, CALCIMAR, KEFLEX, AMINOPHYLLINE, XANAX AND KLOTRIX.

13. RELEVANT TESTS LABORATORY DATA

CT SCAN; SPUTUM SAMPLES; ECG SHOWED JUNCTIONAL RHYTHM
HYPERCALCEMIA; ELEVATED: SGPT, GGT, SGOT, CREATININE, BUN
DECREASED: HCT, PLATELETS, RBC

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X CANCER
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15 DAILY DOSE: 200 MG

16 ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18 THERAPY DATES *(From To)*: 05DEC85 - 14JAN86

19 THERAPY DURATION: 40 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG? [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22 CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

BECLOMETHASONE DIPROPIONATE	?	ALBUTEROL	?
FUROSEMIDE		TERBUTALINE SULPHATE	?
THEOPHYLLINE	?	RANITIDINE	?
ACETAMINOPHEN	?	TRIAZOLAM	
NITROGLYCERIN	?	SULFAMETHOXAZOLE, TRIMETHOPRIM	~5WKS
MILK OF MAGNESIA-CASCARA	?	-	

23 OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

PREMATURE VENTRICULAR COMPLEXES, NON-SUSTAINED VENT. TACHYCARDIA, VENT. FIBRILLATION, HISTORY OF MYOCARDIAL INFARCTION, SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE, ARTERIOSCLEROTIC HEART DISEASE.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST. PAUL, MN 55144-1000

24a. IND NDA NO FOR SUSPECT DRUG: 18-830

24b MFR CONTROL NO: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 9/24/86

24d. REPORT SOURCE *(Check one)*: [ ] FOREIGN [X] STUDY [ ] LITERATURE [ ] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT: [X] YES [ ] NO

25a. REPORT TYPE: [ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b TELEPHONE NO *(Include area code)*: [redacted]

26c HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL? [ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80

FORM FDA 639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	72	M	03	08	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

THROMBOCYTOPENIA, LEUKOPENIA
72 y.o. man with history of hypertension, arthritis, pemphigous resected abdominal aneurysm and ventricular tachycardia (latter attempted to be treated with procainamide and Norpace but intolerant to them) was admitted to hospital on 19FEB86 for right chest pain. He was on multiple medications. Ventricular fibrillation and cardiac arrest occurred 21FEB86 resuscitated with lidocaine after which TONOCARD was begun. He also had chronic obstructive pulmonary disease which now became prominent requiring addition of aminophylline and SoluMedrol. He now had multifocal atrial?tachycardia for which verapamil was begun. On 22FEB86 respiratory arrest ensued and i.v. LOPRESSOR was added for multifocal

13. RELEVANT TESTS LABORATORY DATA

See #7, above for hematolotical and bacteriological information.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTIO
- [ ] TREATED WITH Rx DRU
- [x] RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

THERAPY DATES *(From To)*: 28FEB86 - 11MAR86

19. THERAPY DURATION: 11 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?

- [ ] YES [x] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

CIMETIDINE
FUROSEMIDE
VERAPAMIL HCL
ISOSORBIDE DINITRATE
POTASSIUM CHLORIDE
PREDNISONE
GENTAMICIN SULFATE
METOPROLOL TARTRATE
METHYLDOPA
DIGOXIN(LANOXIN)
FLUOCINONIDE
TOCAINIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

PREVIOUS ANTIARRHYTHMIC THERAPY INCLUDED PROCAINAMIDE AND TONACARD. PATIENT WAS REFRACTORY TO BOTH. CHRONIC OBSTRUCTIVE PULMONARY DISEASE. SEE ALSO #7, ABOVE, FOR ADDITIONAL HISTORY

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/14/86

24d. REPORT SOURCE *(Check one)*

- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [x] HEALTH PROFESSIONAL [ ] CONSUMER

15 DAY REPORT

- [ ] YES [x] NO

25a. REPORT TYPE

- [x] INITIAL FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

- [ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

atrial?tachycardia. On 27FEB ZINACEF was added for Citrobacter pulmonary infection. Flecainide (100mg tid) was begun on 28FEB86 which yielded complete control of ventricular ectopy. On 04MAR86 a second respiratory arrest developed (without ventricular arrhythmias). 06MAR84 Staph. conjunctivitis developed. That day a third respiratory arrest occurred. On 08MAR86 thrombocytopenia of 60,000 was noted. TAGAMET and heparin were discontinued. On 11MAR86 a decrease in white count was noticed. On 11MAR86 sputum smear suggested herpetic pneumonia, flecainide D/C'ed acyclovir was begun. A bone marrow on 13MAR86 showed left sided granulocytic maturation with toxic change with differential etiology of infectious vs drug-related basis. NORPACE was begun despite earlier

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACT
- ☐ TREATED WITH Rx OF
- ☐ RESULTED IN, OR PROLONGED, INPATIE HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
17. INDICATION(S) FOR USE	
18. THERAPY DATES *(From/To)*	19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

AMINOPHYLLINE
CEFAZOLIN SODIUM
ALPRAZOLAM
NIFEDIPINE
METHYLPREDNISOLONE
BITOLTEROL MESYLATE
TICARCILLIN DISODIUM
HEPARIN SODIUM

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)* ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER
15 DAY REPORT ☐ YES ☐ NO	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

25b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85). PREVIOUS EDITION IS OBSOLETE

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ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 3)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

intolerance and i.v. acyclovir was added to the oral regimen. on 15MAR Pseudomonas was grown from sputum and i.v. AMIKACIN was added to treatment. The patient died on 17MAR86. The multiple medications the patient was taking before thrombocytopenia was noted are listed in Section 22, below.
ORIGINALLY SUBMITTED AS 15-DAY,ADDITIONAL INFORMATION RECEIVED SHOWED IT TO BE A NON-15 DAY REPORT.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTI
- ☐ TREATED WITH Rx OF
- ☐ RESULTED IN, OR PROLONGED, INPATIE HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

THERAPY DATES *(From To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER
☐ YES ☐ NO

25d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

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FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. ID/INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	56	M	02	18	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#APLASTIC ANEMIA, DEATH#
ONSET ABOUT TWO WEEKS AFTER INITIAION OF TAMBOCOR THERAPY FOR VENTRICULAR ECTOPIC ARRHYTHMIA, WITH RAPID DOWNHILL COURSE; DIED 3/14/86.
(NB: PRIOR TO FLECAINIDE TREATMENT, PT KNOWN TO HAVE LEUKEMIA AND HAD MANIFESTED BONE MARROW ABLATION SECONDARY TO ANTILEUKEMIC DRUGS.)

13. RELEVANT TESTS LABORATORY DATA

3/5/86: SGOT 323; SGPT 450; ALK. PHOS. 266; HGB 10 G/DL; HCT 30; WBC 5000/CU.MM.
3/6/86: WBC 1600/CU.MM.; PLATELETS 9000/CU.MM.; BONE MARROW HYPOPLASTIC PANCYTOPENIA PERSISTED & PROGRESSED THEREAFTER.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*: 22/4/86 - 23/4/86

19. THERAPY DURATION: 1 MONTH

20. DID REACTION ABATE AFTER STOPPING DRUG?

- [ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DISOPYRAMIDE	>1 MONTH	PROCAINAMIDE HCL	>1 MONTH
PHENYTOIN	3 WEEKS	DIGOXIN	3 WEEKS
HEPARIN SODIUM	3 WEEKS	SODIUM WARFARIN	3 WEEKS
TICARCILLIN/CLAVULANATE	10 DAYS	TOBRAMYCIN	10 DAYS
VANCOMYCIN HCL	1 WEEK	CEFTAZADIME	1 WEEK
DOXEPIN HCL	>1 MONTH	RANITIDINE	1 MONTHH

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

PATIENT HAD ACUTE MYELOGENOUS LEUKEMIA; PRIOR THERAPY INCLUDED COURSES OF 6 MERCAPTOPURINE, CYTOSAR, & OTHER CYTOTOXIC AGENTS. DEVELOPED SYMPTOMATIC VENTRICULAR ECTOPIC BEATS , POORLY CONTROLLED BY PRONESTYL + NORPACE, DILANTIN OR DIGOXIN. TAMBOCOR 100MG BID IMPROVED CONDITION, BUT COMPLETE CONTROL OF ARRHYTHMIA ACHIEVED WHEN TAMBOCOR DOSE WAS RAISED TO 150MG BID AFTER 4 DAYS AT 100MG BID. SEPSIS SUPERVENED WHEN BONE MARROW FAILED, & ANTIBIOTIC THERAPY WAS UNAVAILING. CEREBROVASCULAR ACCIDENT 3 MONTHS EARLIER. FINAL HOSPITALIZATION 1/28/86 FOR MULTIPLE PULMONARY EARLIER, AND COURSE WAS FURTHER COMPLICATED BY MULTIPLE PULMONARY

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 4/22/86

24d. REPORT SOURCE *(Check one)*

- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [X] HEALTH PROFESSIONAL
- [ ] CONSUMER

15 DAY REPORT

- [X] YES
- [ ] NO

25a. REPORT TYPE

- [X] INITIAL
- [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

- [ ] YES
- [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

- [ ] YES
- [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PT ID INITIALS *(In Confidence)*	2. AGE	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	73 YRS.	M	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Pancytopenia, death
Report from France indicates patient, while on flecainide, developed pancytopenia and subsequently died. No further details are known.
07JUL86 New information indicates patient was treated with flecainide with good results for several months with no side effects. On his own volition, patient discontinued flecainide and the arrhythmia recurred. flecainide was reintroduced with success 3 weeks prior to death. During this period was also taking valproic acid 1500mg/day for a seizure disorder. Patient died 14JAN86 (cause of death:septicemia)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
HEMOGLOBIN = 6.3 GM/L; PLATELETS = 37000/MM3; PROTHROMBIN = 57%
FIBRINOGEN = NORMAL; BONE MARROW COUNT = BONE MARROW HYPOPLASIA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 300MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: 12/17/86 - 01/07/86

19. THERAPY DURATION: 3 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG? [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
VALPROIC ACID

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
INGUINAL HERNIA; SMOKER; EPILEPSY

ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 6/23/86

24d. REPORT SOURCE *(Check one)*: [X] FOREIGN [ ] STUDY [ ] LITERATURE [ ] HEALTH PROFESSIONAL [ ] CONSUMER

5 DAY REPORT: [X] YES [ ] NO

25a. REPORT TYPE: [ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL? [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5-85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

P. I.D. INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	72	M	02	13	86

5. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, purpura
Patient (72-year-old male) developed extensive purpura 12 days after a myocardial infarction. Also had actinoreticulosis and Mycosis fungoides. During this time, patient was started on flecainide (100 mg qd) for the treatment of frequent PVCs and ventricular tachycardia. Patient died on 02/14/86 from intravascular coagulation considered by physician to be a development of the Mycosis fungoides and not the result of concomitant use of flecainide.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☒ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

02/12/86: Fibrin: 5.6G - Blood platelet: 135,000
02/14/86: Fibrin: 2.4g - Blood platelet: 35,000 - V factor: 59%
Prothrombin time: 43%; cephalin-kaolin time: 85 sec.
= Spreaded intravascular coagulation

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 100 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*: 02/10/86 - 02/13/86

19. THERAPY DURATION: 3 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

HEPARIN SODIUM
DIGOXIN
THEOPHYLLINE
FUROSEMIDE
DOBUTAMINE HYDROCHLORIDE
NONE
ISOSORBIDE DINITRATE
NONE
DOPAMINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Myocardial infarction, actinoreticulosis, Mycosis fungoides.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/14/86

24d. REPORT SOURCE *(Check one)*: ☒ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

5-DAY REPORT: ☒ YES ☐ NO

25a. REPORT TYPE: ☐ INITIAL ☒ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80

Flecanide-Induced Immune Neutropenia

Documentation of a Hapten-Mediated Mechanism of Cell Destruction

Wolfram E. Samlowski, MD; Richard N. Frame, MD; Gerald L. Logue, MD

• Immune-mediated granulocytopenia due to cardiac antiarrhythmic medications is a rare, but potentially dangerous, event. This article characterizes the first case, to our knowledge, of severe granulocytopenia associated with the administration of flecanide acetate, a new class I antiarrhythmic drug. Immunologic studies determined that flecanide was capable of binding to the surface of normal neutrophils. The patient's serum contained an IgG antibody that could specifically bind to the haptenized neutrophils, presumably mediating enhanced destruction of mature granulocytes both in the serum and within the bone marrow. Cessation of flecanide therapy resulted in resolution of the granulocytopenia. The titer of antineutrophil antibody in the patient's serum decreased to background levels within the next five months. Similar antibodies were not found in serum from nonsensitized individuals. The capacity of flecanide to bind to normal neutrophils may prove to be a significant risk factor for the subsequent development of antineutrophil antibodies and agranulocytosis in patients receiving this drug. Careful hematologic monitoring of all patients who are receiving this medication is, therefore, strongly urged.

(*Arch Intern Med* 1987;147:383-384)

Class I antiarrhythmic medications, such as procainamide hydrochloride and quinidine sulfate, have occasionally caused severe, life-threatening neutropenia (< 500 neutrophils per microliter of peripheral blood).[1-3] The mechanism of granulocyte destruction in such cases is frequently immunologically mediated.[4-9] Flecanide acetate, a congener of procainamide, is an experimental class I antiarrhythmic agent that is currently undergoing clinical trials. It has no known hematologic toxicity.[10-12] We have recently observed the first case, to our knowledge, of severe neutropenia and selective marrow depletion of mature granulocytes in association with the ingestion of this drug. Studies were performed to attempt to identify the mechanism by which flecanide therapy mediated the destruction of granulocytes.

REPORT OF A CASE

A 66-year-old man came to the rheumatology clinic complaining of a sore throat and nonproductive cough that had been present for two days. He had a history of psoriatic arthritis, controlled by indomethacin therapy and methotrexate administered orally (5 mg three times per week) for the past five years. There was no prior evidence of hematologic, renal, or hepatic dysfunction on frequent laboratory evaluations. A routine complete blood cell count during this visit to the clinic demonstrated profound leukopenia (leukocyte count of 1400/mm³ [1.4 × 10⁹/L]), and the patient was admitted to the hospital for hematologic evaluation.

The patient's medical history was significant for essential hypertension, which was well controlled with hydrochlorothiazide therapy. Three months prior to admission, he suffered an inferior-wall myocardial infarction, complicated by frequent premature ventricular contractions, including coupled ectopic beats. He agreed to enter a randomized, double-blind trial of antiarrhythmic agents. He received flecanide acetate, a new class I antiarrhythmic drug (100 mg orally, three times per day) with a marked diminution in the frequency of premature ventricular contractions and couplets. Metaprolol was also added to his medication regimen to improve blood pressure control. At the time flecanide therapy was initiated, the leukocyte count was 7800/mm³ (7.8 × 10⁹/L).

Physical examination on admission revealed an elderly man with the cutaneous stigmata of psoriasis, mainly over the extensor aspects of his limbs. He was afebrile, with minimal pharyngeal erythema, without exudates or adenopathy. Cardiopulmonary and abdominal examinations were unremarkable. Symmetrical deformation of multiple joints, particularly in his fingers, was present.

Complete blood cell count disclosed the following values: leukocytes, 1400/mm³ (1.4 × 10⁹/L), with 24% (0.24) mature granulocytes, 2% (0.02) band cells, 44% (0.44) lymphocytes, 14% (0.14) monocytes, and 10% (0.10) eosinophils; hematocrit, 38% (0.38); and platelets, 161 000/mm³ (161 × 10⁹/L). Sequential blood cell counts are plotted in the Figure. Results of a multiphasic chemistry profile (SMA-20) were entirely normal. Urinalysis and chest roentgenograms were unremarkable.

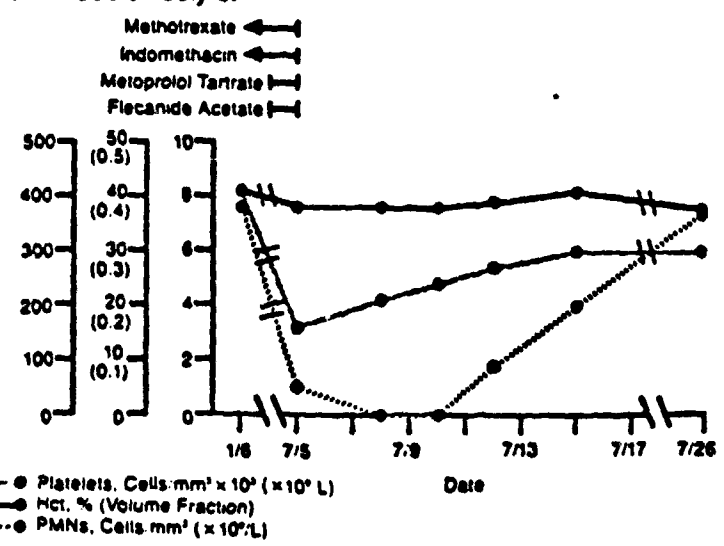
On admission, all medications were discontinued, and a biopsy of the iliac crest bone marrow was performed, which revealed a fatty marrow with sparse foci of normally cellular marrow, containing predominantly erythroid precursors (myeloid to erythroid ratio approximating 1:1). Erythroid morphology was normal. The myeloid series demonstrated normal morphology, but there was total absence of the more mature granulocyte forms. Megakaryocytes appeared to be normal both in number and morphology.

The patient remained asymptomatic and afebrile for the duration of his hospitalization, and peripheral blood leukocyte and absolute neutrophil counts began to improve by the seventh hospital day. He was discharged on the tenth hospital day with a neutrophil count of 4250/mm³ (4.25 × 10⁹/L).

RESULTS

The patient's serum was assessed for antigranulocyte antibodies on two dates, using previously published techniques.[13] The first sample was obtained during the period of granulocytopenia. At this time, IgG antibodies were present in the patient's serum, which bound to the surface of normal donor neutrophils following incubation of the cells with either 3.3 mg/mL or 0.33 mg/mL of flecanide acetate (Table). Incubation of neutrophils with normal serum or buffer, either in the presence or absence of flecanide,

Time course of flecanide-induced granulocytopenia. Patient's absolute neutrophil count (mature polymorphonuclear neutrophils [PMNs] and band cells), platelet count, and hematocrit (Hct) are plotted vs time. Drug therapies that might have contributed to granulocytopenia are stated in upper portion of Figure. Dosages were as follows: methotrexate, 15 mg/wk; indomethacin, 50 mg three times daily; metoprolol tartrate, 50 mg three times daily; and flecanide acetate, 100 mg three times daily. All medications were discontinued on July 5.



Accepted for publication Sept 10, 1986.

From the Division of Hematology-Oncology, Department of Medicine, University of Utah and the Veterans Administration Medical Center, Salt Lake City (Drs Samlowski and Frame), and the Division of Hematology, Department of Medicine of the State University of New York at Buffalo and Buffalo General Hospital (Dr Logue).

Reprints not available.

Granulocyte-Bound IgG*			
	Reagent Added		
	Flecanide Acetate, 3.3 mg/mL	Flecanide Acetate, 0.33 mg/mL	Buffer
Serum obtained during granulocytopenia, 1:10 dilution	240.9 ± 16.7	147.2 ± 4.8	114.3 ± 21.5
Serum obtained during convalescence, 1:10 dilution	94.1 ± 6.5	. . .	89.2 ± 8.1
Control serum, 1:10 dilution	93.4 ± 5.7	67.4 ± 6.1	60.7 ± 7.4
Buffer	51.1 ± 9.7	36.4 ± 5.1	30.6 ± 5.2

*Granulocyte-bound IgG in grams of staphylococcal protein A (SPA) bound per granulocyte times 10^{19}. Binding of radioiodinated SPA to normal paraformaldehyde-fixed neutrophils (2×10^7/mL) that had been previously incubated (60 minutes at 37°C) with equal volume of flecanide acetate (either 3.3 mg/mL or 0.33 mg/mL) or buffer and then extensively washed, was assayed as previously described.[13] Significant increase in SPA binding was observed subsequent to incubation of flecanide-exposed neutrophils with patient's serum, indicating specific binding of an IgG antibody. The results are the mean ± SEM of triplicate assays. Binding of SPA to neutrophils in presence of patient's serum and 3.3 mg/mL of flecanide acetate was statistically different from both the binding of SPA without the addition of drug ($P<.01$) and from antibody-binding derived from normal serum ($P<.001$) at either flecanide dilution by Student's *t* test.

resulted in significantly lower IgG binding. Although the studies shown in the Table were performed utilizing a 1:10 dilution of normal serum, to minimize nonspecific antibody adsorption to neutrophils, similar results were obtained when higher concentrations of serum were used. Parallel assays in the presence of normal serum or buffer did not result in significantly increased binding of radioiodinated staphylococcal protein A. Neutrophils that were exposed to each of the other medications which the patient was taking, including methotrexate, hydrochlorothiazide, metoprolol, or indomethacin at either 1.0 or 0.1 mg/mL, failed to demonstrate any potentiation of immunoglobulin binding in the presence of either the patient's serum or the control serum (data not shown). Additionally, increases in neutrophil-bound IgM and C3 complement[14] could not be detected on the surface of the flecanide-haptenated cells following incubation with the patient's serum (data not shown). Assay of a second serum sample, obtained during convalescence five months after the cessation of flecanide therapy, revealed the virtual disappearance of the flecanide-specific antibody (Table).

COMMENT

Drug-induced granulocytopenia is a rare and potentially fatal complication of antiarrhythmic drugs. Among the class I antiarrhythmic drugs, the incidence of this complication varies widely. Procainamide therapy causes granulocytopenia in the range of 0.6% to 4.4% of patients to whom this drug is administered.[8] The incidence of granulocytopenia induced by quinidine sulfate therapy is harder to establish, but numerous case reports document its occurrence.[4-7] Lidocaine hydrochloride therapy has not been associated with granulocytopenia, but therapy with tocainide hydrochloride, a congener of lidocaine, has been reported to produce this complication in approximately 0.18% of treated patients.[14] No reports of granulocytopenia or agranulocytosis associated with newer therapeutic agents, such as flecanide or encanide, have, as yet, been reported in the literature, to our knowledge.[10-12]

We observed a patient with the delayed onset of granulocytopenia, which we believe to be related to the administration of flecanide therapy. This patient developed a severe reduction in circulating neutrophils three months after institution of flecanide therapy. A bone marrow examination revealed normal erythroid and immature myeloid maturation, but a striking lack of mature granulocytes. The hematologic findings were most compatible with selective, immunologically mediated destruction of mature granulocytes in the peripheral blood and the bone marrow. Since the patient was receiving multiple medications that have previously been associated with granulocytopenia, immunologic testing was performed to determine which drug was the responsible agent.

The immunologic studies in our patient revealed that the granulocytopenia was mediated by haptenization of flecanide onto the surface of normal neutrophils. The hapten-neutrophil complex was quite stable, and could not be easily eluted from the cell surface by extensive washing of the neutrophils. This hapten was recognized by specific antibodies in our patient's serum, and resulted in a marked increase in the ability of antibody to bind to neutrophils. Fixation of the IgG antibody from the serum of our patient on the cell surface probably resulted in the immunologic destruction of the granulocytes. None of the other medications that the patient was taking was found to increase antibody binding to normal neutrophils.

The most important finding in this case is the observation that flecanide, a new investigational class I antiarrhythmic drug, is capable of haptenizing normal neutrophils from random donors. The fact that our patient was capable of immunologically recognizing such hapten-coated neutrophils suggests that this drug may cause similar complications in other patients. Further studies need to be performed to establish the frequency of clinically significant granulocytopenia following the administration of flecanide therapy. We recommend that if flecanide therapy is utilized, it be used cautiously, with regular assessment of blood cell counts to detect the potential onset of hematologic complications.

This study was supported in part by a Veterans Administration Research Associate Award, an American Cancer Society (New York) clinical fellowship, a National Institutes of Health (Bethesda, Md) grant (1RO1-AM31895-03), and the Richard Wahle Endowment Research Fund of the State University of New York at Buffalo.

The helpful editorial suggestions of James P. Kushner, MD, are sincerely appreciated.

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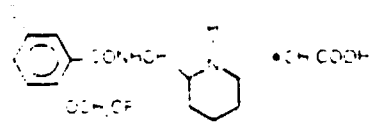
14. *Tonocard (Tocainide hydrochloride)*, product information package insert. West Point, Pa, Merck, Sharp & Dohme, 1985.

TAMBOCOR®
(flecainide acetate) B.I.D.

DESCRIPTION

TAMBOCOR® (flecainide acetate) is an antiarrhythmic drug available as tablets of 100 mg for oral administration.

Flecainide acetate is benzamide, N-(2-piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)-, monoacetate. The structural formula is given below:



Flecainide acetate is a white crystalline substance with a pK_a of 9.3 in aqueous solution and 48.4 mg/ml at 37° C.

TAMBOCOR tablets also contain microcrystalline cellulose and starch.

CLINICAL PHARMACOLOGY

TAMBOCOR has local anesthetic activity and depresses the membrane responses that underlie impulse initiation and conduction in nerve and muscle. Flecainide is a class Ic antiarrhythmic drug.

Electrophysiology. In the TAMBOCOR dose range that produces plasma concentrations in the therapeutic range, the greatest effect on the electrophysiologic properties of the heart is the prolongation of the refractory period and conduction. Effects on the cardiac action potential are modest and include a prolongation of the effective refractory period, which is greater than the prolongation of the action potential duration. Significant effects on intracardiac conduction are observed at the lowest plasma concentrations associated with therapeutic effects, and the PR interval and QRS complex are somewhat increased. These effects may become significant in patients with sinus node dysfunction or bundle branch block. See Warnings.

TAMBOCOR causes a dose-related and plasma-level-related decrease in single and multiple PVCs and can suppress recurrences of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful (90% or better suppression of the induction of ventricular tachycardia by programmed electrical stimulation). Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 µg/ml may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 µg/ml. Plasma levels above 0.7 to 1.0 µg/ml are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally.

In animals and isolated myocardium, a negative inotropic effect of flecainide has been demonstrated. Decreases in ejection fraction, consistent with a negative inotropic effect, have been observed after single administration of 200 to 250 mg of the drug in man; both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses (see Warnings).

Metabolism in Humans. Following oral administration, the absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range, 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (*first-pass effect*). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life with steady-state levels approached in 3 to 5 days; once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one fifth as potent) and the meta-O-dealkylated lactam of flecainide (*non-active metabolite*). These two metabolites (primarily conjugated) account for most of the *remaining portion of the dose*. Several minor metabolites (3% of the dose or less) are also found in urine; only 5% of an oral dose is excreted in feces. In patients, free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 µg/ml).

When urinary pH is very alkaline (8 or higher), as may occur in rare conditions (e.g., renal tubular acidosis, strict vegetarian diet), flecainide elimination from plasma is much slower.

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma (See Dosage and Administration).

In patients with congestive heart failure (NYHA class III), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 14 hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar (See Dosage and Administration).

From age 20 to 80, plasma levels are only slightly higher with advancing age. Flecainide elimination from plasma is somewhat slower in elderly subjects than in younger subjects. Patients up to age 80 + have been safely treated with usual dosages.

The extent of flecainide binding to human plasma proteins is about 40%, and is independent of plasma drug level over the range of 0.05 to about 3.4 µg/ml. Thus clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma drug levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs (see Warnings, Drug Interaction).

INDICATIONS AND USAGE

TAMBOCOR is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

TAMBOCOR is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of Tambocor, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, TAMBOCOR, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients depending on their cardiac status and underlying cardiac disease (see Dosage and Administration).

The effects of TAMBOCOR in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including TAMBOCOR, has been shown to have a favorable effect on mortality or sudden death.

CONTRAINDICATIONS:

TAMBOCOR is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Proarrhythmic Effects. **TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias.**

In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. Their frequency appears to be related to dose and to the underlying cardiac disease.

Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%, moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule (see Dosage and Administration).

Patients with less severe arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal.

The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).

Heart Failure. TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of preexisting CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg bid (see Dosage and Administration) and patients should be monitored carefully. Close attention must be given to maintenance of cardiac function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics; others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 µg/ml.

Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose-related increases in PR, QRS and QT intervals.

PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one third of patients may develop new first-degree AV heart block (PR interval > 0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study, 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur, and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythmia associated with Tambocor induced QT prolongation and bradycardia.

Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block, or right bundle branch block associated with a left hemiblock occurs, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally threshold changes are within the range of multiprogrammable pacemakers and, when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture.

Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

PRECAUTIONS:

Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administra-

[illegible] of TAMBOCOR to healthy subjects [illegible] dose of 600 mg a 13% [illegible] [illegible] hours.

[illegible] healthy subjects receiving TAMBOCOR [illegible] concurrent plasma flecainide levels were [illegible] and propranolol levels were increased [illegible] controlled studies in this formulation [illegible] TAMBOCOR and propranolol were each found to [illegible] pharmacodynamic effects when the drugs were administered [illegible] the effects were additive. The effects of concomitant [illegible] TAMBOCOR and propranolol on [illegible] were seen in addition to those [illegible] patients who were receiving beta-blockers concurrently [illegible] increased incidence of side effects [illegible] in addition to the negative inotropic effects [illegible] and flecainide should be recognized.

Following [illegible] peak flecainide plasma [illegible] In one study [illegible] drugs which may be administered concomitantly with flecainide [illegible] extent of flecainide binding to human plasma proteins is either unchanged or only slightly [illegible] Accordingly, interactions with other drugs which are highly [illegible] and anticoagulants would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction. Limited data in patients receiving known enzyme inducers, phenytoin, phenobarbital, carbamazepine, indicate only a 30% increase in flecainide elimination. In healthy subjects receiving rifampin 600 mg daily for one week, plasma flecainide levels were decreased by about 30% and half-life decreased by about 40%.

When [illegible] is added to flecainide therapy, plasma flecainide levels may increase, and dose reduction in some patients may [illegible] dosage should be reduced. See Dosage and Administration.

There has been little experience with the coadministration of TAMBOCOR and other class IC drugs. Because some of these drugs have negative inotropic properties and the effects of combination therapy with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless in the judgement of the physician the benefits of this combination outweigh the risks. There has been little experience with the coadministration of TAMBOCOR with quinidine or diazepam. No recommendations concerning concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day, seven times the usual human dose, did not reveal any adverse effect on male or female fertility.

Pregnancy. Pregnancy Category C. Flecainide has been shown to have teratogenic effects (club paws, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times but not three times the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg, respectively, however, delayed sternebria and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. Limited data suggest that flecainide is excreted in human milk. Because of the drug's potential for serious adverse effects in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 16 years of age have not been established.

Hepatic Impairment. Since flecainide elimination from plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma level monitoring is required to guide dosage. (See Plasma Level Monitoring); dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days).

ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR, described in detail in Warnings section, were new or exacerbated ventricular arrhythmias which occurred in 7% of patients, and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/ml.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic

and no causal dose and effect relationship with TAMBOCOR has been established. In the post-marketing surveillance studies, there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure, and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects are based on a multicenter efficacy study utilizing starting doses of 200 mg/day, with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table 1

Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 429 Patients at Any Dose	Incidence by Dose During Upward Titration 200 mg/Day (N=426)	300 mg/Day (N=293)	400 mg/Day (N=100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance†	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.

†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day, and a maintenance dose of 400-600 mg/day, the incidence of these adverse experiences was similar except for dizziness (32%) and visual disturbances (28%).

The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies. *Body as a Whole* — malaise, fever. *Cardiovascular* — bradycardia, sinus pause or arrest. *Gastrointestinal* — vomiting, diarrhea, dyspepsia, anorexia. *Skin* — rash. *Visual* — diplopia. *Nervous System* — hypoesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus. *Psychiatric* — malaise, anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients. *Body as a Whole* — Swollen lips, tongue and mouth, arthralgia, bronchospasm, myalgia. *Cardiovascular* — angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension. *Gastrointestinal* — flatulence. *Urinary System* — polyuria, urinary retention. *Hematologic* — leukopenia, thrombocytopenia. *Skin* — urticaria, exfoliative dermatitis, pruritus. *Visual* — eye pain or irritation, photophobia, nystagmus. *Nervous System* — twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor. *Psychiatric* — amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the T-wave, a reduction in myocardial rate and contractility, conduction disturbances, hypotension, and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: removal of unabsorbed drug from the gastrointestinal tract, administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol, mechanically assisted respiration, circulatory assists such as intra-aortic balloon pumping, and transvenous pacing in the event of conduction block. Because of the long plasma half-life of flecainide (12 to 27 hours in patients receiving usual doses), and the possibility of markedly non-linear elimination kinetics at very high doses, these supportive treatments may need to be continued for extended periods of time.

Hemodialysis is not an effective means of removing flecainide from the body. Since flecainide elimination is much slower when urine is very alkaline (pH 8 or higher), theoretically, acidification of urine to promote drug excretion may be beneficial in overdose cases with very alkaline urine. There is no evidence that acidification from normal urinary pH increases excretion.

DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels in patients with normal renal and hepatic function may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, **increases in dosage should be made no more frequently than once every four days**, since during the first 2 to 3 days of therapy the optimal effect of a given dose may not be achieved.

For sustained ventricular tachycardia, patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most such patients do not require more than 150 mg every 12 hours (300 mg/day) and the maximum dose is 400 mg/day.

For patients with symptomatic nonsustained ventricular tachycardia (couplets or premature ventricular complexes the recommended starting dose is also 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day and the plasma level is below 0.6 μg/ml, the dosage may be cautiously increased to a maximum of 600 mg/day.

Use of higher initial doses and more rapid dosage adjustments has resulted in an increased incidence of proarrhythmic events and congestive heart failure, particularly during the first few days of dosing (see Warnings). Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients, efficacy at the lower dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction (see Warnings). The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg bid every four days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

In patients with severe renal impairment (creatinine clearance of 35 ml/min/1.73 square meters or less), the initial dosage should be 100 mg once daily (or 50 mg bid); when used in such patients, frequent plasma level monitoring is required to guide dosage adjustments (see Plasma Level Monitoring). In patients with less severe renal disease, the initial dosage should be 100 mg every 12 hours; plasma level monitoring may also be useful in these patients during dosage adjustment. In both groups of patients, dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days), observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady-state plasma level is reached following a dosage change.

Based on theoretical considerations, rather than experimental data, the following suggestion is made: when transferring patients from another antiarrhythmic drug to TAMBOCOR, allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting TAMBOCOR at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

When flecainide is given in the presence of amiodarone, reduce the usual flecainide dose by 50% and monitor the patient closely for adverse effects. Plasma level monitoring is strongly recommended to guide dosage with such combination therapy (see below).

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 μg/ml. The probability of adverse experiences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 μg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Plasma level monitoring is required in patients with severe renal failure or severe hepatic disease, since elimination of flecainide from plasma may be markedly slower. Monitoring of plasma levels is strongly recommended in patients on concurrent amiodarone therapy and may also be helpful in patients with congestive heart failure and in patients with moderate renal disease.

HOW SUPPLIED:

TAMBOCOR is supplied as white, round, scored tablets containing 100 mg of flecainide acetate and embossed with RIKER on one side and TR 100 on the other side.

Tambocor, 100 mg tablet, is available in:
Bottles of 100 — NDC #0089-0307-10.
Boxes of 100 in unit dose blister strips — NDC #0089-0307-16.

Store at controlled room temperature 15°-30°C (59°-86°F) in a tight, light resistant container.

Manufactured by: TR-5
Riker Laboratories, Inc. 3M
St. Paul, Minnesota 55144

Riker Laboratories, Inc./3M

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

ORIGINAL

3M

October 28, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

REPORTS

Dear Sir/Madam:

Enclosed are copies of follow-up Adverse Reaction Reports [redacted] and [redacted]. These are duplicate literature reports of two previously reported cases, [redacted] and [redacted]

Please delete [redacted] and [redacted] from your records to prevent duplicate counts.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Attachments

Certified Mail - P 504 523 838

CENTER FOR DRUGS AND BIOLOGICS
REC'D
NOV 06 1987
HFN-110

11/12

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ACUTE MYOCARDIAL INFARCTION
This patient was started on flecainide 200 mg daily as part of a study for control of non-sustained ventricular tachycardia. The dose may have been increased but the maximum allowed in the study was 400 mg daily. This patient had a history of coronary artery disease and angina. During the study, the patient died of acute myocardial infarction. [Literature report: "Flecainide in the treatment of nonsustained ventricular tachycardia"; Annals of Internal Medicine 1986; 105; 493-498].
FDA NOTE: This case was previously reported as [redacted]. Please delete [redacted] from your records to avoid duplication.

13. RELEVANT TESTS LABORATORY DATA
None.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200-400 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
10/16/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [X] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-72)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	-	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ACUTE MYOCARDIAL INFARCTION
This patient was started on flecainide 200 mg daily as part of a study for control of non-sustained ventricular tachycardia. The dose may have been increased but the maximum allowed in the study was 400 mg daily. The patient had a history of coronary artery disease. During the study, the patient died of hemodynamic consequences of an acute myocardial infarction. [Literature report: "Flecainide in the treatment of non-sustained ventricular tachycardia"; Annals of Internal Medicine 1986; 105; 493-398].
FDA NOTE: It was discovered that this was previously reported as case [redacted]. Please delete [redacted] from the files to avoid duplication.

13. RELEVANT TESTS/LABORATORY DATA
None.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200-400 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
UNKNOWN - UNKNOWN

19. THERAPY DURATION
UNKNOWN

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
10/16/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [X] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CF 14.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

ORIGINAL

3M

October 16, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

D

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are two (2) Follow-up Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Attachments: Follow-up Report
- [redacted] (initial sent 9/17/87)
- [redacted] (initial sent 8/13/87)

Certified Mail P 504 523 724

RECEIVED
DIVISION OF DRUG AND
BIOLOGICAL PRODUCT EXPER.
1987 OCT 22 AM 12:44

CENTER FOR
REC'D
OCT 26 1987
HFN-110
DRUGS AND BIOLOGICS

Prob. due to Amiodarone not Flecainide
CL 10/29/87

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	63	M	01	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#HEMOPTYSIS, NAUSEA, ANOREXIA, FEVER, DYSPNEA, INTERSTITIAL FIBROSIS#
This 63 year old white male has a medical history of Myocardial Infarction, Pulmonary Embolism, Thrombophlebitis, Class I Congestive Heart Failure, and Malignant Arrhythmias. He was hospitalized on 01-16-87 for hemoptysis, accompanied by nausea, anorexia, fevers and increasing dyspnea. He was placed on a respirator and all oral medication was stopped. His condition progressively worsened and he expired on 02-10-86. The immediate cause of death was listed on the death certificate as shock due to sepsis and respiratory insufficiency associated with amiodarone. He had been on Flecainide 50mg bid for 17 days. It is the opinion of the investigator that the event was not

13. RELEVANT TESTS/LABORATORY DATA

TEMPERATURE: 101.4
CHEST X-RAY: DIFFUSE BILATERAL INTERSTITAL INFILTRATES.
LABS: WBC-16,900, WITH 79% PMN, 6%-BANDS , PLATELETS-343,000, HGB-12.2.
BLOOD GASES: PH-7.47, PCO2-33, PO2-45, BICARB-24.
AUTOPSY: INTERSTITIAL FIBROSIS (PULMONARY)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 100MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: CARDIAC DYSRHYTHMIA NOS

THERAPY DATES *(From/To)*: 12/31/85 - 01/16/86

19. THERAPY DURATION: 17 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ATENOLOL	7 DAYS	ACETAMINOPHEN	36 DAYS
ASPIRIN	18 DAYS	AMIODARONE	34 DAYS
PROPRANOLOL	14 DAYS	SODIUM WARFARIN	15 DAYS
DIOCYTL SODIUM SULFOSUCCINATE	21 DAYS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 10/ 2/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
due to Flecainide therapy.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-700)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	63	M	01	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

HEMOPTYSIS
This 63 year old white male has a medical history of Myocardial Infarction, Pulmonary Embolism, Thromb phlebitis, Class I Congestive Heart Failure, and Malignant Arrhythmias. He was hospitalized on 01-16-87 for hemoptysis, accompanied by nausea, anorexia, fevers and increasing dyspnea. He was placed on a respirator and all oral medication was stopped. His condition progressively worsened and he expired on 02-10-86. The immediate cause of death was listed on the death certificate as shock due to sepsis and respiratory insufficiency associated with amiodarone. He had been on Flecainide 50mg bid for 17 days. It is the opinion of the investigator that the event was not

13. RELEVANT TESTS LABORATORY DATA
TEMPERATURE: 101.4
CHEST X-RAY: DIFFUSE BILATERAL INTERSTITAL INFILTRATES.
LABS: WBC-16,900, WITH 79% PMN, 6%-BANDS , PLATELETS-343,000, HEB-12.8.
BLOOD GASES: PH-7.47, PCO2-33, PO2-45, BICARB-24.
AUTOPSY: INTERSTITIAL FIBROSIS (PULMONARY)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [x] TREATED WITH Rx DRUG
- [x] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
100MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
CARDIAC DYSRHYTHMIA NOS

18. THERAPY DATES *(From/To)*
12/31/85 - 01/16/86

19. THERAPY DURATION
17 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ATENOLOL	7 DAYS	ACETAMINOPHEN	36 DAYS
ASPIRIN	18 DAYS	AMIODARONE	34 DAYS
PROPRANOLOL	14 DAYS	SODIUM WARFARIN	15 DAYS
DIOCYTL SODIUM SULFOSUCCINATE	21 DAYS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
9/ 4/87

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
due to Flecainide therapy.

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRU
- ☐ RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

13.1

NOV 4 1987

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA 18-830

TOMBOCOR (flecainide acetate)

Sponsor: Riker

Type of Submission: ADR

Date of Submission: 10/12/87 Date of Assignment: 10/28/87

Date of Review: 10/28/87

Reviewer: Sughok K. Chun, M.D. HFN-110

A. Resume:

This is a follow up report of #[redacted]: A 74 Y/M started on flecainide (200 mg/day) on 4/15/86. Patient also had COPD and was in CHF. Approximately 16 days after beginning flecainide patient was hospitalized with the chief complaint of epigastric pain and nausea. Lab data revealed an increase bilirubin, serum creatinine, and BUN. Patient showed signs of cholestatic jaundice. A cholesystectomy on 05/04/86 showed no obstruction and was otherwise unremarkable. Patient continued to show evidence of elegated liver enzymes and acute renal failure. Death occured on 05/09/86.

Autopsy report: Drug induced cholestatis may have occurred, but it does not account for all the clinical and pathological findings.

Final Anatomic Diagnosis: intrahepatic cholestasis, acute gastritis, acute and chronic pancreatitis, atherosclerosis of coronary arteries and abdominal aorta, diverticulosis, acute bronchopneumonia, adrenal atrophy (received prednisone in life), left ventricle fibrosis, cardiomegaly, chronic passive congestion and hemosiderosis (lungs), centrilobular necrosis (liver), myocytolysis of left ventricle of heart, mural thrombi in heart, right kidney infarct, lung embolus.

S.K. Chun 11/04/87

Sughok K. Chun, M.D.

cc: Orig
HFN-110
HFN-110/CSO
HFN-110/SChun
clb/11/2/87/0040C

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

ORIGINAL

13.1

3M

October 12, 1987

REPORTS
D

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is a Follow-up Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Attachments: Follow-up Report
- [redacted] (initial sent 6/18/86)

Certified Mail P 504 523 719

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	74	M	05	01	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ACUTE RENAL FAILURE; CHOLESTATIC JAUNDICE; ELEVATED LIVER ENZYMES; EPIGASTRIC PAIN DEATH

Patient (74-year-old male) was started on flecainide (200 mg/day) for the treatment of ventricular arrhythmias. Patient also had chronic obstructive pulmonary disease and was in congestive heart failure. Approximately 16 days after beginning flecainide patient was hospitalized with the chief complaint of epigastric pain and nausea. Lab data revealed an increase bilirubin, increase serum creatinine, and increase BUN. Patient showed signs of cholestatic jaundice. A cholesystectomy on 05/04/86 showed no obstruction and was otherwise unremarkable. Patient continued to show evidence of elevated liver enzymes and acute

13. RELEVANT TESTS LABORATORY DATA

Lab values: 1. Increase liver enzymes--SGOT 3X Normal
2. Bilirubin 5/1/86 = 1.8; 8/8/86 = 6.6 Normal (<1.5)
3. Creatinine 5/1/86 = 2.7; 5/8/86 = 7.0
4. Urine Output 5/8/86 less than 600 ml per day
5. Cholesystectomy 5/4/86 Negative findings

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

ILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*: 04/15/86 - 05/03/86

19. THERAPY DURATION: 19 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN(LANOXIN)
POTASSIUM CHLORIDE
PREDNISONE
FUROSEMIDE
PROBENECID

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Patient was allergic to quinidine.
Chronic renal failure; chronic obstructive pulmonary disease; congestive heart failure; streptococcus pneumonia - 1985; acute myocardial infarct - 1978, 1983, 1984; syncopy.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

ATE RECEIVED Y MANUFACTURER: 9/21/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

renal failure. Death occurred on 05/09/86.
Autopsy report: Drug induced cholestasis may have occurred, but it does not account for all the clinical and pathological findings. Final Anatomic Diagnosis: intrahepatic cholestasis, acute gastritis, acute and chronic pancreatitis, atherosclerosis of coronary arteries and abdominal aorta, diverticulosis, acute bronchopneumonia, adrenal atrophy (received prednisone in life), left ventricle fibrosis, cardiomegaly, chronic passive congestion and hemosiderosis (lungs), centrilobular necrosis (liver), myocytolysis of left ventricle of heart, mural thrombi in heart, right kidney infarct, lung embolus.

13. RELEVANT TESTS/LABORATORY DATA

Autopsy findings showed severe cardiac disease, acute renal failure, liver necrosis and intrahepatic bile duct obstruction.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED / MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	72	M	05	01	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, acute renal failure, cholestatic jaundice, elevated liver enzymes, epigastric pain

Patient (72-year-old male) was started on flecainide (100 mg b.i.d.) for the treatment of ventricular arrhythmias. Patient also had chronic obstructive pulmonary disease and was in congestive heart failure. Approximately four days after beginning flecainide patient was hospitalized with the chief complaint of epigastric pain and nausea. Lab data revealed an increase bilirubin, increase serum creatinine, and increase BUN. Patient showed signs of cholestatic jaundice. A cholesystectomy on 05/04/86 showed no obstruction and was otherwise unremarkable. Patient continued to show evidence of elevated liver enzymes and acute

13. RELEVANT TESTS/LABORATORY DATA

Lab values: 1. Increase liver enzymes--SGOT 3X Normal
2. Bilirubin 5/1/86 = 1.8; 5/8/86 = 6.6 Normal (<1.5)
3. Creatinine 5/1/86 = 2.7; 5/8/86 = 7.0
4. Urine Output 5/8/86 less than 600 ml per day
5. Cholesystectomy 5/4/86 Negative findings

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☒ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

AILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR ARRHYTHMIA

THERAPY DATES *(From/To)*: 04/25/86 - 05/03/86

19. THERAPY DURATION: 8 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN(LANOXIN)
POTASSIUM CHLORIDE
PREDNISONE
FUROSEMIDE
PROBENECID

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Patient was allergic to quinidine.
Chronic renal failure.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

DATE RECEIVED BY MANUFACTURER: 5/ 9/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NC.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT IDINITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

renal failure. Death occurred on 05/09/86.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

Autopsy findings showed severe cardiac disease, acute renal failure, liver necrosis and intrahepatic bile duct obstruction.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*

☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT

☐ YES ☐ NO

25a. REPORT TYPE

☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?

☐ YES ☐ NO

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612) 736-5016

13.1

3M

October 9, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are three (3) Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Enclosure: 15 Day Reports
- [redacted]
- [redacted]
- [redacted]

Certified Mail P 504 523 718

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6 REACTION ONSET MO.	DA.	YR.
[redacted]	73	F	09	04	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

BRADYCARDIA, QRS-WIDENING, PULMONARY EDEMA Death
This 73 y.o. woman had a history of coronary heart disease, PVC's (Lown 4B), diabetes mellitus, and renal function impairment. She was started on flecainide 300 mg daily in March 1987 for control of PVC's. On 04SEP87 at 6pm the woman was hospitalized with bradycardia of 20-30 beats/minute. She was pale with cold sweats. QRS widening of 0.2 sec was observed; systolic blood pressure was 130 but decreased with time. Acute pulmonary edema developed, and the woman died at 9pm on 04SEP87.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
Creatinine 2 mg% [normal range: 0.6-1.5 mg/100 ml]
Potassium 6.9 mEq/l (04SEP87) [normal: 3.5-5]
Plasma flecainide level 1.235 mcg/ml (04SEP87)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

18. THERAPY DATES *(From To)*
03/??/87 - 09/04/87

19. THERAPY DURATION
6 MONTHS

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NIFEDIPINE
ISOSORBIDE MONO-NITRATE
SPIRONOLACTONE/FUROSEMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. [redacted] SUSPECT DRUG /18 330

24b. MFR CONTROL NO. [redacted]

24c. DATE RECEIVED BY MANUFACTURER
9/23/87

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612)736-5016

ORIGINAL

3M

September 30, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

REPORTS
D

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is a Follow-up Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Attachments: Follow-up Report
[redacted] (initial sent 9/11/87)

Certified Mail P 504 523 709

10/26/87

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved. OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	29	F	08	26	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

BLURRED VISION, ATRIAL FIBRILLATION, VENTRICULAR FIBRILLATION Death
This 29 y.o. woman with a history of hypertrophic cardiomyopathy and paroxysmal atrial tachycardia(PAT) resistant to quinidine and verapamil was hospitalized on 10AUG87 to begin flecainide acetate therapy. After 72 hours she was released from the hospital on a dose of 200 mg/day with no evidence of QRS widening. During the first 5 days of therapy she noticed prolonged atrial fibrillation and initiated self-medication with quinidine and verapamil(in addition to flecainide) but for only 2 doses before she spoke with the physician and was told to stop all medication for about 18 hours before restarting flecainide at 300 mg/day. After several days at this level she developed severe blurred vision(18AUG87)

13. RELEVANT TESTS/LABORATORY DATA
27AUG87: Plasma sample taken 12-24 hours following death had flecainide level of 2.26 mcg/ml. Experience has shown postmortem samples have artificially elevated flecainide levels.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
PAROX ATRIAL TACHYCARDIA

18. THERAPY DATES *(From/To)*
08/10/87 - 08/26/87

19. THERAPY DURATION
16 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
3M PHARMACEUTICALS INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
9/ 9/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID-INITIALS (In Confidence)	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	29	F	08	26	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
BLURRED VISION, ATRIAL FIBRILLATION, VENTRICULAR FIBRILLATION# Death
This 29 y.o. woman with a history of hypertrophic cardiomyopathy and paroxysmal atrial tachycardia(PAT) resistant to quinidine and verapamil was hospitalized on 10AUG87 to begin flecainide acetate therapy. After 72 hours she was released from the hospital on a dose of 200 mg/day with no evidence of QRS widening. During the first 5 days of therapy she noticed prolonged atrial fibrillation and initiated self-medication with quinidine and verapamil(in addition to flecainide) but for only 2 doses before she spoke with the physician and was told to stop all medication for about 16 hours before restarting flecainide at 300 mg/day. After several days at this level she developed severe blurred vision(18AUG87)

13. RELEVANT TESTS/LABORATORY DATA
None

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTIO
- [X] TREATED WITH Rx DRU
- [X] RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
PAROX ATRIAL TACHYCARDIA

18. THERAPY DATES *(From/To)*
08/10/87 - 08/26/87

19. THERAPY DURATION
16 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
8/27/87

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [X] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

131

OCT 5 1987

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Medical Officer's Short Form Review

NDA# 18,830

DRUG: Tambocor (flecainide) Tablets

SPONSOR: Riker

TYPE OF SUBMISSION: ADR

DATE OF SUBMISSION: September 17, 1987

DATE OF REVIEW: October 2, 1987

REVIEWER: Sughok K. Chun, M.D. HFN-110

A. RESUME:

15 Day Reports

[redacted] "Hypotonia, Seizure"

The 24 y/o mother of this newborn was in her 9 mo of pregnancy when she was started on flec for control of WPW syndrome. She had previously received metoprolol during the pregnancy but was switched to flec. Initial flec dose was 200 mg daily, but was increased after five days to 300 mg daily for better control. Two wks after starting on flec, she was given an additional 50 mg of flec because ECG showed lessened effect of flec, probably because of an increased volume of distribution due to pregnancy. Labor was induced with pitocin and the child was monitored with an invasive fetal monitor. According to the physician, the child was not in danger at any time. The baby was delivered approxi 5 h after hospitalization. There were no problems associated with delivery - no trauma and no forceps use. The baby was full term and showed no evidence of problems at delivery. At time of delivery, the mother's plasma flec level was 0.63 mcg/ml, and the cord blood flec level was 0.44 mcg/ml. The woman elected to not breast feed. On Sept. 4 information from the physician revealed that the baby has severe neurologic damage, showing no suck reflex and experienceing seizures and poor tone. In the physician's opinion, the abnormality is probably not due to flec use because of the short duration of in utero exposure. Further information is being sought. (NOTE: The mother had four prior pregnancies, three which ended by spontaneous abortion. The remaining pregnancy resulted in the birth of a normal child. Physician stated that the woman had no tachycardia with prior pregnancy. Since delivery the woman has not had any episodes of tachycardia and is sporadically taking flec.)

Comment: I called the sponsor (Jeanne M. Fox, Sr. Regulatory Coordinator) on October 2, 1987 and asked when the baby was born that we could figure out the lapse time of neurologic damage symptoms.

[redacted] "DEMENTIA"
The patient, a 70 y/F, experienced a MI 2 yrs ago, followed by onset of episodic VT. Several anti-arrhythmic drugs were tried, but none was tolerated until flec was initiated on , 198 . The arrhythmia was promptly controlled by flec. About a year ago she developed significant anxiety and mental depression. On March , 1987, she required hospitalization for increasing depression, in the hospital she exhibited frank evidence of dementia. All medications were discontinued except flec, with no consequent improvement. Flec was then stopped and the signs of dementia subsided, although anxiety persisted.

Comment: I called the sponsor on October 2, 1987 and asked how long the Pt had been treated flec. at the time of mental symptoms

[redacted] "CVA" in a 81 y/F after 3 days of flec. Rx.
[redacted]: "Sudden death due to MI" after 2 yrs. Flec Rx.
[redacted] "Hemoptysis, sepsis diffuse pulmonary information" prob due to amiodarone. Flec for 17 days.

Follow Up Report.

[redacted]ELEVATED SED RATE, MARKED ANEMIA, CHF
This 73 y/M with insulin dependent diabetes, ASHD, recurrent syncope, lupus from procainamide, and quinidine intolerance was started in JAN 1, 87 on flec at 300 mg/day for PAT. In MAY 1, 87 his LVEF was 33%. After 6 mo of Rx he had chest pain and was transferred from nursing home to an emergency room and found in CHF. Therapy (not defined) cleared the CHF but at admission he was also found to have a fever, weakness, elevated sed rate (136 mm/hr) and marked anemia (Hgb 8.8, Hct 28%). The following tests were normal; CPK, LDH, electrolytes, serum iron, folic acid, BUN, creatinine, uric acid, coagulation profile. ANA and rheumatoid factor were negative and lupus anticoagulant was positive. All stools were consistently negative for occult blood and elevated haptoglobins eliminated hemolysis. Colonoscopy was imcomplete due to retained stools. Anemia was thought NOT due to bleeding because of normal iron stores. After flec was stopped the sed rate remained elevated at 125 mm.hr. Two units of packed red cells raised Hgb to 12 gm but at discharge (11 days after last flec dose) Hgb was 11.9 gm with a 33% Hct. After discharge his PAT was controlled with encainide.

[redacted] "APNEA, CYANOSIS"

This 1 mo old premature infant was born with non-immune hydrops secondary to SVT. After multiple drug failures flec was started at a dose of 6 mg/8h which effectively controlled the tachycardia. Two weeks after discharge, on 7/17/87, the child suddenly experienced an episode of apnea and cyanosis requiring stimulation and artificial breathijng (CPR). The child was hospitalized and has not had any further episodes or sequelae. Flec level at hospitalization was 0.91 mcg/ml. Sleep study showed no abnormalities. The child was sent home on a monitor. 9/8/87: Total daily dose corrected to 18mg (6mg q6h).

S.K. Chun 10/2/87

Sughok K. Chun, M.D. HFN-110

cc: Orig. NDA
HFN-110
HFN-110/CSO
HFN-110/SKChun
ayg/10/02/87/0901e

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612) 736-5016

September 17, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor®(flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are four (4) Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Enclosure: 15 Day Reports

[redacted]

Certified Mail P 504 523 515

SEP 22 12:14

19/2

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	63	M	01	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

HEMOPTYSIS
This 63 year old white male has a medical history of Myocardial Infarction, Pulmonary Embolism, Thrombophlebitis, Class I Congestive Heart Failure, and Malignant Arrhythmias. He was hospitalized on 01-16-87 for hemoptysis, accompanied by nausea, anorexia, fevers and increasing dyspnea. He was placed on a respirator and all oral medication was stopped. His condition progressively worsened and he expired on 02-10-86. The immediate cause of death was listed on the death certificate as shock due to sepsis and respiratory insufficiency associated with amiodarone. He had been on Flecainide 50mg bid for 17 days. It is the opinion of the investigator that the event was not

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

13. RELEVANT TESTS LABORATORY DATA

TEMPERATURE: 101.4
CHEST X-RAY: DIFFUSE BILATERAL INTERSTITAL INFILTRATES.
LABS: WBC-16,900, WITH 79% PMN, 6%-BANDS , PLATELETS-343,000, HGB-12.2
BLOOD GASES: PH-7.47, PCO2-33, PO2-45, BICARB-24.
AUTOPSY: INTERSTITIAL FIBROSIS (PULMONARY)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?

- [ ] YES
- [X] NO
- [ ] NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
100MG	ORAL

17. INDICATION(S) FOR USE
CARDIAC DYSRHYTHMIA NOS

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION
12/31/85 - 01/16/86	17 DAYS

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

- [ ] YES
- [ ] NO
- [X] NA

III. CONCOMITANT DRUGS AND HISTORY

CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

ATENOLOL	7 DAYS	ACETAMINOPHEN	56 DAYS
ASPIRIN	18 DAYS	AMIODARONE	34 DAYS
PROPRANOLOL	14 DAYS	SODIUM WARFARIN	15 DAYS
DIOCYTL SODIUM SULFOSUCCINATE	21 DAYS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
[redacted] /18-830	[redacted]

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
9/ 4/87	[ ] FOREIGN [X] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
[X] YES [ ] NO	[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
due to Flecainide therapy.

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612)736-5016

3M

September 17, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor®(flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are three (3) Follow-up Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Attachments: Follow-up Report
- [redacted] (initial sent 6/16/87)
- [redacted] (initial sent 8/31/87)
- [redacted] (initial sent 8/3/87)
(follow-up sent 8/21/87)

Certified Mail P 504 523 514

CENTER FOR
REC'D
SEP 24 1987
HFN-110
DRUGS AND BIOLOGICS

10/4/87

FAX SEP 22 11:12 14

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT IDENTIFICATION (In Confidence)	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	72	M	04	27	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
#OCCLUSION OF CORONARY ARTERY, HYPERTENSION# Death
This 72 y.o. man had a history of ischemic heart disease, left ventricular failure, and sustained ventricular tachycardia since 1980. He experienced episodes of palpitations and angina, approximately once per month, with each lasting more than 30 minutes. He had no history of myocardial infarction. Flecainide 200 mg daily was started on 6/17/85. Plasma flecainide levels remained at about 0.3 mcg/ml throughout therapy. On 4/27/87, the man died suddenly at home. Results at autopsy show cause of death to be atheromatous occlusion of the right coronary artery.
9/10/87 Added blood pressure readings to lab data.

13. RELEVANT TESTS/LABORATORY DATA
Plasma flecainide levels throughout two years of therapy: 0.3 mcg/ml

Date	Blood Pressure
23DEC85	170/80
27MAR86	190/90
03JUN86	140/80

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From/To)*
06/17/85 - 04/27/87

19. THERAPY DURATION
22 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

TRIAMTERENE/CYCLOTHIAZIDE	>2 YEARS	ISOSORBIDE DINITRATE	>2 YEARS
NITROGLYCERIN	>2 YEARS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See 87 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
9/10/87

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6 REACTION ONSET MO.	DA.	YR.
[redacted]	72	M	06	27	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***OCCLUSION OF CORONARY ARTERY, HYPERTENSION* Death**
This 72 y.o. man had a history of ischemic heart disease, left ventricular failure, and sustained ventricular tachycardia since 1980. He experienced episodes of palpitations and angina, approximately once per month, with each lasting more than 30 minutes. He had no history of myocardial infarction. Flecainide 200 mg daily was started on 6/17/85. Plasma flecainide levels remained at about 0.3 mcg/ml throughout therapy On 4/27/87, the man died suddenly at home. Results at autopsy show cause of death to be atheromatous occlusion of the right coronary artery and hypertension.

13. RELEVANT TESTS LABORATORY DATA

Plasma flecainide levels throughout two years of therapy: 0.3 mcg/ml

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTIO
- [ ] TREATED WITH Rx DRU
- [ ] RESULTED IN, OR PROLONGED, INPATIEI HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*: 06/17/85 - 04/27/87

19. THERAPY DURATION: 22 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?

- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

BUMETANIDE/KCL	>2 YEARS	ISOSORBIDE DINITRATE	>2 YEARS
NITROGLYCERIN	>2 YEARS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

See 87 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 5/26/87

24d. REPORT SOURCE *(Check one)*

- [x] FOREIGN [ ] STUDY [ ] LITERATURE
- [x] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT

- [x] YES [ ] NO

25a. REPORT TYPE

- [x] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In Confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?

- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

13.1

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

OCT 1 [illegible]

NDA: 18-830

Name of Drug: Tombocor (Flecainide acetate) Tab

Sponsor: Riker

Type of Submission: ADR

Date of Submission: September 11, 1987

Date of Assignment: September 29, 1987

Date of Review: September 30, 1987

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

The following 3 ADR's were submitted.

(1) [redacted] *ANXIETY, NEAR SYNCOPE, HYSTERIA*
This 18 y/m was being treated with flec. 200 mg daily for 8 mos. He experienced anxiety, near syncope, and hysteria which has continued for one month. He is currently hospitalized and continues to exhibit the above mentioned reactions, plus severe thrashing movements. The pt is not on any other medications at this time. The physician will attempt to rule out an hysterical conversion reaction or temporal lobe epilepsy.

(2) [redacted] *BLURRED VISION, ATRIAL FIBRILLATION, VENT FIB* Death
This 29 y/f with a Hx of hypertrophic cardiomyopathy and PAT resistant to quinidine and verapamil was hospitalized on 8/10/87 to begin flec. therapy. After 72 h she was released from the hospital on a dose 200 mg/day with no evidence of QRS widening. During the first 5 days of therapy she noticed prolonged A Fib and initiated self-medication with quinidine and verapamil (in addition to flec.) but for only 2 doses before she spoke with the physician and was told to stop all medication for about 18 h before restarting flec. at 300 mg/day. After 8 days at this level she developed severe blurred vision 8/18 but, it occurred about 10 h following a dose and lasted 2 h. Th. next day her physician changed the dose schedule to 100 mg tid rather than 150 mg mg bid. Another severe blurred vision episode again lasting 2 h occurred on 8/25. On 8/26/87, she collapsed at a bus stop and was transported to the hospital. She was in VF which was unresuscitatable and she died. Plasma flec. levels were not obtained. The pt. had no evidence of hepatic or renal disease. the reported considers this to be a proarrhythmic event because the patient had no prior evidence of ventricular involvement. Autopsy results are pending.

(3) [redacted] *VT, HYPOTENSION, LEUKOCYTOSIS, ELEVATED LIVER FUNCTION TESTS, WIDENED QRS, RBBB, SUICIDE ATTEMPT*
This 28 y/F was hospitalized 2 h after a suicide attempt when she had ingested 3800 mg flec., 50 mg diazepam, 20 mg loperamide, and 100 gm ethyl alcohol. On admission, the woman was somnolent with unobtainable BP and HR of 160/min. An initial ECG showed VT and RBBB. Flec level at admission was 3.7 mcg/ml. The woman was placed on mechanical ventilation and given phenobarbital, diazepam, dopamine, and sodium bicarbonate. BP increased to 70/40. Heart rhythm converted to sinus tachycardia with intermittent PVC's.

Physostigmine was given. Gastric lavage, activated charcoal solution, forced diarrhea and diuresis were given. ECG showed a regular sinus rhythm of 85/min. 12 h later the woman was weaned off the ventilator. ECG showed no further episodes of ventricular arrhythmia. Lab tests showed leukocytosis and elevated liver function tests. The woman was discharged from the hospital in good condition three days after the suicide attempt. [Literature report: "Life-threatening flecainide toxicity" Winkelman, Leinberger. Annals of Internal Medicine, 106: 807-814, 1987.

LABORATORY DATA

Hours after Overdose	Flecainide Serum Level	PR Interval	QRS Duration	QT Interval	JT Interval
2	3.7 mcg/ml	--	0.16 sec.	0.35 sec	--
4.5	2.5	0.2 sec	0.12	0.44	0.402 sec
8	1.75	0.2	0.11	0.43	0.395
9	1.68				
19	1.15	0.19	0.1	0.36	0.354
35	0.768	0.18	0.09	0.35	0.321
59	0.4	0.16	0.08	0.34	0.324
BASELINE:	0	0.15	0.065	0.34	0.3131

S.K. Chun 10/1/87
Sughok K. Chun, M.D.

cc:
Orig. NDA: 18-830
HFN-80/DDIR
HFN-110
HFN-110/CSO
HFN-110/SChun/9/30/87
klr/9/30/87/09281

ORIGINAL

Regulatory Affairs
Riker Laboratories, Inc.

Building 270-3A-01, 3M Center
St. Paul, Minnesota 55144-1000
(612) 736-5016

3M

September 11, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject. 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are three (3) Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Enclosure: 15 Day Reports
- [redacted]
- [redacted]

Certified Mail P 504 523 521

CENTER FOR
REC'D
SEP 15 1987
HFN-110
DRUGS AND BIOLOGICS

80 SEP 21 08

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	29	F	08	26	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

BLURRED VISION, ATRIAL FIBRILLATION, VENTRICULAR FIBRILLATION Death
This 29 y.o. woman with a history of hypertrophic cardiomyopathy and paroxysmal atrial tachycardia(PAT) resistant to quinidine and verapamil was hospitalized on 10AUG87 to begin flecainide acetate therapy. After 72 hours she was released from the hospital on a dose of 200 mg/day with no evidence of QRS widening. During the first 5 days of therapy she noticed prolonged atrial fibrillation and initiated self-medication with quinidine and verapamil(in addition to flecainide) but for only 2 doses before she spoke with the physician and was told to stop all medication for about 18 hours before restarting flecainide at 300 mg/day. After several days at this level she developed severe blurred vision(18AUG87)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
None

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
PAROX ATRIAL TACHYCARDIA

18. THERAPY DATES *(From/To)*
08/10/87 - 08/26/87

19. THERAPY DURATION
16 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
8/27/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

but, it occurred about 10 hours following a dose and lasted 2 hours. The next day her physician changed the dose schedule to 100 mg tid rather than 150 mg bid. Another severe blurred vision episode again lasting 2 hours occurred on 25AUG87. On 26AUG87, she collapsed at a bus stop and was transported to the hospital. She was in ventricular fibrillation which proved unresuscitatable and she died. Plasma flecainide levels were not obtained. The patient had no evidence of hepatic or renal disease. The reported considers this to be a proarrhythmic event because the patient had no prior evidence of ventricular involvement. Autopsy results are pending.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

ORIGINAL

13-1

REPORTS
P-7

3M

October 16, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

RECEIVED
CENTER FOR DRUGS AND BIOLOGICS
OCT 23 1987
CENTRAL DOCUMENTS ROOM

Dear Sir/Madam:

Pursuant to 21 CFR 314.80, enclosed is the Periodic ADR Report in duplicate for Tambocor® (flecainide acetate) NDA 18-830. There are 39 FDA-1639 forms in this submission, 32 of which are initial reports and 7 are follow-up reports.

The time period covered by this report is June 11, 1987 to September 10, 1987.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

CENTER FOR DRUGS AND BIOLOGICS
REC'D
OCT 27 1987
HFN-170

Noted
SCD - 10/28/87

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-729)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	67	M	04	15	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
"VENTRICULAR FIBRILLATION" Death
This 67 year old man was admitted to hospital 4/13/87 with pneumonia & severe congestive heart failure, complicated by frequent premature ventricular contractions with coupling; he experienced one brief episode of ventricular tachycardia. A multitude of drugs was started to combat his disorders (see below). On 4/14/87 flecainide 100mg bid was started to control his arrhythmia. On 4/15/87, after 3 doses of flecainide, he developed ventricular fibrillation (unresuscitable) and died.

13. RELEVANT TESTS LABORATORY DATA
None known

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*
04/14/87 - 04/15/87

19. THERAPY DURATION
3 DOSES

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

CEFAZOLIN SODIUM
ERYTHROMYCIN
ALBUTEROL
POTASSIUM CHLORIDE
TRIAMTERENE, HYDROCHLOROTHIAZI
SODIUM WARFARIN
TOBRAMYCIN
FUROSEMIDE
THEOPHYLLINE
INSULIN ZINC
DIGOXIN
OXTRIPHYLLINE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
see #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
6/23/87

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [X] HEALTH PROFESSIONAL
- [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES
- [X] NO

25a. REPORT TYPE
- [X] INITIAL
- [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES
- [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES
- [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: O'1B No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	71	F	05	11	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

DEATH, CAUSE UNKNOWN
This 71 y/o woman with a history of coronary artery disease and arrhytmias was found dead in her car after 12 days of flecainide acetate therapy. Concomitant medication was amitriptyline. Postmortem drug screening found plasma flecainide levels of 9.9 mcg/ml(heart) and 9.1 mcg/ml (subclavian), an amitriptyline level of 0.18 mcg/ml and a nortriptyline level of 0.18 mcg/ml. The therapeutic plasma level for flecainide is 0.2 - 1.0 mcg/ml. Autopsy rendered anatomical diagnoses of arteriosclerotic and hyptertensive cardiovascular disease with opinion that death was due to natural causes.

13. RELEVANT TESTS/LABORATORY DATA
See #7 above for autopsy informatin.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: UNKNOWN

THERAPY DATES *(From To)*: 04/29/87 - 05/11/87

19. THERAPY DURATION: 12 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

AMITRIPTYLINE HCL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-13-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 8/26/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	83	F	07	27	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

DEATH, CAUSE UNKNOWN
This 83 y/o woman had frequent runs of non-sustained ventricular tachycardia (15-20 beats) detectable on ECG. She had symptoms with these runs, but no hemodynamic consequences such as syncope. She was in generally good health for her age having slight left ventricular hypertrophy and a nearly normal ejection fraction. She had failed arrhythmia control with several antiarrhythmics and was entered into hospital for starting flecainide therapy. She was on no other medications at the time. One 100 mg tablet of flecainide was given, and eight hours later she was discovered dead. No autopsy was obtained.

13. RELEVANT TESTS/LABORATORY DATA
See 87, above

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [x] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*
07/27/87 - 07/27/87

19. THERAPY DURATION
ONE DOSE

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [x] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [x] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Please see 87 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
7/30/87

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [x] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [x] NO

25a. REPORT TYPE
- [x] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	??	??	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
DEATH, CAUSE UNKNOWN
This man was taking flecainide 200 mg daily for several months when he died of unknown causes. Further information is requested from the physician.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
CARDIAC DYSRHYTHMIA NOS

18. THERAPY DATES *(From/To)*
??/87 - ??/87

19. THERAPY DURATION
MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See 87 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-030

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
7/28/87

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT? X
☐ YES ☒ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	64	F	06	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

"Hepatitis"
64 y.o. woman entered hospital with shortness of breath and with aim to change her medication for treatment of frequent premature ventricular contractions. She was currently on 4gm procainamide daily. This was discontinued and flecainide 100mg bid started. After 3 days flecainide increased to 400mg/d, but after 2 days of that flecainide reduced again to 200mg/d due to GI complaints. After 2 days of that, marked elevation of transaminases and bilirubin appeared without elevation of alk. phos. Flecainide stopped. (Aminophylline and SOLU MEDROL d/c'ed when GI complaints appeared.) Dignosis of hepatitis is entertained.
13OCT86 M.D. advised patient died. His suspicions of flecainide's

13. RELEVANT TESTS/LABORATORY DATA
23JUN86 Bilirubin 4.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTIO
- [ ] TREATED WITH Rx DRU
- [X] RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*: 06-16-86 - 06-23-86

19. THERAPY DURATION: 7 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ N/A

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
AMINOPHYLLINE
METHYLPREDNISOLONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Shortness of Breath has been present some time and seems to relate to a primary pulmonary condition, not clearly defined, rather than to cardiac status. General cardiac status appears to be good without failure.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-11-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: 18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 10/13/86

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1996

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	64	F	06	13	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#Hepatitis#
64 y.o. woman entered hospital with shortness of breath and with aim to change her medication for treatment of frequent premature ventricular contractions. She was currently on 4gm procainamide daily. This was discontinued and flecainide 100mg bid started. After 3 days flecainide increased to 400mg/d, but after 2 days of [illegible] flecainide reduced again to 200mg/d due to GI complaints. After [illegible]ys of that, marked elevation of transaminases and bilirubin appeare[illegible]ut elevation of alk. phos. Flecainide stopped. (Aminophylline an[illegible] MEDROL d/c'ed when GI complaints appeared.) Dignosis of hepa[illegible]tis is entertained. 130CT86 M.D. advised patient died. His suspicions of flecainide's

13. RELEVANT TESTS/LABORATORY DATA
23JUN86 Bilirubin 4.

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTIO
- [ ] TREATED WITH Rx DRU
- [X] RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*
06-16-86 - 06-23-86

19. THERAPY DURATION
7 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
AMINOPHYLLINE
METHYLPREDNISOLONE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Shortness of Breath has been present some time and seems to relate to a primary pulmonary condition, not clearly defined, rather than to cardiac status. General cardiac status appears to be good without failure.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
10/13/86

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFR-738)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

involvement are reduced as many other medications were involved before and after its discontinuation. He promises a full report.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTI
- ☐ TREATED WITH Rx DF
- ☐ RESULTED IN, OR PROLONGED, INPATIE HOSPITALIZATION
- ☐ RESULTED IN SEVER OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG
☐ YES ☐ NO ☐ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*	19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)* ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER
25. 15 DAY REPORT ☐ YES ☐ NO	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURE
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

ORIGINAL 14-day REPORTS

3M

February 9, 1988

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are three (3) Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Enclosure: 15 Day Reports
- [redacted]
- [redacted]
- [redacted]

Certified Mail P 504 523 846

FEB 17 AM 8:45

RECEIVED
FEB 19 1988
HFN-110
NATIONAL CENTER FOR DRUGS AND BIOLOGICS

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	77	M	10	16	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

ACUTE MYOCARDIAL INFARCTION Death
This 77 y.o. man suffered an acute myocardial infarction on 13JUL87 and was started on flecainide 200 mg daily for control of subsequent paroxysmal supraventricular tachycardia. After three months of therapy, he suffered a second acute myocardial infaction on 16OCT87 and was dead on arrival at the hospital.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA
None.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
SUPRAVENTRICULAR ARRHYTH

THERAPY DATES *(From-To)*
07/13/87 - 10/16/87

19. THERAPY DURATION
3 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

FUROSEMIDE	3 MONTHS	DIGOXIN	3 MONTHS
POTASSIUM CHLORIDE	3 MONTHS		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
1/25/88

24d. REPORT SOURCE *(Check one)*
[X] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

25.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

25b. TELEPHONE NO. *(Include area code)*

25c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

25d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80

14.1

FEB 23 1988

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

MEDICAL OFFICER'S SHORT FORM REVIEW

NDA # 18,830

SPONSOR: Riker

DRUG: Tambocor

TYPE OF SUBMISSION: ADR

DATE OF SUBMISSION: January 25, 1988

DATE OF REVIEW: February 22, 1988

REVIEWER: Sughok K. Chun, M.D. HFN-110

A. Resume:

[redacted] BLURRED VISION, AFib, VF, DEATH

A 29 Y/F with a Hx of hypertropnic cardiomyopathy was on flec 300 mg for 4-5 days. She noticed blurred vision 10 hrs post-dose for 2 hrs. While still on flec for 2 wks she collapsed at a bus stop and was brought to hosp. ECG showed VF and she died. Flec level from post mortem plasma (12-24hrs) was 2.26 mg/ml.

[redacted]/TAM-PAED-2

A 10 Y/M with cogenital heart disease complained hearing loss of left ear after flec. 200mg/d for 3 mos.

S K Chun 2/23/88

Sughok K. Chun, M.D.

cc: Orig./NDA # 18,830
HFN-110
HFN-110/CSO
HFN-110/SKC
ayg/02/23/88/0057a

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

January 25, 1988

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are two (2) Follow-up Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Attachments: Follow-up Reports
- [redacted] (Initial sent 9/11/87)
- [redacted] (Initial sent 12/10/87)

Certified Mail P 504 523 829

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID-INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	29	F	08	26	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***BLURRED VISION, ATRIAL FIBRILLATION, VENTRICULAR FIBRILLATION* Death**
This 29 y.o. woman with a history of hypertrophic cardiomyopathy and paroxysmal atrial fibrillation resistant to quinidine and verapamil was hospitalized on 8AUG87 to initiate therapy revision and to add flecainide acetate. Hospital discharge was on 12AUG87 with flecainide dose at 200 mg/day & no QRS widening. During the initial 5 days of therapy she noticed prolonged atrial fibrillation and initiated self-medication with quinidine and verapamil(in addition to flecainide) but for only 2 doses before she spoke with the physician and was told to stop all medication for about 18 hours before restarting flecainide at 300 mg/day. After several days at this level she developed severe blurred vision(18AUG87)

13. RELEVANT TESTS LABORATORY DATA

27AUG87: Plasma sample taken 12-24 hours following death had flecainide level of 2.26 mcg/ml. Experience has shown postmortem samples have artificially elevated flecainide levels.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☒ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
300 MG	ORAL

17. INDICATION(S) FOR USE
ATRIAL FIBRILLATION

18. THERAPY DATES *(From: To)*	19. THERAPY DURATION
08/10/87 - 08/26/87	16 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

CONCOMITANT DRUGS AND HISTORY

CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

22. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Thyrotoxicosis; idiopathic hypertrophic subaortic stenosis (IHSS).

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG	24b. MFR CONTROL NO.
[redacted] /18-830	[redacted]

DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE *(Check one)*
1/ 8/88	☐ FOREIGN ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
☒ YES ☐ NO	☐ INITIAL ☒ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

PATIENT ID: INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	29	F	08	26	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
BLURRED VISION, ATRIAL FIBRILLATION, VENTRICULAR FIBRILLATION= Death
This 29 y.o. woman with a history of hypertrophic cardiomyopathy and paroxysmal atrial tachycardia(PAT) resistant to quinidine and verapamil was hospitalized on 10AUG87 to begin flecainide acetate therapy. After 72 hours she was released from the hospital on a dose of 200 mg/day with no evidence of QRS widening. During the first 5 days of therapy she noticed prolonged atrial fibrillation and initiated self-medication with quinidine and verapamil(in addition to flecainide) but for only 2 doses before she spoke with the physician and was told to stop all medication for about 18 hours before restarting flecainide at 300 mg/day. After several days at this level she developed severe blurred vision(18AUG87)

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTION
- [X] TREATED WITH Rx DRU
- [X] RESULTED IN, OR PROLONGED, INPATIEN HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
None

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
PAROX ATRIAL TACHYCARDIA

18. THERAPY DATES *(From/To)*
08/10/87 - 08/26/87

19. THERAPY DURATION
16 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
8/27/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE. Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

FEB 11 1988

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

NDA 18-830 Tombocor (flecainide acetate) tab

SPONSOR: Riker

TYPE OF SUBMISSION: ADR

DATE OF SUBMISSION: January 5, 1988, January 18, 1988, January 19, 1988

DATE OF REVIEW: February 8, 1988

REVIEWER: Sughok K. Chun, M.D., HFN-110

A. Resume:

1/19/86 Submission

[redacted] "PAIN IN LEGS, ELEVATED CPK, LEUKOCYTOSIS, EOSINOPHILIA"
This 70 y/m with intermittant AFib has been treated for 1-2 yrs with flec at 200 mg/day. Two-three wks ago he developed pain in his thighs and calves, especially when walking and he has become increasingly weak. WBC 17000 with eosinophils 22%, sed rate 63, and 2 of 4 hepatic enzyme levels were slightly elevated. His pain was treated with ibuprofen. Concomitant medication was digoxin. Flec was d/ced & placed on verapamil on 8/27/87. After 5 wks he felt stronger, eating better and walking more; but the disease progressed through pruritis, anemia, elevated creatinine, BUN and productive cough before showing improvement by 12/16/87.

1/18/88 Submission

[redacted] "PSYCHOSIS" This nurse was being treated with flec at therapeutic doses (duration and exact dose unknown) when she locked herself in the bathroom of her home and threatened suicide.

1/5/88 Submission

[redacted] "JAUDICE, PULMONARY EMBOLUS"
A 54 obese y/f who had been on flec for 3 wks was hospitalized with Dx of pulm embolism and obstructive jaundice.

[redacted] "SEIZURE, HYPOTUNIA"
Follow-up report of newborne infant. The infant at 10 days of age, suck reflex and hypotonia slightly improved but still incapable of spontaneous oral feeding. ELISA test for toxoplasma antibodies (-).

[redacted]
QRS-Widening, cardiac insufficiency, elevated CPK, possible drug interaction (AMIODARONE).

12/18/87 Submission

[redacted] "LEUKOPENIA, SEPTICEMIA, DISSEMINATED INTRAVASCULAR COAGULATION, THROMBOCYTOPENIA, FEVER, RASH, HEPATIC FAILURE, RENAL FAILURE, GASTROINTESTINAL HEMORRHAGE" Death

A 53 y/m with long Hx of severe CAD had an episode of cardiac arrest on 10/4/87, was rescusitated, admitted to hosp & 4-artery coronary artery bypass performed on 10/12/87. Post-operatively, he developed episodes of wide QRS ectopy, & was started on flec 100 mg bid on 10/15/87. Discharged 10/17/87, he was taking flec, dipyridamole, & aspirin, & oxycodone-acetamenophen prn. He fared well until 10/28/87, when he developed mild fever, for which he was given indomethacin, but found that drug intolerable after 2 doses. Aspirin dose was then increased, & fever was controlled. A diffuse rash began, followed by nausea, vomiting, diarrhea, marked weakness, & sore throat. He was seen by his surgeon 11/4/87, all drugs were stopped, & he was admitted to hosp. Temperature on admission was 38.4C, spiked to 39.6C 24 hrs later, & thereafter generally followed a diurnal spiking pattern, ranging from 37.0/37 6 AM to 38.8/39 4 PM, until terminal 2 days, when it was often normal. Initial hemogram showed profound leukopenia: 300 WBC, all lymphocytes. Hematocrit, 31.8mm on 11/17/87, was 36, then 30.4. Blood culture grew E. coli. Shortly after admission he became severely hypotensive, had a brief episode of VT (Rx with IV lidocaine), & transferred to CCU. Vigorous antibiotic therapy included imipenem-cilistatin, tobramycin, & metronidazole. Evidences of renal & hepatic failure appeared early & progressed inexorably. Leukopenia did not respond to steroid therapy. Platelet count was normal in AM 11/5/87, but dropped to 77,000 that evening, & declined to 12,000 within the next 14 hrs. Rectal & upper GI bleeding supervened, to be stemmed from time to time by platelet infusions. Repeated WBC transfusions were ineffectual. Renal dialysis was performed on 11/8 & 11/9, but rapid deterioration of condition prevented repitition, & acidosis was uncontrollable. On 11/11/87 VT-VF- cardiac arrest at 11:50pm. Fibrin Split Products were 10ug/ml (normal) on 11/5/87, but rose to the 10 40 ug/ml range by early 11/6/87, & remained in that range thereafter. The patient had been given tocainide 400 mg q8h from 10/9/87 to 10/14/87, immediately prior to initiation of flec. He also received diltiazem & temazepam during that period.

Auto, y-Provisional Anatomic Diagnosis: Severe generalized arteriosclerosis with total occlusion of right coronary artery, and 95% occlusion of 3 left coronaries; bypass grafts patent; bivenricular hypertrophy; bowel ischemia with widespread infarction; hemorrhagic ascites; septic(?) skin rash; aplastic bone marrow with reactive histiocytosis; severe 5-lobe pneumonia; hemorrhagic tracheitis; severe erosive esophagitis; hepatic central passive congestion, severe, with ? focal microabscess formation; severe jaundice.

Cause of Death: multiple organ failure, consquent to sepsis following development of agranulocytosis.

[redacted] "HEPATITIS, JAUNDICE, POSSIBLE DRUG INTERACTION"

This pt was being treated with concomitant flec, cimetidine, and warfarin for more than 1 yr. The pt developed hepatitis and jaundice. The three medications were all d/c at the same time.

[redacted] "CONGENITAL INTERVENTRICULAR SEPTAL DEFECT"

The 23 y/o mother was treated with flec for WPW syndrome for 5 mos when she became pregnant. Her medical Hx includes a cardiac arrest about 1 yr prior to flec. Flec (300 mg/day) & propranolol (240 mg/day) continued throughout pregnancy. After a normal gestation period an infant girl was born without complication. Birth weight was 6.1 pounds. Ultrasound during pregnancy showed a normal baby but an echocardiogram after birth confirmed a small interventricular septal defect. The reporter considers the septum defect to be coincidental to flec Rx. This defect is not requiring treatment at this time because a small defect usually spontaneously resolves. Neither maternal nor infant flec blood levels were obtained at the time of birth. The infant was not breast fed.

S. K. Chun 2/10/88

Sughok K. Chun, M.D.

cc:
~~Orig.~~
HFN-110
HFN-110/CSO
HFN-110/SChun
sh:2/08/88;2/09/88:0936h

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

ORIGINAL

REPORTS

3M

December 18, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are two (2) Follow-up Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Attachments: Follow-up Reports
- [redacted] (Initial sent 11/30/87)
- [redacted] (Initial sent 12/10/87)

Certified Mail P 504 523 789

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1988

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	53	M	10	29	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

LEUKOPENIA, SEPTICEMIA, DISSEMINATED INTRAVASCULAR COAGULATION, THROMBOCYTOPENIA, FEVER, RASH, HEPATIC FAILURE, RENAL FAILURE, GASTRO-INTESTINAL HEMORRHAGE Death

Man 53 years old with long history of severe coronary artery disease had an episode of cardiac arrest on 10/4/87, was rescusitated, admitted to hospital & 4-artery coronary artery bypass performed on 10/12/87. Post-operatively, he developed episodes of wide QRS ventricular ectopy, & was started on flecainide 100mg bid on 10/15/87. Discharged 10/17/87, he was taking flecainide, dipyridamole, & aspirin, & oxycodone-acetamenophen prn. He fared well until 10/28/87, when he developed mild fever, for which he was given indomethacin, but found that drug intolerable after

13. RELEVANT TESTS LABORATORY DATA

TEST	unit	normal	11/4	11/5	11/6	11/7	11/8	11/9	11/10	11/11
WBC	M/cmm	4.5-11	.3	.1	.1	.1	.1,.2	.3,.5	.3,.5	.2,.5
gran.	%	40-60	0	2, 0	13	0	0, 5	22,30	30,15	24,33
lymph.	%	20-40	100	98,100	84	100	100,95	76,70	69,84	76,67
HCT	%	40-54	36.0	28.1	42.6	39.7	33.1	30.1	29.5	27.6

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☒ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200MG

16. ROUTE OF ADMINISTRATION
ORAL

INDICATION(S) FOR USE
VENTRICULAR TACHYCARDIA

17. THERAPY DATES *(From/To)*
10/15/87 - 11/04/87

19. THERAPY DURATION
2 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DILTIAZEM HCL		DIPYRIDAMOLE	
ASPIRIN		TEMAZEPAM	5 DAYS
RANITIDINE HCL	1 DOSE	OXYCODONE HCL, ACETAMINOPHEN	3 DOSES
INDOMETHACIN	2 DOSES		

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

History of subendocardial myocardial infarction. See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

DATE RECEIVED BY MANUFACTURER
12/ 3/87

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET: MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

2 doses. Aspirin dose, which had been 325mg/day, was then increased, & fever was controlled. A diffuse rash then began, followed by nausea, vomiting, diarrhea, marked weakness, & sore throat. He was seen by his surgeon 11/4/87, all drugs were stopped, & he was admitted to hospital late that night. Temperature on admission was 38.4C, spiked to 39.6C 24 hours later, & thereafter generally followed a diurnal spiking pattern, ranging from 37.0/37.6 AM to 38.8/39.4 PM, until terminal 2 days, when it was often <normal. Initial hemogram showed profound leukopenia: 300 WBC, all lymphocytes. Hematocrit, 31.8mm on 11/17/87, was 36, then 30.4 Blood culture grew E. coli. Shortly after admission he became severely hypotensive, had a brief episode of ventricular tachycardia (treated

13. RELEVANT TESTS/LABORATORY DATA

Plat.M/cmm	>133		235	12,15	12		55,12	43,14	11,45
BUN mg/dl	<27	40	54	61	84	93,66	90	75	71
Na meq/L	>134	132	126	127	135	145	144	141	143
K meq/L	3-4.5	4.9	3.9	4.1	5.8	5.6	5.6	6.0	5.4
Cl meq/L	100-112	101	99	102	99	94	94	97	95

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

DICATION(S) FOR USE

HERAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT ☐ YES ☐ NO

25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 3)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET: MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

with IV lidocaine), & transferred to coronary care unit. Vigorous antibiotic therapy included imipenem-cilistatin, tobramycin, & metronidazole Evidences of renal & hepatic failure appeared early & progressed inexorably. Leukopenia did not respond to steroid therapy. Platelet count was normal in AM 11/5/87, but dropped to 77,000 that evening, & declined to 12,000 within the next 14 hours. Rectal & upper gastrointestinal bleeding supervened, to be stemmed from time to time by platelet infusions. Repeated white blood cell transfusions were ineffectual. Renal dialysis was performed on 11/8 & 11/9, but rapid deterioration of the patient's condition prevented repitition, & acidosis was uncontrollable. Weight increased 10Kg. On 11/11/87 ventricular tachycardia started, was

13. RELEVANT TESTS/LABORATORY DATA

CO2 mM/L	22-29	20	12	7	6	21	18	9	13
Glu mg/dl	70-110	111	232	159	4,143	149	189	115	204
Creat "	.5-1.4	2.0	3.5	4.3	5.9	5.9,4.5	5.6	4.7	4.3
TProt g/dl	6-8		3.7		3.4	3.1	3.0	3.5	3.5
Alb g/dl	3.4-5		2.1		2.2	2.0	2.0	2.6	2.5

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines,biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

DICATION(S) FOR USE

17. THERAPY DATES *(From/To)*

19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(in confidence)*

25.-25a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

25b. TELEPHONE NO. *(Include area code)*

25c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

25d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 4)					

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

converted with lidocaine, recurred promptly, superceded by ventricular fibrillation, then unresuscitable cardiac arrest at 11:50PM.
Fibrin Split Products were <10ug/ml (normal) on 11/5/87, but rose to the >10 <40ug/ml range by early 11/6/87, & remained in that range thereafter
The patient had been given tocainide 400mg q8h (1200mg/day) from 10/9/87 to 10/14/87, immediately prior to initiation of flecainide. He also received diltiazem & temazepam during that period.
Autopsy -Provisional Anatomic Diagnosis: Severe generalized arteriosclerosis with total occlusion of right coronary artery, 95% occlusion l.main l.ant. descend. & l.circumflex coronary arteries; bypass grafts patent; biventricular hypertrophy; bowel ischemia with widespread infarction;

13. RELEVANT TESTS/LABORATORY DATA

Ca	mg/dl	8.3-11	6.3	5.3	4.2	6.0	6.4	6.6
P	mg/dl	2.5-5	2.8	11.8	11.4	9.5	7.8	6.0
Chol	"	>125	91	56	46	41	41	44
UricAc	"	<8.4	6.0	12.5	13.3	14.1	8.0	6.8
TBili	"	<1.6	4.7	12.5	15.5	22.1	31.7	38.5

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

DICATION(S) FOR USE

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

DATE RECEIVED Y MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers cv 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted] (PAGE 5)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

hemorrhagic ascites-2L; septic(?) skin rash; aplastic bone marrow with reactive histiocytosis; severe 5-lobe pneumonia; hemorrhagic tracheitis; severe erosive esophagitis; hepatic central passive congestion, severe, with ?focal microabscess formation; severe jaundice.
Cause of Death: multiple organ failure, consequent to sepsis following development of agranulocytosis.
NB: Following are details of transfusion therapies, relevant to hematologic data shown in #13 below.
Platelets: 11/8, 10 units; 11/9, 4 units; 11/10, 8 units; 11/11, 7 units
Packed RBC: 11/8, 3 units; 11/9, 4 units; 11/11, 3 units.
Packed WBC: 11/8, 1 unit; 11/9, 1 unit; 11/10, 1 unit; 11/11, 1 unit.

13. RELEVANT TESTS LABORATORY DATA

CjBili	" .1-.4	3.6		10.3			
LDH	IU/L <216	200	1808	>1000	>1000	>1000	>1000
SGOT	" <43	78	648	1701	733	659	333
SGPT	" <45	251		646			
GGT	" <44	219		60			

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

DATE RECEIVED / MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 6)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

13. RELEVANT TESTS LABORATORY DATA

AlkPtase" <141 188 69 106 62 64 80
Blood Culture: E.coli sterile sterile
Bronchial Wash: negative for Acid Fast Bacilli
Serum Antinuclear Antibody: negative. Hepatitis B Antigen: negative.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

)ICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

)ATE RECEIVED / MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	53	M	10	29	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

LEUKOPENIA, SEPTICEMIA, DISSEMINATED INTRAVASCULAR COAGULATION, THROMBOCYTOPENIA, FEVER, RASH, HEPATIC FAILURE, RENAL FAILURE, GASTRO-INTESTINAL HEMORRHAGE Death
Man 53 years old with long history of severe coronary artery disease had an episode of cardiac arrest on 10/4/87, was rescusitated, admitted to hospital & 4-artery coronary artery bypass performed on 10/12/87. Post-operatively, he developed episodes of wide QRS ventricular ectopy, & was started on flecainide 100mg bid on 1015/87. Discharged 10/17/87, he was taking flecainide, dipyridamole, & aspirin, & oxycodone-acetamenophen prn. He fared well until 10/28/87, when he developed mild fever, for which he was given indomethacin, but found that drug intolerable after

13. RELEVANT TESTS LABORATORY DATA
see #7 above. Details to be added.

8.-12. CHECK ALL APPROPRIATE TO REACTION
- [X] DIED DUE TO REACTI
- [ ] TREATED WITH Rx OF
- [X] RESULTED IN, OR PROLONGED, INPATIE HOSPITALIZATION
- [ ] RESULTED IN SEVER OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRICULAR TACHYCARDIA

18. THERAPY DATES *(From To)*: 10/15/87 - 11/04/87

19. THERAPY DURATION: 2 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG
- [ ] YES [X] NO [ ] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DILTIAZEM HCL		DIPYRIDAMOLE	
ASPIRIN		TEMAZEPAM	5 DAYS
RANITIDINE HCL	1 DOSE	OXYCODONE HCL, ACETAMINOPHEN	3 DOSES

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
History of subendocardial myocardial infarction. See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 11/ 9/87

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [X] YES [ ] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURE
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 2)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

2 doses. Aspirin dose, which had been 325mg/day, was then increased, & fever was controlled. A diffuse rash then began, followed by nausea, vomiting, diarrhea, marked weakness, & sore throat. He was seen by his surgeon 11/4/87, all drugs were stopped, & he was admitted to hospital late that night. Temperature on admission was 38.4C, spiked to 39.6C 24 hours later, & thereafter generally followed a diurnal spiking pattern, ranging from 37.0/37.6 AM to 38.8/39.4 PM, until terminal 2 days, when it was often <normal. Initial henogram showed profound leukopenia: 100 WBC, all lymphocytes. Hematocrit, 31.8mm on 11/17/87, was 30.4mm. Blood culture grew E. coli. Shortly after admission he became severely hypotensive, had a brief episode of ventricular tachycardia (treated

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTI
- ☐ TREATED WITH Rx OF
- ☐ RESULTED IN, OR PROLONGED, INPATIE HOSPITALIZATION
- ☐ RESULTED IN SEVER OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG

☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*

☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT

☐ YES ☐ NO

25a. REPORT TYPE

☐ INITIAL ☐ FOLLOWUP

NOTE Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTUF

☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?

☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-728)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)* [redacted] (PAGE 3)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

with IV lidocaine), & transferred to coronary care unit. Vigorous antibiotic therapy included imipenem-cilistatin, tobramycin, & metronidazole Evidences of renal & hepatic failure appeared early & progressed inexorably. Leukopenia did not respond to steroid therapy. Platelet count was normal in AM 11/5/87, but dropped to 76,000 that evening, & declined to 12,000 within the next 24 hours. Rectal & upper gastrointestinal bleeding supervened, to be stemmed from time to time by platelet infusions. Repeated white blood cell transfusions were ineffectual. Renal dialysis was performed on 11/8/87, but rapid deterioration of the patient's condition prevented repitition, & acidosis was uncontrollable. Weight increased 10Kg. On 11/11/87 ventricular tachycardia started, was

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

DAILY DOSE

16. ROUTE OF ADMINISTRATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Required of manufacturers by 21 CFR 314.80.

PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1990

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted] (PAGE 4)					

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

converted with lidocaine, recurred promptly, superceded by ventricular fibrillation, then unresuscitable cardiac arrest at 11:50PM.
Fibrin Split Products were <10ug/ml (normal) on 11/5/87, but rose to the >10 <40ug/ml range by early 11/6/87, & remained in that range thereafter
The patient had been given tonocard 400mg q8h (1200mg/day) from 10/9/87 to 10/14/87, immediately prior to initiation of flecainide. He also received diltiazem & temazepam during that period.
Autopsy report to follow, with details of laboratory data.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx OF
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612) 736-5016

ORIGINAL

REC'D

3M

December 18, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed are three (3) Adverse Reaction Reports (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

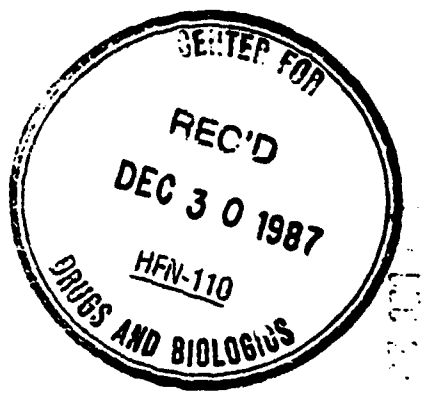
Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Enclosure: 15 Day Reports
- [redacted]
- [redacted]
- [redacted]

Certified Mail P 504 523 788



DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)* [redacted]

2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
88	F	11	30	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*
MYOCARDIAL INFARCTION Death
This 88 y.o. woman was being treated with flecainide 200 mg daily for control of paroxysmal atrial fibrillation. After approximately one year of therapy, she suffered a myocardial infarction and died.

8.-12. CHECK ALL APPROPRIATE TO REACTION
- ☒ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
Myocardial infarction confirmed by enzyme levels. (Exact values being sought from physician).

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

ICATION(S) FOR USE
ATRIAL FIBRILLATION

18. THERAPY DATES *(From/To)*
11/??/86 - 11/30/87

19. THERAPY DURATION
1 YEAR

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

ATE RECEIVED MANUFACTURER
12/ 7/87

24d. REPORT SOURCE *(Check one)*
☒ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☒ YES ☐ NO

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S SHORT FORM REVIEW

FEB 2 1988

NDA #: 18-830

Name of Drug: Tombocor (flecainide acetate) tablets

Sponsor: Riker Lab.

Type of Submission: Periodic ADR Report

Date of Submission: January 8, 1988

Date of Review: January 20, 1988

Date of Assignment: January 25, 1988

Reviewer: Sughok K. Chun, M.D., HFN-110

A. Resume:

From Spontaneous, Domestic Sources
For Time Period September 11, 1987-December 10, 1987

I. Initial Reports This Period

A. Serious Labeled

Manufacturing Report No.		Reaction Term
1.	[redacted] 73 Y/M	Cardiac failure developed within days and progressed to death in 3 weeks.
2.	[redacted] ?/?	ECG abnormal, very wide DRS with plasma Flec 4.0 mcg/ml.
3.	[redacted] ?/F	Rx for SVT, soon after starting Flec, developed wide QRS VAs and died in VF.
4.	[redacted] 18 Y/F	After 4 mos. Rx Hx of chest pain, increased QT internal and AFlu 2:1 conduction, cardiovert-1, Cont-Flec with lower dose.
5.	[redacted] 70 Y/M	VT/VF on second day and died. Cardiomyopathy, CHF.

6.	TT-87-297 86 Y/F	Worsened CHF, increase VAs, QRS widening.

B. Nonserious

Manufacturing Report No.		Reaction Term
1.	[redacted]	Arrhythmia
2.	[redacted] 52 Y/F	Vision blurred 22 mos. Rx HTN returned.
3.	[redacted] ?/M	Hypotension and asthenia at high attitude. SVAs 8 mos. Rx.
4.	[redacted] ?/M	Tremor, agitation, insomnia after third dose of Flec--probably due to AFlu.
5.	[redacted] 61 Y/M	Retinal hemorrhage. Dx: . Willerbrand disease, warfarin Rx.
6.	[redacted] 77 Y/F	Alopecia
7.	[redacted] 64 Y/F	Vision abnormal eye pain 1wk Rx.
8.	[redacted] ?/?	Arrhythmia increased.
9.	[redacted] ?/M	Palpitation 4-5 mos. Rx drug interaction with indomethacin.
10.	[redacted] 45 Y/F	Hair thinning--7 mos. Rx.
11.	[redacted] 30 Y/F	Drug interaction (tneopylline level decreased. Dechallenge and Rechallenge (+)).
12.	[redacted] 70 Y/F	Dizziness, vision abnormal, tremor, headache, nausea after 1 mo. Rx, decrease the dose.
13.	[redacted] 67 Y/	Tinnitus 10 mos. Rx.
14.	[redacted] ?/F	PR internal increases after 2 wks Rx.
15.	[redacted] 62 Y/F	Vision abnormal, Ataxia after 1 mo Rx.

16. [redacted] 46 Y/F Paresthesia.

Flec was initiated 10/28/87 at a dose of 50 mg bid, increased to 100 mg bid on 10/30/87. On 10/29/87 she became aware of numbness (paresthesia) in her left foot; this progressed by ascension the next day, and was followed by the appearance of paresthesia in the right foot, which also progressed during the following days to involve the entire leg. Flec was discontinued on 11/2/87 (6 th day of therapy). Thereafter, defervescence of paresthesia occurred gradually and recovery was complete 2 weeks after flec was stopped.

17. [redacted] 65 Y/M Bradycardia (50/min)

Flec for AFLU and had a good control, but has developed bradycardia (pulse rate in low 50s) which has persisted for 10 days. Today (11/4/87) he decreased the dose on his own to 100 mg daily; he states that his pulse rate "is still low."

18. [redacted] ?/F Psychosis

19. [redacted] 65 Y/M Rash on forehead after 20 days Rx.

20. [redacted] ?/M Chest pain while on high dose.

21. [redacted] 70 Y/F Hepatic func abnormal 2 wks Rx.

22. [redacted] 55 Y/M Anorexia and fatigue

II. Follow-up Reports This Period

Manufacturing Report No.	Reaction Term
1. [redacted]	Death, cause unknown.
2. [redacted]	Breast pain male.
3. [redacted]	ECG abnormal.
4. [redacted]	Bradycardia, arrhythmia

5. [redacted] Ataxia.

6. [redacted] Death, cause unknown.

7. [redacted] ECG abnormal.

NARRATIVE OF ACTION TAKEN

After review of the ADRS received this quarter, the sponsor concluded that current U.S. prescribing information for Flec tablets continues to describe safety information approximately and, therefore, is not in need of revision at this time.

COMMENTS: The following cases should be explored further. Theoplyllin drug interaction ([redacted]), paresthesia ([redacted]), gynecomastia in male ([redacted], possible drug interaction with amiodarone ([redacted]). [redacted] (78 Y/F) had discontinued amiodarone and started Flec developed bradycardia, hypothermia and muscle weakness one month later. A myoneural "myasthenia-like" block was discovered. (Thyroid function and a negative neostigmine test appeared to rule out typical myestnenia.) One wk later failure was still present along with A-V block, and shock-induced acute renal failure was evident. The muscular weakness progressed to bilateral ptosis, and for a time facial paralysis was present. Flec was discontinued and by 48 hours later abnormalities of ejection fraction, renal failure and muscle weakness had resolved. A repeat electromyogram 1 mo following the acute event was interpreted as normal.

I called the sponsor (Jeanne M. Fox, Sr. Reg. Coordinator) on January 26, 1988, and discussed above cases. If there are more similar cases developed they should be added to the labeling.

S.K. Chun 2/1/88

Sughok K. Chun, M.D.

cc: ✓Orig. NDA
HFN-110
HFN-110/CSO
HFN-110/SChun:1/27/88
ef:1/17/88:1/29/88:0169F

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

ORIGINAL

REPORTS

3M

January 8, 1988

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir/Madam:

Pursuant to 21 CFR 314.80, enclosed is the Periodic ADR Report in duplicate for Tambocor® (flecainide acetate) NDA 18-830. There are 35 FDA-1639 forms in this submission, 28 of which are initial reports and 7 are follow-up reports.

The time period covered by this report is September 11, 1987 to December 10, 1987.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

desk copy: Dr. SK Chun
HFN 110
Division of Cardio-Renal Drug Products

P-006
Lic

ORIGINAL

110

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	73	M	04	04	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

#Congestive Heart Failure#
This 73 y.o. man had had ventricular arrhythmia for more than a year during which time he took PROCAN SR. On 01APR86 this was discontinued and replaced by flecainide 100mg bid. but in that day arrhythmia came back and dosage of flecainide increased to 100mb tid. Within a few days edema began to develop which progressed until death on 22APR86.
Austopsy diagnosis was congestive heart failure and post surgical status for carcinoma of prostate. (No carcinoma remaining.)
FDA PLEASE NOTE: IS USP RPT 70490 WHICH THEY SUBMITTED TO FDA 06JUN86 AS FOLLOW-UP TO THEIR REPORT 70489 OF 02JUN86.

13. RELEVANT TESTS LABORATORY DATA
AUTOPSY (SEE #7, ABOVE)

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
300 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From/To)*
04-01-86 - 04-22-86

19. THERAPY DURATION
21 DAYS

20. DID REACTION ABATE AFTER STOPPING DRUG?
- [ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
- [ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
PROCAINAMIDE HCL > 1 YR

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
Had had arrhythmia more than one year. Mechanical condition of heart not reported. Post surgical status for carcinoma of prostate.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
6/ 6/86

24d. REPORT SOURCE *(Check one)*
- [ ] FOREIGN [ ] STUDY [ ] LITERATURE
- [X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
- [ ] YES [X] NO

25a. REPORT TYPE
- [X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
- [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	F			

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

VENTRICULAR ARRHYTHMIA, VENTRICULAR FIBRILLATION, WIDENED QRS Death
This woman with a history of tuberculosis was discharged from the hospital under therapy with flecainide acetate for supraventricular arrhythmia. Shortly thereafter she was readmitted to the hospital with widened QRS interval and ventricular arrhythmia and died in ventricular fibrillation.

13. RELEVANT TESTS LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [X] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [X] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: UNKNOWN

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: SUPRAVENTRICULAR ARRHYTH

18. THERAPY DATES *(From To)*: / / - / /

19. THERAPY DURATION: ?

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 9/25/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE Required of manufacturers by 21 CFR 314.80

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	70	M	11	01	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

***VENTRICULAR TACHYCARDIA, VENTRICULAR FIBRILLATION* Death**
This 70 year old man was admitted to hospital 10/17/87 in congestive heart failure, with pleural effusion & biochemical evidences of impaired renal & hepatic function. He was known to have cardiomyopathy, had had a myocardial infarction some time ago, and had been having episodes of non-sustained ventricular tachycardia (up to 15 complexes/run) which were only mildly symptomatic. With vigorous treatment (multiple diuretics, captopril, heparin) cardiac functional equilibrium was restored. Ejection fraction was 14% on 10/26/87, & Holter monitor revealed 50-100 premature ventricular contractions/hour, with 6 runs/hour of ventricular tachycardia (up to 10 complexes/run) & 20 runs/hour of supraventricular

13. RELEVANT TESTS LABORATORY DATA

	Bilirubin mg/dl	BUN mg/dl	Creatinine mg/dl	Potassium meq/L	Glucose mg/dl	Uric Acid mg/dl
10/17/87	2.0	38	1.8	4.5	normal	17.5
10/30/87	2.3	60	2.5	4.5	normal	--
NORMAL	<1.0	<25	<1.5	3.5-5.0		<7.0

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: **200MG**

16. ROUTE OF ADMINISTRATION: **ORAL**

17. INDICATION(S) FOR USE: **VENTRICULAR TACHYCARDIA**

18. THERAPY DATES *(From To)*: **10/30/87 - 11/01/87**

19. THERAPY DURATION: **4 DOSES**

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

FUROSEMIDE 2 WEEKS
SPIRONOLACTONE 2WEEKS
SODIUM LEVOTHYROXINE YEARS
CAPTOPRIL

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

see #7 above

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: **11/24/87**

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS.

3. SEX

4.-6. REACTION ONSET — MO. | DA. | YR.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

tachycardia (up to 20 complexes/run). QRS was .12. Flecainide 100mg q12h was begun in the evening of 10/30/87. On 11/1/87 at 12:23P ventricular tachycardia commenced (rate: 160/minute), followed shortly by ventricular fibrillation. Electrical cardioversion aborted the fibrillation, but junctional ventricular tachycardia with retrograde conduction supervened shortly. Further attempts to control the arrhythmia, including intravenous Na-lactate & bicarbonate, were unsuccessful, & the man expired at 1:01P. A flecainide blood level was not obtained.

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND NDA. NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE. Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

25.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

25c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	65	M	05	02	86

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

Death, cause unknown.
This 65 y.o. man, believed to have generally good cardiac status, was experiencing multifocal premature ventricular complexes for which he was prescribed flecainide 100 mg bid. About a week after starting the drug he stepped out of the shower and died suddenly. No autopsy was obtained. The physician is uncertain as to a causative role of flecainide in this death.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN. OR PROLONGED. INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: VENTRI PREMATURE BEATS

18. THERAPY DATES *(From To)*: 04-26-86 - 05-02-86

19. THERAPY DURATION: 1 WEEK

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Patient had history of arteriosclerotic heart disease.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES, INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 11/20/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4-6. REACTION ONSET MO.	DA.	YR.
[redacted]	---	M	--	--	--

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

DEATH, CAUSE UNKNOWN
This man was taking flecainide 200 mg daily for several months when he died of unknown causes. Further information is requested from the physician.
Follow-up information received 21SEP87: Echocardiogram taken 01AUG86 showed good ventricular function with an ejection fraction of 66%. An aortic valve prosthesis showed moderate calcification. Echocardiogram on 04AUG86 showed frequent unifocal PVC's at 100-200 per hour. There was no repetitive activity. One short run of paroxysmal atrial tachycardia was noted. The man was taking tocainide 1200 mg daily. He was switched to flecainide 200 mg daily on 09SEP86; a follow-up visit on 18SEP86 showed

13. RELEVANT TESTS LABORATORY DATA
None.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRI PREMATURE BEATS

8. THERAPY DATES *(From To)*
09/09/86 - UNKNOWN

19. THERAPY DURATION
> 2 MONTHS

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
NONE KNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
See #7 above.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
RIKER LABORATORIES INC.
225-1S-C, 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND NDA. NO. FOR SUSPECT DRUG
[redacted] /18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
9/21/87

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☒ NO

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26c. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

NOTE: Required of manufacturers by 21 CFR 314.80.

FORM FDA 1639 (5 85) PREVIOUS EDITION IS OBSOLETE

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)* [redacted] (PAGE 2)

2. AGE YRS

3. SEX

4-6. REACTION ONSET: MO. | DA. | YR.

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

sinus rhythm without arrhythmias. The man was last seen in the emergency room on 15NOV86 after falling from a ladder. There was no evidence of arrhythmia. Sometime after this, the man died of unknown causes. The physician does not have further information. He states that he does not believe this to be proarrhythmia as the man had normal ventricular function and was prescribed the recommended dose of flecainide.

8.-12. CHECK ALL APPROPRIATE TO REACTION

- ☐ DIED DUE TO REACTION
- ☐ TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN SEVERE OR PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS LABORATORY DATA

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines biologics)*

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

18. THERAPY DATES *(From/To)*

19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a. IND/NDA NO. FOR SUSPECT DRUG

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE *(Check one)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOW-UP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Division of Cardio-Renal Drug Products
Medical Officer's Short Form Review

NDA #18-330

Name of Drug: TONBOCOR (Flecamide acetate) Tablet

Sponsor: Riker

Type of Submission: ADR

Date of Submission: 12/10/87 Date of Assignment: 12/29/87

Date of Review: 12/29/87

Reviewer: Sughok K. Chun, M.D. HFN-110

A. Resume:

[redacted] HEPATITIS, JAUNDICE, POSSIBLE DRUG INTERACTION*
This pt was being treated with concomitant flec, cimetidine, and warfarin for more than 1 yr. The pt developed hepatitis and jaundice. All medications were discontinued at the same time. Further details are requested.

[redacted] *ASTHENIA, CARDIOVASCULAR COLLAPSE. QRS WIDENING, HYPOTENSION*
This 38 y/f has a 5 yr Hx of sustained VT and cardiomyopathy. The pt was started on flec 200 mg daily for 18 days developed weakness and cardiovascular collapse. The pulse was 60/min and B/P 90/40 mm Hg. Plasma flec level was 0.144mcg/ml. EKG showed QRS 0.44 sec Flec was d/ced. Serum potassium levels and renal function were normal. Elevated AST (8005 IU) and ALT (6522 IU).

[redacted] HYPOGLYCEMIA; RESPIRATORY ARREST; CHF; CARDIAC ARREST* Death
This 94 y/f with a Hx of diabetes, artnritis, angina and multiple PVCs was started on flec at 200 mg/day. Concomitant medication: furosemide and digoxin. This event was initially reported as a possible digoxin interaction but final review found no evidence to support it. The woman was admitted to the hospital after 3 wks of flec Rx because she was unresponsive. Congestive heart failure was found and hypoglycemia (glucose 31) was treated with IV dextrose. The next day she was alert, oriented, and coherent. Two days later she collapsed with respiratory arrest, the ECG telemetry was a straight line (preceding rhythm normal) and she died.

[redacted] LEUKOPENIA, SEPTICEMIA, DISSEMINATED INTRAVASCULAR COAGULATION, THROMBOCYTOPENIA, FEVER, RASH, HEPATIC FAILURE, RENAL FAILURE, GI HEMORRHAGE* Death

The 53 y/m with long Hx of severe CAD had an episode of cardiac arrest on 10/4/87, was rescusitated, admitted to hospital & 4 coronary artery bypass performed on 10/12/87. Post-operatively, he developed episodes of wide QRS

ventricular ectopy, & was started on flec 100 mg bid on 10/15/87. Discharged 10/17/87. Concomitant Rx: dipyridamole, aspirin and oxocodone-acetamenophen prn. He fared well until 10/28/87, when he developed mild fever, for which he was given indomethacin, but found that drug intolerable after 2 doses. Aspirin dose, which had been 325mg/day, was then increased, & fever was controlled. A diffuse rash appeared followed by nausea, vomiting, diarrhea, marked weakness, & sore throat. He was seen by his surgeon 11/4/87, all drugs were stopped, & he was admitted to hospital late that night. Temperature on admission was 38.4°C, spiked to 39.6°C 24 hours later, & thereafter generally followed a diurnal spiking pattern, ranging from 37.0/37.6 AM to 38.8/39.4 PM, until terminal 2 days when it was often normal. Initial hemogram showed profound leukopenia; 100 WBC, all lymphocytes. HCT 31.8mm, 30.4mm. Blood culture grew E. Coli. Shortly after admission he became severely hypotensive, had a brief episode of VT (treated with IV lidocaine), & transferred to CCU. Vigorous antibiotic Rx included imipenem-cilistatin, tobramycin, & metronidazole. Evidence of renal & hepatic failure appeared early & progressed inexorably. Leukopenia did not respond to steroid Rx. Platelet count was normal in AM 11/5/87, but dropped to 75,000 that evening, & declined to 12,000 within the next 24 hrs. Rectal & upper GI bleeding supervened, to be stemmed from time to time by platelet infusions. Repeated WBC transfusions were ineffectual. Renal dialysis was performed on 11/8/87, but rapid deterioration & acidosis was uncontrollable. Weight gained 10Kg. On 11/11/87 VT started which was converted with lidocaine but recurred promptly, superceded by VF, then unresuscitable cardiac arrest at 11:50PM

Fibrin Split Products were less than 10ug/ml (normal) on 11/5/87, but rose to the greater than>10<40ug/ml range by early 11/6/87, & remained in that range thereafter. The pt had been given tonocard 400mg q8h from 10/9/87 to 10/14/87, immediately prior to initiation of flec. He also received deltiazem & temazepam during that period.
Autopsy report to follow, with details of laboratory data.

S K Chun 12/31/87
Sughok K. Chun, M.D., HFN-110

cc:
Orig.
HFN-110
HFN-110-/CSO
HFN-110/SChun
es/12/30/87/0024d

Regulatory Affairs
Riker Laboratories, Inc.

270-3A 3M Center
St. Paul, Minnesota 55144
(612)736-5016

ORIGINAL

REPORTS
D

3M

December 10, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Subject: 15-Day Alert Report Follow-up
Tambocor® (flecainide acetate) 100 mg Tablet, NDA 18-830

Dear Sir/Madam:

Enclosed is a Follow-up Adverse Reaction Report (Form FDA 1639) pertaining to serious and unlabeled adverse experiences which occurred in association with the use of the subject product.

Sincerely,

Jeanne M. Fox

Jeanne M. Fox
Sr. Regulatory Coordinator

JMF/jf

Attachments: Follow-up Report
- [redacted] (Initial sent 7/15/87)

Certified Mail P 504 523 778

CENTER FOR
REC'D
DEC 22 1987
HFN-110
DRUGS AND BIOLOGICS

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT

(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	94	F	02	06	87

7. DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

HYPOGLYCEMIA; RESPIRATORY ARREST; CHF; CARDIAC ARREST Death
This 94 y/o woman with a history of diabetes, arthritis, angina and multiple PVCs was started on flecainide acetate therapy at 200 mg/day. Concomitant medication was furosemide and digoxin. This event was initially reported as a possible digoxin interaction (reporters opinion) but final review found no evidence to support it. The woman was admitted to the hospital after 3 weeks of flecainide therapy because she was unresponsive. Congestive heart failure was found and hypoglycemia (glucose 31) was treated with IV dextrose. The next day she was alert, oriented, and coherent. Two days later she collapsed with respiratory arrest, the ECG telemetry was a straight line(preceding rhythm normal) and she died.

13. RELEVANT TESTS/LABORATORY DATA

	6FEB87	7FEB87	9FEB87
GLUCOSE	31	91	86

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

15. DAILY DOSE: 200 MG

16. ROUTE OF ADMINISTRATION: ORAL

17. INDICATION(S) FOR USE: ...ITRI PREMATURE BEATS

18. THERAPY DATES *(From/To)*: 01/ /87 - 02/09/87

19. THERAPY DURATION: 3 WEEKS

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [ ] NO [X] NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

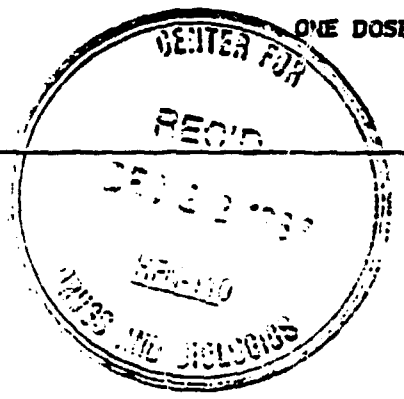
III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN
LIDOCAINE ONE DOSE
FUROSEMIDE
TETANUS TOXOID ONE DOSE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

ECG:left bundle branch block with secondary ST-T changes; angina; degenerative arthritis of knees, hands, and wrist.



IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-1S-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA NO. FOR SUSPECT DRUG: [redacted] /18-830

24b. MFR CONTROL NO.: [redacted]

24c. DATE RECEIVED BY MANUFACTURER: 12/ 3/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

[redacted]

26b. TELEPHONE NO. *(Include area code)*: [redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986

FDA CONTROL NO.

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.
[redacted]	95	F	03	??	87

DESCRIBE REACTION(S) *(Underline single most important clinical event or reaction term)*

DIGOXIN TOXICITY DEATH

This 95 y/o woman was started on flecainide at 200 mg/day for ventricular arrhythmia. She was also receiving digoxin and has a history of CHF, syncope and PVCs. Flecainide was given for about 3 weeks and for 3-4 days prior to death she was on a monitor but the final record was lost therefore the cause of death was not recorded. The physician suspects digoxin toxicity occurred; digoxin serum levels have not been reported and the causal relationship between flecainide and digoxin remains undetermined (physicians opinion).

13. RELEVANT TESTS/LABORATORY DATA

NONE REPORTED

8.-12. CHECK ALL APPROPRIATE TO REACTION

- [X] DIED DUE TO REACTION
- [ ] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [X] RESULTED IN SEVERE OR PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE
- X LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

TAMBOCOR/FLECAINIDE ACETATE

20. DID REACTION ABATE AFTER STOPPING DRUG?
[ ] YES [X] NO [ ] NA

15. DAILY DOSE
200 MG

16. ROUTE OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
VENTRICULAR ARRHYTHMIA

18. THERAPY DATES *(From To)*
02/ /87 - 03/ /87

19. THERAPY DURATION
3 WEEKS

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
[ ] YES [ ] NO [X] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

DIGOXIN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*

Premature ventricular contractions; syncopy; chronic congestive heart failure.

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

RIKER LABORATORIES INC.
225-15-07 3M CENTER
ST.PAUL, MN 55144-1000

24a. IND/NDA. NO. FOR SUSPECT DRUG
18-830

24b. MFR CONTROL NO.
[redacted]

24c. DATE RECEIVED BY MANUFACTURER
3/12/87

24d. REPORT SOURCE *(Check one)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL [ ] CONSUMER

25. 15-DAY REPORT
[ ] YES [X] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
[redacted]

26b. TELEPHONE NO. *(Include area code)*
[redacted]

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

NOTE: Required of manufacturers by 21 CFR 314.80.

ES-S/V

1 ≥ 1

S/M/S 1.0.01

STATISTICAL REVIEW AND EVALUATION

NDA #: 18-830 / SE1012 Drug Class: 1B Date: SEP 21 1989

Applicant: Riker Laboratories, Inc./3M

Name of Drug: Tambocor (flecainide acetate) tablets, 50, 100, 150, and 200 mg bid.

Indication: Additional indications (to currently approved indications in ventricular arrhythmias): (1) paroxysmal supraventricular tachycardias, including atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, and other supraventricular tachycardias of unspecified mechanism, and (2) paroxysmal atrial fibrillation/flutter.

Documents Reviewed: Volumes 2, 6, and 16-20 of the submission dated July 26, 1989.

Medical Officer: This review has been discussed with the medical officer, Dr. Sughok Chun, and she is in agreement with its conclusions.

Relevant Issues discussed in this Review:

1. The three well-controlled studies presented by the sponsor give evidence that flecainide is effective in controlling PAT and PAF.
2. In Study R-818-565, the results for PAF patients are confounded by a significant period effect, however this is not evident in Study R-818-066.
3. Study R-818-074 indicates a linear dose-response curve, but the analysis only included compliant patients who completed all five study periods.
4. Over 30% of the patients in these three trials failed to complete the studies and 78% experienced some form of adverse reaction. There were a total of 15 cardiac adverse experiences, nine of which were classified as proarrhythmia, and one of which resulted in death.

I. INTRODUCTION

Tambocor (flecainide) was approved in 1985 for the treatment of ventricular arrhythmias. The three studies submitted at this time were designed to evaluate flecainide in the control of paroxysmal supraventricular arrhythmias. These studies were essentially completed by April, 1989, when the National Institutes of Health (NIH) discontinued flecainide from their Cardiac Arrhythmia Suppression Trial (CAST) in post-myocardial infarction patients with asymptomatic ventricular arrhythmias. Flecainide was discontinued due to a higher proportion of mortality and nonfatal cardiac arrest in flecainide patients (16/315 or 5.1%) than in matching placebo patients (7/309 or 2.3%).

Key Words: Crossover study, period effect, multiple comparisons, dose-response.

Paroxysmal supraventricular tachycardias (PSVT) are intermittent arrhythmias of supraventricular origin during which the cardiac rate increases, usually accelerating to 100 to 200 beats/minute and occasionally higher. The three studies submitted with this application were carried out in two groups of patients, those experiencing paroxysmal atrial tachycardia (PAT) and those experiencing paroxysmal atrial fibrillation/paroxysmal atrial flutter (PAF). PSVT is frequently symptomatic, and the effect of flecainide on both the symptoms and the episodes of arrhythmia are of interest in these studies.

The three studies submitted with this NDA utilized transtelephonic monitoring (TTM) to document the arrhythmias. Patients were provided with a compact electrocardiographic (ECG) recorder which could be used during symptoms which the patient perceived to be associated with a PSVT episode. The ECG was transmitted either live or prerecorded by the patient to a single central monitoring station, Survival Technology, Inc, where it was interpreted and documented. Patients were also provided with a diary in which they were asked to record symptomatic attacks in order to document the occurrence, symptoms, duration, date, and time of the TTM recording. Patient compliance with the diaries was not very good.

II. STUDY R-818-065

II.1. Study Description

Study R-818-065 was a randomized, double-blind, placebo-controlled, multicenter, crossover study. The 16-week study was designed to evaluate the efficacy and safety of flecainide in preventing the recurrence of and/or in reducing the frequency of attacks of symptomatic PAT or PAF. Inclusion/exclusion criteria are given on page 074 of volume 16 of the submission. Patients enrolled in the study were required to discontinue all previous antiarrhythmics for at least four half-lives of the medication. They were then provided with TTMs and were required to have two documented attacks of PSVT in a four week treatment-free screening period in order to enter the two treatment phases of this study. These attacks were classified as either PAT or PAF. Patients who had attacks of both PAT and PAF during the screening phase were enrolled in the PAT group. Seventy-three patients qualified for the study, with 39 patients experiencing attacks of PAF and 34 attacks of PAT.

After meeting the entry requirements, patients entered a three-week open-label dose ranging phase. Patients began by taking 100 mg flecainide twice daily. If this regimen was tolerated, their dosage was increased to 150 mg bid during the second week. Again, if this was tolerated, the dosage was increased to 200 mg bid during the third week. If a patient was unable to tolerate the 150 mg or 200 mg dosage, they were returned to the lower tolerable dosing level. If a patient was unable to tolerate flecainide at the initial 100 mg bid dosage, the dose was decreased to 50 mg bid. If this was intolerable, the patient was discontinued from the study This enabled the sponsor to ascertain the maximal tolerable dose for each patient, and efficacy measurements were done at this dose level. The sponsor explained that "the

assumption was, this would represent a maximum therapeutic effect and result in a measure of flecainide's efficacy in the fewest number of patients". Efficacy was not evaluated during the dose ranging phase, although patients were instructed to continue to use TTM and their dairies in order to reinforce their use.

Patients for whom a maximal tolerable dose was found were randomized and entered into the crossover phase of the study. The PAF and PAT patients were randomized separately. The crossover phase was a double-blind, two-period phase where patients received either placebo or flecainide for a maximum of 8 weeks and then were crossed-over to the other treatment for a maximum of 8 weeks. A patient in the first treatment period was allowed to cross to the second treatment period before the end of eight weeks, and a patient in the second treatment period was allowed to terminate the study early, provided that the patient had experienced four documented attacks of PSVT during the current period. The sponsor felt that allowing early crossover or conclusion of the study with the fourth attack of PSVT was a compromise between having an adequate assessment of the overall frequency of attacks while providing patients the option to move to the alternative therapy or stop the ineffective therapy when sufficient information about the frequency of attacks had been reached.

The dose of flecainide used during the crossover phase was the maximal tolerable dose from the prior dose ranging phase. Patients were asked to record and transmit all suspected attacks of PSVT and to record them in their dairy. Investigators contacted patients biweekly to check on adverse experiences and to encourage compliance.

Documented attacks of PSVT were not counted during the first three days of each part of the crossover in order for the drug to reach steady-state during flecainide therapy and for the flecainide effect to be washed-out during placebo therapy. Patients were considered to have completed each treatment period when they had experienced four documented attacks of PSVT or after a total of eight weeks, whichever came first.

The sponsor chose to use a crossover design in an attempt to detect a significant difference between treatments using fewer patients. Also, since the frequency and severity of attacks of PSVT vary widely from patient to patient, it was felt that a crossover design would better control for differences between patients. The sponsor also stated that there was no reason to expect a significant change in the underlying disease status of patients during the duration of the trial and no differential carryover effect of one treatment to another was expected.

The sponsor deemed it ethical to use a placebo control because these arrhythmias are not expected to be life-threatening and the use of a placebo for comparison would minimize the number of patients needed to show efficacy. They did alter the traditional crossover design to allow patients an early crossover when the patient failed to respond to either medication. This minimized the patient's exposure to an ineffective treatment. Investigators were instructed to exclude a patient if the symptoms associated with his or her attacks would prevent that patient from participating in a placebo-controlled trial.

II.2. Sponsor's Analysis

Table 1 gives the number of patients involved in each phase of the study, and the reason given for patients who discontinued the study. The largest number of dropouts was during the Dose Ranging phase of the study. All of the patients who began the second part (treatment period B) of the crossover phase were included in the sponsor's intent-to-treat analysis. Four patients were excluded from the primary analyses done for evaluable patients. These include one PAT patient who was lost to followup in treatment period B and three PAF patients, two because of starting or stopping digoxin during the study and one who took procainamide during treatment period A.

The primary efficacy parameters used to compare the two treatments were: the number of patients having no attacks; the time to the first attack; and the interval between attacks. Secondary efficacy parameters included the rate of attacks and the duration of therapy. Patients from all centers were combined for all analyses. The number of patients from each center was too small to perform any analyses by center. The protocol called for each center to enroll between six and twelve PAT patients and between six and twelve PAF patients, to result in a total of 50 patients with each type of PSVT. Most centers were unable to locate the requested number of patients, and the total sample size was smaller than planned. The 20 evaluable PAT patients came from nine centers, with no center enrolling more than five patients. Four centers had only a single patient in the study. The 29 evaluable PAF patients also came from nine centers, with one center enrolling eight patients, one six patients, and the rest enrolling four or fewer patients. Three centers had only a single patient in the study.

Efficacy results for this study are given in Table 2 of this review. The number of patients who experienced no attacks of PSVT while receiving either flecainide or placebo were compared using McNemar's test. Each treatment period was truncated at 60 days and attacks occurring after that were not counted, as were attacks occurring in the first three days. Four of the 20 PAT patients experienced no PSVT attacks while receiving placebo, and all were also attack free while receiving flecainide. An additional 12 patients, who had experienced attacks while on placebo, experienced no attacks while on flecainide. This was highly statistically significant, with $p < 0.0001$. One of the 29 PAF patients experienced no PSVT attacks while on either treatment, eight were attack free on flecainide but not on placebo, and three had no attacks on placebo but did experience attacks while receiving flecainide. This difference was not statistically significant ($p = 0.228$).

The time to first attack was calculated by ignoring the first three days of each period and considering day four to be the first treatment day. The time to first attack was defined as the number of treatment days until the first documented attack occurred. If a patient experienced no attacks during a treatment period, the censoring time was defined as the total number of treatment days plus one. If a patient continued on a treatment beyond the planned eight weeks, only the first 60 days were counted.

Because of the large amount of censoring (50% of the PAT patients, 80% while receiving flecainide and 20% while on placebo) product limit estimates were used to

estimate the mean, standard error, and median time to first attack. This procedure underestimates the true mean when most censoring occurs at the upper extreme of the data. The estimates affected by this are denoted by ">" in Table 2. The Paired Prentice Wilcoxon (PPW) test for censored paired data was used to test for a treatment difference. The means, medians, and p-values are given in Table 2.

The 20 PAT patients had a statistically significantly longer time to first attack while receiving flecainide (35.0 ± 2.2 days) compared to their time while receiving placebo (12.7 ± 2.2 days). This resulted in a p-value of less than 0.001. The 29 PAF patients also had a longer time to first attack while receiving flecainide (16.6 ± 2.4 days) than while receiving placebo (7.4 ± 1.2 days), with the PPW test resulting in a statistically significant p-value of 0.021.

Analysis of variance for a two-period crossover design was used to determine the effects of sequence, subjects within sequence, period and treatment on the time to first attack. This method does not provide for censored observations, so patients with no attacks were assigned a time to first attack as the number of treatment days plus one A non-parametric method proposed by Gary Koch was also used to examine sequence, period and treatment effects. Table 3 gives the results of both of these analyses.

Patients experiencing PAT demonstrated no significant sequence or period effects in the analysis of time to first attack. The treatment effect was again highly significant for both analyses ($p < 0.001$). The analysis of the PAF patients indicated no sequence effect but both analyses indicated a marginal period effect. This was a result of the longer time to first attack in both treatment during the second period. The means by period for each treatment are given in Table 3 and are demonstrated graphically. The treatment effect was not significant for either analysis for PAF patients.

The interval between attacks was analyzed using the same statistical methods as the time to first attack. For patients with one to four attacks in 60 days, the interval between attacks was defined as the total number of days on treatment divided by the number of attacks. If a patients had an attack on the last day of treatment, then this is just an average of the days between successive attacks. If a patient did not have an attack on the last day of treatment, the time after his or her last attack is combined with the times between successive attacks and divided by the number of attacks. If a patient had more than four attacks in 60 days, the interval between attacks was defined as the number of treatment days up to the fifth attack divided by four. If a patient had no attacks during the 60 day treatment period, the interval between attacks was defined as the number of treatment days plus one.

The results of the PPW test comparing the interval between attacks are given in Table 2. The 20 PAT patients had a statistically significantly longer interval between attacks while receiving flecainide (50.9 ± 3.3 days) compared to their time while receiving placebo (21.2 ± 4.6 days). The PPW test resulted in a p-value of less than 0.001. The 29 PAF patients also had a statistically significantly longer interval between attacks while receiving flecainide (30.6 ± 4.3 days) than while receiving placebo (17.3 ± 3.7 days), with the PPW test resulting in a statistically significant p-value of 0.003.

Table 4 gives the results of the analysis of variance and the non-parametric analysis of the interval between attacks. Patients experiencing PAT demonstrated no significant sequence or period effects in these analyses. The treatment effect was again highly significant for both analyses ($p < 0.001$). The analysis of the PAF patients indicated no sequence effect but both analyses indicated a significant period effect. This was a result of the longer interval between attacks in both treatment during the second period. The means by period for each treatment are also given in Table 4 and are demonstrated graphically. The treatment effect was marginally significant for both analysis for PAF patients, but the significant period effect is a complicating factor.

The rate of attacks was again analyzed by the same statistical methods as the time to first attack. This value is the inverse of the interval between attacks. For patients with one to four attacks in 60 days, the interval between attacks was defined as the number of attacks divided by the number of days on treatment. If a patient had more than four attacks in 60 days, the interval between attacks was defined as four divided by the number of treatment days up to the fifth attack. If a patient had no attacks during the 60 day treatment period, the time to first attack was defined as one divided by the number of treatment days plus one.

The results of the PPW test comparing the rate of attacks are given in Table 2. The 20 PAT patients had a significantly smaller rate of attacks while receiving flecainide (0.03 ± 0.008 attacks/day) compared to their rate while receiving placebo (0.21 ± 0.078 attacks/day). The PPW test resulted in a p-value of less than 0.035. The 29 PAF patients also had a statistically significantly smaller rate of attacks while receiving flecainide (0.09± 0.021 attacks/day) than while receiving placebo (0.23 ± 0.045 attacks/day), with the PPW test resulting in a statistically significant p-value of 0.009.

Table 5 gives the results of the analysis of variance and the non-parametric analysis of the rate of attacks..Patients experiencing PAT demonstrated no significant sequence or period effects in these analyses. The treatment effect was again statistically significant for both analyses ($p = 0.035$ and $p = 0.003$). The analysis of the PAF patients indicated no sequence effect but both analyses indicated a marginally significant period effect ($p = 0.068$ and $p = 0.048$). This was a result of the large decrease in the placebo attack rate during the the second period. The means by period for each treatment are also given in Table 5 and are demonstrated graphically. The treatment effect was significant for both analysis for PAF patients, but the significant period effect is again a complicating factor.

Table 6 contains a summary of the dose level at which the patients began the crossover period. The protocol did not allow dosage adjustments during the four months of the crossover, however eight patients (5 PAT and 3 PAF) had their dosage reduced during this time. Most of the dose reductions were because of noncardiac adverse experiences. This table also summarizes the number of attacks experienced during the crossover phase and the duration of treatment. Contrary to the protocol, a large number of patients were allowed to continue on a treatment after experiencing four episodes of PSVT instead of being allowed an early crossover to the other treatment or early termination of the study. Table 6 also contains the sponsor's

attempt to assess the overall effectiveness of flecainide by categorizing all patients as success, partial success, failure, or undetermined. The evaluable patients who were considered as undetermined success were patients who experienced no episodes of PSVT during either arm of the crossover study. The non-evaluable patients who were considered as undetermined success were patients who discontinued the study early for reasons other than adverse experiences or inadequate response.

II.3. Reviewer's Comments

A large number of patients dropped out of this study, particularly during the dose ranging phase. Of the 34 PAT patients who were enrolled, only 19 (56%) completed the study. Of the 39 PAF patients enrolled, 30 (77%) completed the study. This high dropout rate is probably partially due to the large doses given in an attempt to find a maximal tolerable dose.

This study gives substantial evidence of the effectiveness of flecainide in controlling episodes of PAT, despite the relatively small sample size. The results for all efficacy variables were highly statistically significant in all analyses. Because of the dose ranging phase, patients who could not tolerate flecainide were not included in the study. Also patients for whom flecainide was ineffective were not likely to continue into the crossover phase. These results demonstrate that flecainide is superior to placebo in controlling episodes of PAT for patients who responded to flecainide and were able to tolerate it. It should be noted, however, that ten of 31 (32%) PAT patients dropped out of the study while receiving flecainide.

The results for PAF patients are not consistently significant, and a clear treatment effect is not demonstrated. The analysis of the number of patients with no attacks results in a non-significant p-value of 0.228. The other measures of efficacy did yield significant results in the PPW analysis, but this analysis is not designed for a crossover study and does not account for period or sequence effects. Both the parametric and non-parametric crossover analyses showed that a period effect was present for the PAF patients in this study. These analyses also resulted in a non-significant treatment effect for time to first attack and only a marginally significant effect for interval between attacks. The period effect confounds the results for treatment effect.

In choosing the crossover trial design the sponsor made two major assumptions: (1) That the underlying disease status of the patients would not change during the four months they were included in the trial; and (2) that there would not be any carryover effect from the use of flecainide. The significant period effect demonstrated by the efficacy variables in PAF patients leads this reviewer to doubt one or both of these assumptions, at least for patients experiencing PAF. The results by period for time to first attack, interval between attacks, and rate of attacks are given in Tables 3 - 5. The period effect is evident in the graphs of the results by period for the PAF patients. It should be noted that the results for the flecainide patients were better than the results for the placebo patients in both periods.

The eighteen PAF patients who were randomized to the placebo-flecainide sequence demonstrated a vast improvement during the second period. The time to first attack

increased from 8.1 days to 25.1 days, the interval between attacks increased from 13.3 days to 31.0 days, and the rate of attacks decreased from 0.30 attacks/day to 0.08 attacks/day. The eleven PAF patients who were randomized to the flecainide-placebo sequence, on the other hand, demonstrated almost no difference in their response to the two treatments, and actually had slightly better results while receiving placebo. The time to first attack actually increased from 17.7 days with flecainide to 20.0 days with placebo. The interval between attacks were virtually identical, 23.2 days and 23.4 days. The rate of attacks increased from 0.09 attacks/day to 0.13 attacks/day. It appears that either these patients had improved during the two months of flecainide treatment, or that there was some residual effect which delayed the return of the PSVT episodes. This reviewer calculated the results by period for the PAT patients, and they did not demonstrate this difference between the two drug sequences.

Because of the presence of the period effect, this reviewer analyzed the data using only the first period of the crossover. The results of analysis of variance and the non-parametric Wilcoxon Rank Sum Test are given below. The nonparametric analysis results in significance or marginal significance for all three variables, but the parametric analysis results in significance for only the rate of attacks.

First Period Analysis - PAF Patients - n = 29

	Analysis of Variance	Wilcoxon Rank Sum Test
Time to First Attack	p = 0.1192	p = 0.0561
Interval Between Attacks	p = 0.1599	p = 0.0219
Rate of Attacks	p = 0.0165	p = 0.0206

The sponsor originally intended to use the ventricular rate during attacks as a primary efficacy variable. Because 80% of the PAT patients did not have an attack while receiving flecainide, this analysis was not possible. The analysis was performed for the PAF patients, but included only the 17 patients who experienced at least one attack during each treatment period. The exclusion of over 40% of the patients, including those who were most successful, makes this analysis of questionable value.

III. STUDY R-818-066

III.1. Study Description

Study R-818-066 was identical to Study R-818-065 in design and analysis. The study began with a four week treatment-free screening period to qualify patients for the study, followed by a three week open-label dose ranging phase to determine each patient's maximum tolerated dose of flecainide. Efficacy was not evaluated during this phase. Patients were then randomized to a double-blind two-period crossover phase comparing flecainide with placebo. Attacks of PSVT were documented using transtelephonic monitors (TTMs). Each crossover period lasted for a maximum of eight weeks or four attacks, whichever occurred first.

III.2. Sponsor's Analysis

Table 7 gives the number of patients involved in each phase of the study, and the reason given for patients who discontinued the study. Fourteen of the 17 PAT patients and 21 of the 25 PAF patients who qualified for the study completed both the dose ranging and crossover portions of the study. All of the patients who began the second part (treatment period B) of the crossover phase were included in the sponsor's intent-to-treat analysis. Two PAF patients were excluded from the primary analyses done for evaluable patients, one because of adjustments of digoxin dose during the study and one because of concomitantly receiving propranolol.

The primary efficacy parameters used to compare the two treatments were the same as in Study R-818-065. Patients from all centers were again combined for all analyses because each center was too small to perform any analyses by center. The 17 eligible PAT patients came from five centers, with no center enrolling more than six patients. The 25 eligible PAF patients came from seven centers, with one center enrolling ten patients and the rest enrolling four or fewer patients.

Efficacy results for this study are given in Table 8 of this review. The number of patients who experienced no attacks of PSVT while receiving either flecainide or placebo were compared using McNemar's test. Each treatment period was truncated at 60 days and attacks occurring after that were not counted, as were attacks occurring in the first three days. One of the 14 PAT patients experienced no PSVT attacks while receiving placebo, and was also attack free while receiving flecainide. An additional 10 patients, who had experienced attacks while on placebo, experienced no attacks while on flecainide. This was highly statistically significant, with $p = 0.002$. Six of the 19 PAF patients experienced no PSVT attacks while on flecainide but none were attack free on placebo This difference was statistically significant ($p = 0.031$).

The 14 PAT patients had a statistically significantly longer time to first attack while receiving flecainide (22.0 ± 1.8 days) compared to their time while receiving placebo (15.2 ± 4.9 days). The PPW test resulted in a p-value of 0.001. The 19 PAF patients also had a longer time to first attack while receiving flecainide (18.3 ± 1.6 days) than while receiving placebo (6.3 ± 1.6 days), with the PPW test resulting in a statistically significant p-value of 0.008.

Table 9 gives the results of the crossover analyses on time to first attack. Both the PAT and the PAF groups of patients demonstrated no significant sequence or period effects in the analysis of time to first attack. The treatment effect was again highly significant for both analyses ($p < 0.001$ and $p = 0.002$ for PAT patients, $p = 0.002$ and $p = 0.022$ for PAF patients).

The results of the PPW test comparing the interval between attacks are given in Table 8. The 14 PAT patients had a statistically significantly longer interval between attacks while receiving flecainide (51.3 ± 4.2 days) compared to their time while receiving placebo (18.5 ± 5.4 days). The PPW test resulted in a p-value of 0.001. The 19 PAF

patients also had a statistically significantly longer interval between attacks while receiving flecainide (31.7 ± 4.9 days) than while receiving placebo (10.2 ± 3.1 days), with the PPW test resulting in a statistically significant p-value of 0.001.

Table 9 gives the results of the analysis of variance and the non-parametric analysis of the interval between attacks. Both the PAT and the PAF groups of patients demonstrated no significant sequence or period effects in the analysis of interval between attacks. The treatment effect was again highly significant for both analyses ($p < 0.001$ and $p = 0.002$ for PAT patients, $p = 0.002$ and $p = 0.022$ for PAF patients).

The results of the PPW test comparing the rate of attacks are given in Table 8. The 14 PAT patients had a significantly smaller rate of attacks while receiving flecainide (0.03 ± 0.01 attacks/day) compared to their rate while receiving placebo (0.23 ± 0.07 attacks/day). The PPW test resulted in a p-value of less than 0.013. The 19 PAF patients also had a statistically significantly smaller rate of attacks while receiving flecainide (0.07± 0.02 attacks/day) than while receiving placebo (0.30 ± 0.06 attacks/day), with the PPW test resulting in a statistically significant p-value of 0.003.

Table 9 gives the results of the analysis of variance and the non-parametric analysis of the the rate of attacks. Both the PAT and the PAF groups of patients demonstrated no significant sequence or period effects in the analysis of interval between attacks. The treatment effect was again highly significant for both analyses ($p = 0.013$ and $p = 0.005$ for PAT patients, $p = 0.003$ and $p = 0.001$ for PAF patients).

Table 10 contains a summary of the dose level at which the patients began the crossover period. The protocol did not allow dosage adjustments during the four months of the crossover, however four patients (1 PAT and 3 PAF) had their dosage reduced during this time. Most of the dose reductions were because of noncardiac adverse experiences. This table also summarizes the number of attacks experienced during the crossover phase and the duration of treatment. Contrary to the protocol, a large number of patients were allowed to continue on a treatment after experiencing four episodes of PSVT instead of being allowed an early crossover to the other treatment or early termination of the study. Table 10 also contains the sponsor's opinion of the overall effectiveness of flecainide in this study.

III.3. Reviewer's Comments

Fewer patients dropped out of Study R-818-066 than did from Study R-818-065. Fourteen of the 17 enrolled PAT patients (82%) completed the study as did 21 of the 25 PAF patients (84%). The total number of patients enrolled was smaller than the number enrolled in Study R-818-065, but all of the variables resulted in statistically significant differences between flecainide and placebo in all of the analyses for both the PAT patients and the PAF patients. No period or sequence effect was evident in the crossover analysis for time to first attack, interval between attacks, and rate of attacks. This reviewer examined the data by period, and the results were consistent. This study gives strong evidence of the ability of flecainide to reduce the frequency of PSVT attacks in both PAT and PAF patients.

IV. STUDY R-818-074

IV.1. Study Description

Study R-818-074 was a 20-week, phase II, double-blind, placebo-controlled, multicenter, dose-response study in patients with frequent attacks of PSVT. The inclusion/exclusion criteria for this study were similar to those of the two phase III studies previously discussed. The study began with a two week treatment-free screening period, later amended to four weeks, during which patients had to document two attacks of PSVT using transtelephonic monitors (TTMs).

Patients were then randomly assigned to one of four different ascending dose treatment sequences, each consisting of five 4-week treatment periods. During four of these periods the patient received flecainide twice daily at four ascending dosage regimens, 25 mg, 50 mg, 100 mg, and 150 mg. A placebo period was randomly inserted before or during the ascending dosage sequence. Patients were allowed to move on to the next treatment period before the end of four weeks if they had experienced four attacks of PSVT.

The primary efficacy parameters were number of patients having no attacks, time to first attack, interval between attacks, rate of attacks, and ventricular rate during attacks. Analyses were performed separately for patients with PAT and PAF. This study involved 17 centers, and data from all centers were combined for all analyses. No center contributed more than eight total patients. Eleven centers each enrolled from one to six PAT patients, for a total of 28 PAT patients, and 16 centers each enrolled from one to five PAF patients, giving a total of 45 PAF patients.

IV.2. Sponsor's Analysis

Table 11 gives the number of patients involved in each phase of the study, and the reason given for patients who discontinued the study. The number of PAT patients who dropped out of the study was relatively constant throughout the five periods, but the number of PAF drop-outs increased during the last two periods. Because flecainide was given in ascending doses and the placebo period could not be at the end, all patients in Period 5 were receiving the maximum dose. A total of 11 PAT patients and 17 PAF patients dropped out during the study. Three PAT patients who completed the study were excluded from the primary analyses done for evaluable patients because they were not study-drug compliant.

Efficacy results for this study are given in Tables 12 and 13 of this review. For each dose level of flecainide, McNemar's test was used to compare the number of patients who experienced no attacks of PSVT with the number who experienced no attacks while receiving placebo. Each treatment period was truncated at 31 days and attacks occurring after that were not counted, as were attacks occurring in the first three days. The sponsor used Bonferroni's adjustment to account for the multiple comparisons, and the significance level used for McNemar's test was 0.05/4 = 0.0125. Repeated

measures analysis of variance was used to test the linearity of dose response, and Cochran's test for a randomized complete block design was also used to compare the number of patients with no attacks across all five treatments.

The PAT patients indicated an increasing number of patients with no attacks with increasing dose, but none of the direct comparisons with placebo were significant at the p = 0.0125 level. The analysis of variance demonstrated a significant linear dose response with $p < 0.001$ and Cochran's test demonstrated a significant difference between the groups, with $p = 0.008$. The PAF patients also indicated an increasing number of patients with increasing dose, and the two larger doses, 100 mg and 150 mg bid, were significantly different from placebo ($p < 0.001$). Both Cochran's test and the analysis of variance also gave statistically significant results with $p < 0.001$).

The sponsor performed an "Intention To Treat" analysis of the number of patients who experienced complete suppression. McNemar's test was used to compare the results of each dose with placebo, using all patients who were compliant and had results on both placebo and the flecainide dose being compared. Bonferroni's adjustment was again used to maintain an overall significance level of 0.05. The results (given in Tables 12 and 13) were similar to the analysis of the "included" patients. None of the pairwise comparisons indicated significant differences for the PAT patients, but the two larger doses, 100 mg and 150 mg bid, showed statistically significant improvement for the PAF patients.

The time to first attack was censored in over half the PAT patients and over 30% of the PAF patients. The product limit estimate was used to get the median when it was defined, and the sample median of the data was reported when the number of censored observations was too large to get a product limit estimate. This is indicated in Tables 12 and 13 by a ">", since the sample median is a lower bound for the median. The Paired Prentice Wilcoxon (PPW) test for censored paired data was again used to compare each dosage level with the placebo group. Although the median time to first attack in the PAT patients was larger for the three higher doses, the PPW results were not significant for any dose at the $p = 0.0125$ level. For the PAF patients, the 100 mg and 150 mg bid groups had a significantly longer time to first attack with $p < 0.001$.

The results of the PPW test comparing the interval between attacks are similar to those for time to first attack, with the same doses giving significant results. The rate of attacks were compared across all five doses using analysis of variance to detect a treatment effect. The nonparametric Friedman test for a randomized complete block design was also used. Neither test gave significant results for the PAT patients, but the analysis of variance was marginally significant ($p = 0.088$) and Friedman resulted in a significant p=value of 0.001 for the PAF patients.

IV.3. Reviewer's Comments

The results of Study R-818-074 are hampered by the small sample size, especially for the PAT patients, and by the relatively short time they remained at each dose level. Patients receiving flecainide 25 mg bid do not seem to do much better than when

receiving placebo, but patients receiving flecainide 50 mg, 100 mg, or 150 mg bid appear to show improvement. Because patients remained at each dose level for only a month, over half of the patients experienced no attacks while receiving the highest three doses. As a result of these problems, the multiple comparisons of an individual dose level to placebo never achieved statistical significance. A linear dose response across the four dose levels is clearly significant ($p < 0.001$).

The PAF patients, with twice as many patients involved in this study, demonstrated statistically significantly better response while receiving flecainide 100 mg and 150 mg bid than while receiving placebo. For this group of patients, both the flecainide 25 mg and 50 mg bid results were similar to the placebo results. However, the study indicated a substantial increase in efficacy at the 100 mg bid level. A linear dose response across the four dose levels is clearly significant ($p < 0.001$).

The number of patients who discontinued this study before its completion causes this reviewer to question the validity of the results of the dose-response analysis. The sponsor only included patients who completed all five periods of the study and were study drug compliant (14 of 28 PAT patients and 28 of 45 PAF patients). However, many patients had completed most of the periods before dropping out, as can be seen in the "Intention to Treat" analysis in Tables 12 and 13. The sponsor should do an "Intent to Treat" analysis of dose response for Study R-818-074, using all evaluated patients, in order to assess the impact of the dropouts on the dose response relationship and check the validity of the claimed linear dose response relationship.

V. SAFETY

A summary of the adverse experiences in these three studies are given in Table 14 for the PAT patients and Table 15 for the PAF patients. The sponsor claims that the most commonly reported adverse experiences were consistent with those known for patients treated with flecainide for ventricular arrhythmias. The sponsor explains that because the patients in Studies R-818-065 and R-818-066 were titrated to their maximum tolerated dose, the frequency of adverse experiences is higher than was reported in the ventricular studies. They feel that the adverse experience rates of Study R-818-074 most clearly indicate the true incidence because patients in that study were not dosed to tolerance.

In their safety summary the sponsor included information on adverse experiences for patients during the long-term, open-label follow-up studies to R-818-065, R-818-066, and R-818-074. They also included information from the controlled study IND 23308 Oral, which involved 17 PAT patients and eight PAF patients, and from the uncontrolled study R-818-EG-11 which included 17 PAT patients and two PAF patients. Therefore their safety summary included information on a total of 108 PAT patients and 117 PAF patients.

All patients were reviewed for cardiac adverse experiences, which included proarrhythmic events, congestive heart failure, significant conduction disturbance, myocardial infarction, and death. Proarrhythmic events were defined as an event

which meets one or more of the following criteria:

1. A worsening of a pre-existing supraventricular arrhythmia.
2. An emergence of atrial flutter, atrial fibrillation, or atrial arrhythmia not previously diagnosed.
3. An emergence of a clinically significant ventricular arrhythmia with no prior history or diagnosis.

Proarrhythmic events were further categorized into three groups:

1. Serious, resulting in the death of the patient.
2. Serious, non-lethal defined as worsened arrhythmias which required immediate termination with drugs, overdrive pacing, or cardioversion, or which were associated with hypotensive symptoms which did or could have resulted in immediate harm to the patient.
3. Nonserious, defined as worsened arrhythmias which spontaneously resolved.

The sponsor defined supraventricular proarrhythmic events as occurring within 14 days of the initiation of flecainide therapy or a change in flecainide dose.

None of the 108 PAT patients involved in this clinical trials program died. During the course of the studies, four (4%) experienced a cardiac adverse event. One patient in study R-818-074 experienced intractable PAT while receiving flecainide 50 mg/day and this was classified as a proarrhythmic event. Another patient in this study developed new congestive heart failure while taking flecainide 100 mg/day. A patient receiving 200 mg/day during study R-818-066 experienced a conduction disturbance, and a patient discontinued during the dose-ranging phase of R-818-065 because of a possible myocardial infarction. The two patients who experienced either a proarrhythmic event or a possible MI were discontinued from their study, but the remaining two patients completed the double-blind study and continued into long-term, open-label therapy.

None of the 117 PAF patients experienced new or worsened congestive heart failure or a myocardial infarction. One patient experienced a proarrhythmic event on flecainide during dose-ranging in the R-818-065 study and died. This 59 year old male had received 200 mg/day flecainide for seven days followed by two days of 300 mg/day therapy. He collapsed at home, was taken to the hospital, but remained unresponsive and died the following day. The investigator felt his death was possibly related to flecainide therapy.

Seven other PAF patients were considered to have had proarrhythmic events and three were considered to have conduction disturbances secondary to flecainide. Four of these seven proarrhythmic events resolved spontaneously so were classified as nonserious. Three proarrhythmic events were considered serious but non lethal. These included one patient with a prolonged episode of atrial fibrillation, one with a sustained episode of atrial flutter, and a third with wide complex tachycardia requiring direct-current cardioversion.

VII. TRANSTELEPHONIC MONITORING

The sponsor analyzed the use of transtelephonic monitoring in the study of arrhythmias and the degree of correlation between symptoms and attacks of PSVT. They found that over 85% of the symptomatic calls from PAT and PAF patients were associated with arrhythmias (PSVT and others) which were considered likely to have caused the symptoms. About two-thirds of these calls were true PSVT attacks and one-third were related to other arrhythmias which probably had caused the symptoms. The symptoms which were most consistently associated with attacks of PSVT, in order of occurrence, were tachycardia, palpitations, dyspnea, chest pain, and dizziness.

VII. OVERALL SUMMARY AND CONCLUSIONS

The three studies discussed in this review provide convincing evidence of the efficacy of flecainide in reducing the frequency of attacks of PSVT in patients who respond to the drug and can tolerate it. Study R-818-065 demonstrates efficacy in patients experiencing PAT. The results of this study for patients with PAF was not convincing, and was confounded by a significant period effect. However, PAF patients did generally better while receiving flecainide. Study R-818-066 resulted in both PAT and PAF patients having statistically significantly lower frequency of attacks while receiving flecainide. Study R-818-074 was primarily a dose response study, but gave additional efficacy evidence. Patients involved in these trials had symptomatic PSVT episodes. The patient had to recognize the symptoms of an attack in order to activate the TTM. Asymptomatic PSVT episodes, if they were present, were not recorded.

The choice of efficacy variables used to evaluate anti-arrhythmic drugs is difficult. In Studies R-818-065 and R-818-066, simply comparing the number of patients having no PSVT attacks during the two crossover periods seems simplistic, and ignores the majority of the information garnered by the studies. However, the number of patients having no attacks is the only efficacy variable which was not hampered by the large amount of censoring. In the PAT patient group, about 80% of the patients in each study did not experience a PSVT attack during two months of flecainide therapy. Over 30% of the PAF patients also had no attacks while receiving flecainide. This high percentage of censored observations makes statistical analysis of the results difficult.

The sponsor provided three separate analyses of time to first attack, interval between attacks, and rate of attacks. The Paired Prentice Wilcoxon (PPW) test for censored paired data was used to test for a treatment difference. However, this analysis is not designed for a crossover study. Analysis of variance for a two-period crossover design was used to determine the effects of sequence, subjects within sequence, period and treatment on the efficacy variables, but this method does not provide for censored observations. A non-parametric crossover method proposed by Gary Koch was also used to examine sequence, period and treatment effects. Because of the

obvious non-normality of the data, this analysis was important. The three somewhat diverse statistical analyses all had similar results.

Over 30% of the patients in the three studies discontinued before completing their study. The great majority of dropouts in Studies R-818-065 and R-818-066 occurred during the dose-ranging phase, and were because of adverse experiences or inadequate response. These patients were not randomized and were not included in any of the efficacy analyses. Therefore, these studies do not demonstrate the efficacy of flecainide for all patients with PSVT attacks, but only for those who respond to flecainide and can tolerate it.

The patients who discontinued Study R-818-074 before its completion had been randomized and some had completed most of the five study periods before dropping out. The sponsor compared the individual doses of flecainide with placebo in an "Intention to Treat" analysis, but only included patients who completed all five periods of the study and were study drug compliant (14 of 28 PAT patients and 28 of 45 PAF patients) in the dose response analysis. The sponsor should analyze the data for all evaluated patients to assess the impact of the dropouts on the dose response relationship and check the validity of the claimed linear dose response relationship.

Almost 80% of the patients involved in these studies experienced some form of adverse reaction. The sponsor claims that the most commonly reported adverse experiences were consistent with those known for patients treated with flecainide for ventricular arrhythmias. The frequency of adverse experiences is higher than was reported in the ventricular studies because patients in two of these three studies were dosed to tolerance. There were a total of 15 cardiac adverse experiences, of which nine were classified as proarrhythmia. One patient died from a proarrhythmic event while receiving flecainide.

These studies were designed to determine if flecainide was more effective than placebo in controlling the frequency of attacks of PSVT. In order to detect any difference in mortality, the sample sizes of these studies would have needed to be much larger, and the studies would have to be of a much greater duration. A large, long-term, multicenter, placebo-controlled trial for the safety and efficacy of flecainide in patients with PSVT, similar to the CAST trial, would be necessary in order to determine if the risk of sudden death is reduced or increased for patients with supraventricular arrhythmias.

The overall summary and conclusions section may be conveyed to the sponsor.

Nancy D. Smith

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9/19/89

for Dr. Dubey H.L. 9/21/89

cc:
Orig. NDA 19-770
HFD-110
HFD-110/Dr. Lipicky
HFD-110/Dr. Chun
HFD-110/Mrs. Morgenstern
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Dr. Smith
✓ Chron.
N.Smith/x30263/SERB/WriteNow/9-12-89

This review contains 17 pages of text and 15 pages of attached tables.

TABLE 1

STUDY R-818-065 - PATIENT ACCOUNTABILITY

	PAT	PAF
Patients who Qualified	34	39
Patients who Discontinued	3	0
Cardiac Adverse Experience	(2)	(0)
Personal	(1)	(0)
Patients Entering Dose Ranging Phase	31	39
Patients who Discontinued	9	6
Cardiac Adverse Experience	(1)	(1)
Noncardiac Adverse Experience	(2)	(0)
Personal	(3)	(2)
Death	(0)	(1)
Inadequate Response	(0)	(1)
Intercurrent Disease	(0)	(1)
Protocol Compliance	(2)	(0)
Loss to Followup	(1)	(0)
Patients Entering Crossover Period A	22	33
Patients who Discontinued	1	1
Personal	(1, placebo)	(0)
Inadequate Response	(0)	(1, flecainide)
Patients Entering Crossover Period B	21	32
Patients who Discontinued	2	2
Cardiac Adverse Experience	(0)	(1, flecainide)
Noncardiac Adverse Experience	(0)	(1, flecainide)
Inadequate Response	(1, placebo)	(0)
Loss to Followup	(1, flecainide)	(0)
Patients Completing Crossover	19	30
Patients Included in Sponsor's Analysis	20	29

TABLE 2

STUDY R-818-065 - EFFICACY RESULTS

	PAT N = 20		PAF N = 29	
	Placebo	Flecainide	Placebo	Flecainide
Patients with No Attacks	4	16	4	9
P-value	< 0.001		0.228	
Time to First Attack (Days)				
Mean ± SE	> 12.7 ± 2.2	> 35.0 ± 2.2	> 7.4 ± 1.2	> 16.6 ± 2.4
Median	11.5	> 55 *	3.0	15.0
P-value	< 0.001		0.021	
Interval Between Attacks (Days)				
Mean ± SE	> 21.2 ± 4.6	> 50.9 ± 3.3	> 17.3 ± 3.7	> 30.6 ± 4.3
Median	12.8	> 55 *	6.3	27
P-value	< 0.001		0.003	
Rate of Attacks (Attacks/Day)				
Mean ± SE	0.21 ± 0.078	0.03 ± 0.008	0.23± 0.045	0.09 ± 0.021
Range	(0.02 - 1.33)	(0.02 - 0.17)	(0.02 - 1.00)	(0.02 - 0.57)
P-value	0.035		0.009	

* Estimate based on median treatment duration. Only 4/20 (20%) of PAT patients had an attack while receiving flecainide.

TABLE 3

STUDY R-818-065 - CROSSOVER ANALYSIS
Time to First Attack (Days)

PAT PATIENTS (N = 20)

	Sequence Effect P-value	Period Effect P-value	Treatment Effect P-value
Analysis of Variance	0.418	0.626	< 0.001
Non-parametric Analysis	0.543	0.732	< 0.001

PAF PATIENTS (N = 29)

	Sequence Effect P-value	Period Effect P-value	Treatment Effect P-value
Analysis of Variance	0.690	0.063	0.150
Non-parametric Analysis	0.686	0.051	0.170

PAF PATIENTS (N = 29)

Time to First Attack
(days)

	Period A	Period B
Placebo	8.1 n=18	20.0 n=11
Flecainide	17.7 n=11	25.1 n=18

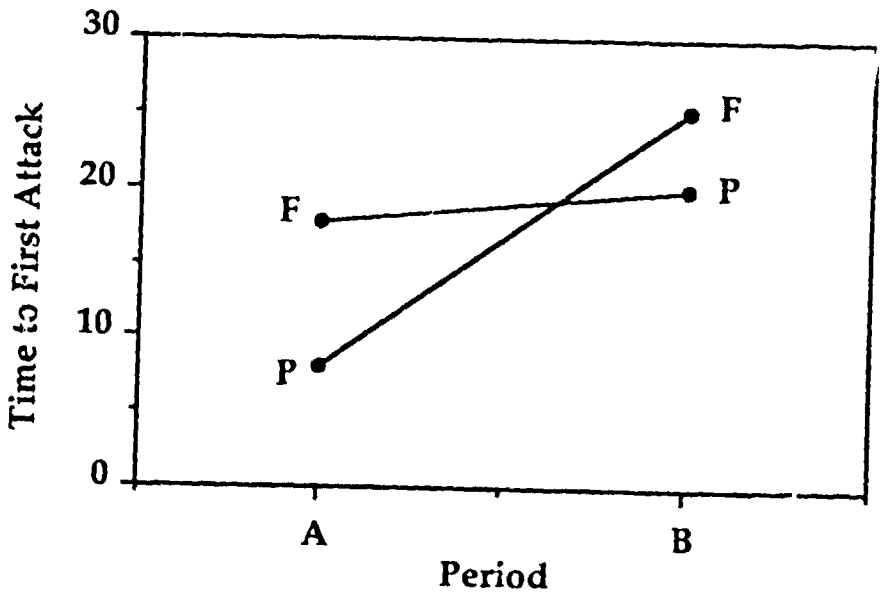


TABLE 4

STUDY R-818-065 - CROSSOVER ANALYSIS
Interval Between Attacks (Days)

PAT PATIENTS (N = 20)

	Sequence Effect P-value	Period Effect P-value	Treatment Effect P-value
Analysis of Variance	0.375	0.214	< 0.001
Non-parametric Analysis	0.447	0.271	< 0.001

PAF PATIENTS (N = 29)

	Sequence Effect P-value	Period Effect P-value	Treatment Effect P-value
Analysis of Variance	0.848	0.047	0.053
Non-parametric Analysis	0.822	0.048	0.039

PAF PATIENTS (N = 29)

Interval Between Attacks
(days)

	Period A	Period B
Placebo	13.3 n=18	23.4 n=11
Flecainide	23.2 n=11	31.0 n=18

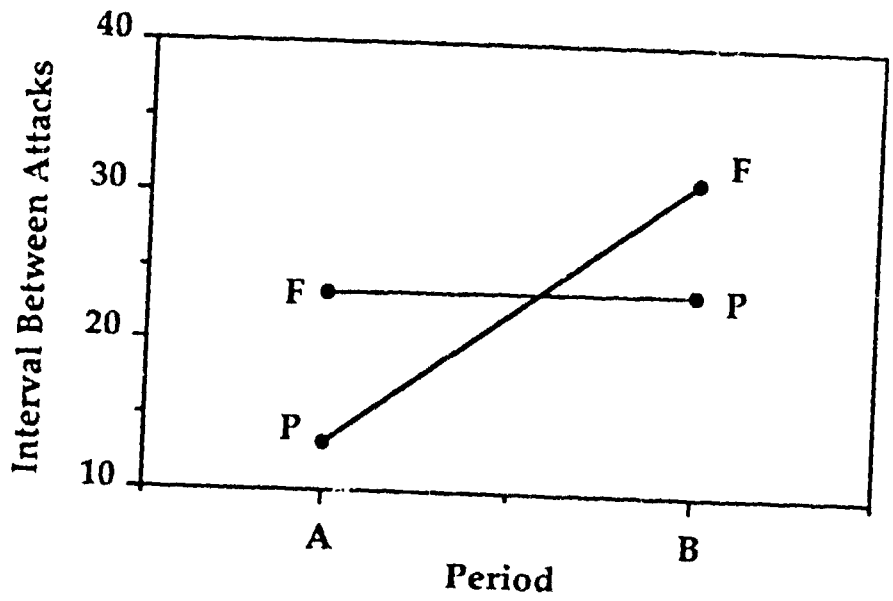


TABLE 5

STUDY R-818-065 - CROSSOVER ANALYSIS
Rate of Attacks (Attacks/Day)

PAT PATIENTS (N = 20)

	Sequence Effect P-value	Period Effect P-value	Treatment Effect P-value
Analysis of Variance	0.827	0.734	0.035
Non-parametric Analysis	0.621	0.305	0.003

PAF PATIENTS (N = 29)

	Sequence Effect P-value	Period Effect P-value	Treatment Effect P-value
Analysis of Variance	0.141	0.068	0.009
Non-parametric Analysis	0.164	0.048	0.007

PAF PATIENTS (N = 29)

Rate of Attacks
(number of attacks per day)

	Period A	Period B
Placebo	0.30 n=18	0.13 n=11
Flecainide	0.09 n=11	0.08 n=18

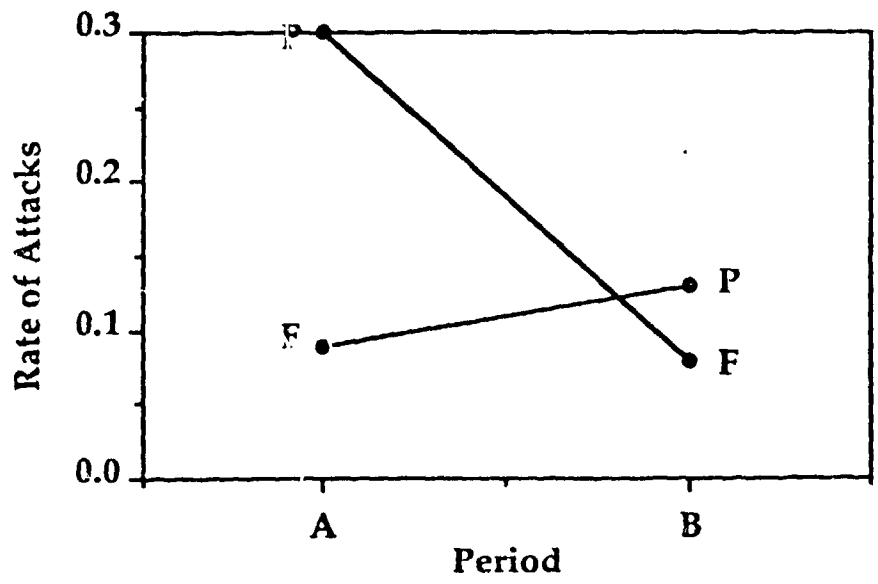


TABLE 6

STUDY R-818-065

Dose taken during Crossover Phase

	PAT	PAF
100 mg/day	0	1
200 mg/day	6	9
300 mg/day	8	12
400 mg/day	8	11

Number of Attacks during the Crossover Phase

Number of Attacks	PAT (N = 20)		PAF (N = 29)	
	Placebo	Flecainide	Placebo	Flecainide
0	4	16	4	9
1	4	3	4	1
2	1	1	4	8
3	1	0	2	2
4	6	0	6	5
5	2	0	5	4
6	1	0	4	0
7	1	0	0	0

Intention To Treat

	PAT			PAF		
	Evaluable	Excluded	Total	Evaluable	Excluded	Total
Success	14	0	14	7	1	8
Partial Success	1	0	1	14	1	15
Failure	1	3	4	7	5	12
Undetermined	4*	8**	12	1*	3**	4

* Patient had no attacks on placebo or flecainide.

** Patient discontinued for reasons other than inadequate response or adverse experience.

TABLE 7

STUDY R-818-066 - PATIENT ACCOUNTABILITY

	PAT	PAF
Patients who Qualified	17	25
Patients who Discontinued	0	0
Patients Entering Dose Ranging Phase	17	25
Patients who Discontinued	2	3
Cardiac Adverse Experience	(0)	(3)
Personal	(1)	(0)
Inadequate Response	(1)	(0)
Patients Entering Crossover Period A	15	22
Patients who Discontinued	1	1
Noncardiac Adverse Experience	(1, flecainide)	(1, flecainide)
Patients Entering Crossover Period B	14	21
Patients who Discontinued	0	0
Patients Completing Crossover	14	21
Patients Included in Sponsor's Analysis	14	19

TABLE 8

STUDY R-818-066 - EFFICACY RESULTS

	PAT N = 14		PAF N = 19	
	Placebo	Flecainide	Placebo	Flecainide
Patients with No Attacks	1	11	0	6
P-value	0.002		0.031	
Time to First Attack (Days)				
Mean ± SE	> 15.2 ± 4.9	> 22.0 ± 1.8	6.3 ± 1.6	> 18.3 ± 3.6
Median	9.5	> 61 *	3.0	10.0
P-value	0.001		0.008	
Interval Between Attacks (Days)				
Mean ± SE	> 18.5 ± 5.4	> 51.3 ± 4.2	10.2 ± 3.1	> 31.7 ± 4.9
Median	7.3	> 61 *	6.0	29
P-value	0.001		0.001	
Rate of Attacks (Attacks/Day)				
Mean ± SE	0.23 ± 0.07	0.03 ± 0.01	0.30± 0.06	0.07 ± 0.02
Range	(0.02 - 0.75)	(0.02 - 0.22)	(0.02 - 1.00)	(0.02 - 0.33)
P-value	0.013		0.003	

* Estimate based on median treatment duration. Only 3/14 (21%) of PAT patients had an attack while receiving flecainide.

TABLE 9

STUDY R-818-066 - CROSSOVER ANALYSIS

Time to First Attack (Days)

	Sequence Effect P-value	Period Effect P-value	Treatment Effect P-value
PAT PATIENTS (N = 14)			
Analysis of Variance	0.198	0.300	< 0.001
Non-parametric Analysis	0.439	0.197	0.002
PAF PATIENTS (N = 19)			
Analysis of Variance	0.611	0.432	0.002
Non-parametric Analysis	0.375	0.800	0.022

Interval Between Attacks (Days)

	Sequence Effect P-value	Period Effect P-value	Treatment Effect P-value
PAT PATIENTS (N = 14)			
Analysis of Variance	0.460	0.572	< 0.001
Non-parametric Analysis	0.699	0.245	0.002
PAF PATIENTS (N = 19)			
Analysis of Variance	0.626	0.180	< 0.001
Non-parametric Analysis	0.398	0.128	< 0.001

Rate of Attacks (Attacks/Day)

	Sequence Effect P-value	Period Effect P-value	Treatment Effect P-value
PAT PATIENTS (N = 14)			
Analysis of Variance	0.720	0.470	0.013
Non-parametric Analysis	0.796	0.439	0.005
PAF PATIENTS (N = 19)			
Analysis of Variance	0.667	0.969	0.003
Non-parametric Analysis	0.866	0.554	0.001

TABLE 10

STUDY R-818-066

Dose taken during Crossover Phase

	PAT	PAF
100 mg/day	1	1
200 mg/day	2	2
300 mg/day	7	9
400 mg/day	5	9
600 mg/day	0	1

Number of Attacks during the Crossover Phase

Number of Attacks	PAT (N = 14)		PAF (N = 29)	
	Placebo	Flecainide	Placebo	Flecainide
0	1	11	0	6
1	2	2	2	2
2	2	0	0	4
3	2	0	7	1
4	5	0	8	3
5	1	0	1	0
6	1	1	0	1
7	1	0	1	2

Intention To Treat

	PAT			PAF		
	Evaluable	Excluded	Total	Evaluable	Excluded	Total
Success	12	0	12	8	0	8
Partial Success	0	0	0	8	1	9
Failure	2	2	4	3	5	8
Undetermined	0	1*	1	0	0	0

* Patient discontinued for reasons other than inadequate response or adverse experience.

TABLE 11

STUDY R-818-074 - PATIENT ACCOUNTABILITY

	PAT	PAF
Patients Entering Period 1	28	45
Patients who Discontinued	5	4
Cardiac Adverse Experience	(1-F 25 mg)	(0)
Noncardiac Adverse Experience	(1-P, 2-F 25 mg)	(1-F 25 mg)
Personal	(1-P)	(0)
Other	(0)	(1-P, 1-F 25 mg)
Loss to Followup	(0)	(1-P)
Patients Entering Period 2	23	41
Patients who Discontinued	2	1
Inadequate Response	(0)	(1-F 25 mg)
Other	(2-P)	(0
Patients Entering Period 3	21	40
Patients who Discontinued	0	2
Cardiac Adverse Experience	(0)	(1-F 50 mg)
Personal	(0)	(1-F 50 mg)
Patients Entering Period 4	21	38
Patients who Discontinued	2	5
Cardiac Adverse Experience	(1-P)	(1-F 100 mg)
Noncardiac Adverse Experience	(1-F 100 mg)	(1-P, 1-F 100 mg)
Personal	(0)	(1-P, 1-F 100 mg)
Patients Entering Period 5	19	33
Patients who Discontinued	2	5
Noncardiac Adverse Experience	(2-F 150 mg)	(4-F 150 mg)
Personal	(0)	(1-F 150 mg)
Patients Completing Crossover	17	28
Patients Included in Sponsor's Analysis	14	28

TABLE 12

STUDY R-818-074 - EFFICACY RESULTS
PAT Patients (N=14)

	Placebo	25 mg	50 mg	100 mg	150 mg
Patients with No Attacks	4 (29%)	5 (36%)	8 (57%)	9 (64%)	12 (86%)
P-value versus Placebo *		1.000	0.219	0.125	0.021
Analysis of Variance for Linear Dose Response			p < 0.001		
Cochran's Test for Treatment Difference			p = 0.008		
Intention to Treat Analysis (including all patients who were evaluated)					
Patients with No Attacks	6/24(25%)	7/26(27%)	12/23(52%)	13/23(57%)	13/22(59%)
P-value versus Placebo *		1.000	0.070	0.039	0.092
Time to First Attack (Days)					
Median	11.0	7.0	> 24.0 **	> 26.0 **	> 28.0 **
Range	(1.0 - >29)	(1.0 - >29)	(1.0 - >29)	(4.0 - >29)	(1.0 - >29)
P-value versus Placebo *		0.708	0.164	0.041	0.027
Interval Between Attacks (Days)					
Median	19.8	26.0	> 26.0 **	28.0	> 28.0 **
Range	(0.8 - >29)	(4.0 - >29)	(0.5 - >29)	(3.8 - >29)	(1.0 - >29)
P-value versus Placebo *		0.706	0.255	0.021	0.024
Rate of Attacks (Attacks/Day)					
Mean ± SE	0.19 ± 0.36	0.09 ± 0.08	0.26± 0.53	0.07 ± 0.07	0.11 ± 0.26
Median	0.06	0.04	0.04	0.04	0.04
Range	(0.03 - 1.33)	(0.03 - 0.25)	(0.03 - 2.00)	(0.03 - 0.27)	(0.03- 1.00)
Analysis of Variance	p = 0.286				
Friedman Test	p = 0.436				

* The sponsor used Bonferroni's adjustment for four comparisons and considered the treatment to be significantly different from placebo only if $p \leq 0.0125$.
** Product limit estimate is not defined. Value reported is sample median.

TABLE 13

STUDY R-818-074 - EFFICACY RESULTS
PAF Patients (N=28)

	Placebo	25 mg	50 mg	100 mg	150 mg
Patients with No Attacks	2 (7%)	5 (18%)	6 (21%)	15 (54%)	17 (61%)
P-value versus Placebo *		0.375	0.289	< 0.001	< 0.001
Analysis of Variance for Linear Dose Response			p < 0.001		
Cochran's Test for Treatment Difference			p < 0.001		

Intention to Treat Analysis (including all patients who were evaluated)

Patients with No Attacks	5/41(12%)	5/42(12%)	8/39(21%)	17/39(44%)	14/34(41%)
P-value versus Placebo *		1.000	0.344	0.004	0.003

Time to First Attack (Days)

Median	3.0	4.0	5.0	> 25.5 **	> 14.5 **
Range	(1.0 - >27)	(1.0 - >29)	(1.0 - >29)	(4.0 - >29)	(1.0 - >29)
P-value versus Placebo *		0.877	0.123	< 0.001	< 0.001

Interval Between Attacks (Days)

Median	7.2	6.5	8.2	28.0	> 25.5 **
Range	(1.0 - 28)	(1.0 - >29)	(0.5 - >29)	(1.0 - >29)	(1.8 - >29)
P-value versus Placebo *		0.995	0.419	< 0.001	< 0.001

Rate of Attacks (Attacks/Day)

Mean ± SE	0.22 ± 0.23	0.21 ± 0.22	0.24± 0.38	0.14 ± 0.22	0.11 ± 0.13
Median	0.14	0.15	0.12	0.04	0.04
Range	(0.04- 1.00)	(0.03 - 1.00)	(0.03 - 2.00)	(0.03 - 1.00)	(0.03- 0.57)
Analysis of Variance	p = 0.088				
Friedman Test	p = 0.001				

* The sponsor used Bonferroni's adjustment for four comparisons and considered the treatment to be significantly different from placebo only if $p \leq 0.0125$.

** Product limit estimate is not defined. Value reported is sample median.

TABLE 14

ADVERSE EXPERIENCES - PAT PATIENTS

(Percent of patients with at least one report of the adverse experience)

	R-818-065 (N=31)	R-818-066 (N=17)	R-818-074 (N=26)
Autonomic Nervous System Disorders	2 (6%)	2 (12%)	4 (15%)
Body as a Whole - General Disorders	16 (52%)	8 (47%)	6 (23%)
Cardiovascular Disorders, General	2 (6%)	1 (6%)	2 (8%)
Centr & Periph Nerv Syst Disorders	13 (42%)	7 (41%)	9 (35%)
Endocrine Disorders	0	0	1 (4%)
Gastro-Intestinal System Disorders	12 (39%)	5 (29%)	7 (27%)
Hearing and Vestibular Disorders	3 (10%)	0	0
Heart Rate and Rhythm Disorders	2 (6%)	1 (6%)	2 (8%)
Metabolic and Nutritional Disorders	0	0	1 (4%)
Musculo-Skeletal System Disorders	1 (3%)	0	1 (4%)
Psychaitric Disorders	3 (10%)	6 (35%)	1 (4%)
Resistance Mechanism Disorders	1 (3%)	0	0
Respiratory System Disorders	7 (23%)	4 (24%)	3 (12%)
Skin and Appendages Disorders	1 (3%)	2 (12%)	1 (4%)
Vascular (Extracardiac) Disorders	0	0	1 (4%)
Vision Disorders	9 (29%)	12 (71%)	3 (12%)
White Cell and Res Disorders	1 (3%)	0	0
% of Patients Reporting at least one A.E.	25 (81%)	16 (94%)	17 (65%)

TABLE 15

ADVERSE EXPERIENCES - PAF PATIENTS

(Percent of patients with at least one report of the adverse experience)

	R-818-065 (N=39)	R-818-066 (N=25)	R-818-074 (N=43)
Autonomic Nervous System Disorders	2 (5%)	4 (16%)	3 (7%)
Body as a Whole - General Disorders	14 (36%)	12 (48%)	10 (23%)
Cardiovascular Disorders, General	1 (3%)	2 (8%)	1 (2%)
Centr & Periph Nerv Syst Disorders	25 (64%)	17 (68%)	13 (30%)
Endocrine Disorders	1 (3%)	0	0
Gastro-Intestinal System Disorder	14 (36%)	9 (36%)	6 (14%)
Hearing and Vestibular Disorders	0	0	2 (5%)
Heart Rate and Rhythm Disorders	6 (15%)	7 (28%)	2 (5%)
Metabolic and Nutritional Disorders	1 (3%)	0	0
Musculo-Skeletal System Disorders	0	0	5 (12%)
Platelet, Bleeding & Clotting Disorders	0	1 (4%)	1 (2%)
Psychaitric Disorders	8 (21%)	12 (48%)	5 (12%)
Reproductive Disorders, Female	1 (3%)	0	0
Resistance Mechanism Disorders	0	0	1 (2%)
Respiratory System Disorders	7 (18%)	2 (8%)	5 (12%)
Skin and Appendages Disorders	0	5 (20%)	1 (2%)
Urinary System Disorders	2 (5%)	0	0
Vascular (Extracardiac) Disorders	0	0	2 (5%)
Vision Disorders	21 (54%)	16 (64%)	9 (21%)
White Cell and Res Disorders	0	0	1 (2%)
% of Patients Reporting at least one A.E.	32 (82%)	23 (92%)	29 (67%)

NDA 18830

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-830

OCT 31 1985

Riker Laboratories
Attention: Florence N. Wong, Pharm.D.
270-3A 3M Center
St. Paul, Minnesota 55144

Dear Dr. Wong:

Please refer to your December 21, 1982 new drug application resubmitted on February 25, 1985 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tambocor (flecainide acetate, R-818) 100 and 200 mg Tablets.

We also acknowledge receipt of your amendments dated September 5 and 27, 1985; and October 14 and 24, 1985.

We have completed the review of this application including the submitted draft labeling and the application is approved effective on the date of this letter.

The labeling should be revised exactly as in the enclosed draft. Twelve copies of the final printed version of the revised labeling must be submitted to FDA prior to marketing. Marketing of the drug before the changes specified above are made and submitted to FDA renders the product misbranded under 21 U.S.C. 352.

Should additional information relating to the safety and effectiveness of these drug products become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

We would be pleased to meet with you to discuss the design of post-marketing trials that would potentially lead to less restrictive labeling.

Please submit one market package of the drug when available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact:

Mr. Denver Presley, Jr.
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Robert Temple

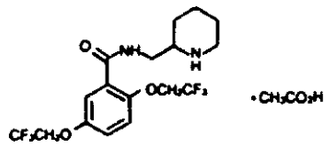
Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

TAMBOCOR®
(flecainide acetate)
Tablets

DESCRIPTION:

TAMBOCOR® (flecainide acetate) is an antiarrhythmic drug available in tablets of 100 or 200 mg for oral administration.

Flecainide acetate is benzamide,N-(2-piperidinylmethyl) -2,5-bis (2,2,2-trifluoroethoxy)- ,monoacetate. The structural formula is given below



Flecainide acetate is a white crystalline substance with a pK_a of 9.3. It has an aqueous solubility of 48.4 mg/ml at 37°C.

CLINICAL PHARMACOLOGY:

TAMBOCOR has local anesthetic activity and belongs to the membrane stabilizing (Class I) group of antiarrhythmic agents; it has electrophysiologic effects characteristic of the IC class of antiarrhythmics.

Electrophysiology. In man, TAMBOCOR produces a dose-related decrease in intracardiac conduction in all parts of the heart with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (A/V) nodal conduction time and intraatrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods were observed only in the ventricle. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction (see Warnings).

TAMBOCOR causes a dose-related and plasma-level related decrease in single and multiple PVCs and can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, TAMBOCOR has been successful 30-40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation. Based on PVC suppression, it appears that plasma levels of 0.2 to 1.0 μg/ml may be needed to obtain the maximal therapeutic effect. It is more difficult to assess the dose needed to suppress serious arrhythmias, but trough plasma levels in patients successfully treated for recurrent ventricular tachycardia were between 0.2 and 1.0 μg/ml. Plasma levels above 0.7-1.0 μg/ml are associated with a higher rate of cardiac adverse experiences such as conduction defects or bradycardia. The relation of plasma levels to proarrhythmic events is not established, but dose reduction in clinical trials of patients with ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Hemodynamics. TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally.

In animals and isolated myocardium, a negative inotropic effect of flecainide has been demonstrated. Decreases in ejection fraction, consistent with a negative inotropic effect, have been observed after single administration of 200 to 250 mg of the drug in man; both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses (see Warnings).

Metabolism in Humans. Following oral administration, the absorption of TAMBOCOR is nearly complete. Peak plasma levels are attained at about three hours in most individuals (range 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacid do not affect absorption.

The apparent plasma half-life averages about 20 hours and is quite variable (range 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing plasma levels increase because of its long half-life with steady state levels approached in 3 to 5 days; once at steady state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range,

The apparent plasma half-life averages about 20 hours and is quite variable (range, 12 to 27 hours) after multiple oral doses in patients with premature ventricular contractions (PVCs). With multiple dosing, plasma levels increase because of its long half-life with steady-state levels approached in 3 to 5 days. once at steady-state, no additional (or unexpected) accumulation of drug in plasma occurs during chronic therapy. Over the usual therapeutic range, data suggest that plasma levels in an individual are approximately proportional to dose, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

In healthy subjects, about 30% of a single oral dose (range, 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are meta-O-dealkylated flecainide (active, but about one-fifth as potent) and the meta-O-dealkylated lactam of flecainide (non-active metabolite). These two metabolites (primarily conjugated) account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found in urine; only 5% of an oral dose is excreted in feces. In patients, free (unconjugated) plasma levels of the two major metabolites are very low (less than 0.05 μg/ml).

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma. (See Dosage and Administration.)

In patients with congestive heart failure (NYHA class III), the rate of flecainide elimination from plasma (mean half-life, 19 hours) is moderately slower than for healthy subjects (mean half-life, 14 hours), but similar to the rate for otherwise well patients with PVCs. The extent of unchanged drug excretion in urine is also similar. (See Dosage and Administration.)

The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma drug level over the range of 0.015 to about 3.4 μg/ml. Thus, clinically significant drug interactions based on protein binding effects would not be expected.

Hemodialysis removes only about 1% of an oral dose as unchanged flecainide.

Small increases in plasma digoxin levels are seen during coadministration of TAMBOCOR with digoxin. Small increases in both flecainide and propranolol plasma levels are seen during coadministration of these two drugs (see Precautions, Drug Interactions).

INDICATIONS AND USAGE:

TAMBOCOR is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.

TAMBOCOR is also indicated for the treatment of patients with symptomatic nonsustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of TAMBOCOR, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, TAMBOCOR, like other antiarrhythmics, should be initiated in the hospital. Hospitalization may be necessary for certain other patients depending on their cardiac status and underlying cardiac disease (see Dosage and Administration).

The effects of TAMBOCOR in patients with supraventricular arrhythmias and in patients with recent acute myocardial infarction have not been adequately studied.

No antiarrhythmic agent, including TAMBOCOR, has been shown to have a favorable effect on mortality or sudden death.

CONTRAINDICATIONS:

TAMBOCOR is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:

Proarrhythmic Effects.

TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three-fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias.

In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. Their frequency appears to be related to dose and to the underlying car-

Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule (see Dosage and Administration).

Patients with less serious arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal.

The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).

Heart Failure.

TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 35%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of preexisting CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg bid (see Dosage and Administration) and patients should be monitored carefully. Close attention must be given to maintenance of cardiac function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics, others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/ml.

Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose related increases in PR, QRS, and QT intervals.

PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one-third of patients may develop new first-degree AV heart block (PR interval $\geq$0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus caution should be used when such intervals occur and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythmia associated with Tambocor induced QT prolongation and bradycardia.

Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block or right bundle branch block associated with a left hemiblock occur, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia

Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.

The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally threshold changes are within the range of multiprogrammable pacemakers and when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture.

Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

PRECAUTIONS:

Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin, a 13% ± 19% increase in plasma digoxin levels occurred at six hours postdose.

In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, plasma flecainide levels were increased about 20% and propranolol levels were increased about 30% compared to control values. In this formal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects, when the drugs were administered together, the effects were additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive. In TAMBOCOR clinical trials, patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.

Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction.

There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgment of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.

Pregnancy. Pregnancy Category C. Flecainide has been shown to have teratogenic effects (club paws, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day, respectively, however, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery or increases the possibility of forceps delivery or other obstetrical intervention.

Nursing Mothers. It is not known whether flecainide is excreted in human milk. Because many drugs are excreted in human milk and because of the drug's potential for serious adverse effects in infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.

Use in Patients with Hepatic Impairment. Studies to determine the effect of hepatic impairment upon the elimination of TAMBOCOR have not yet been completed. Because the drug undergoes extensive biotransformation (most likely in the liver), patients with significant hepatic impairment should not receive TAMBOCOR unless the potential benefits clearly outweigh the risks.

ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR described in detail in Warnings section were new or exacerbated ventricular arrhythmias which occurred in 7% of patients and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause or sinus arrest, about 1.2% altogether

(See Warnings) [illegible]

ADVERSE EFFECTS:

The most serious adverse effects reported for TAMBOCOR, described in detail in Warnings section, were new or exacerbated ventricular arrhythmias which occurred in 7% of patients, and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest, about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/ml.

There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign post-marketing surveillance studies, there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure, and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Incidence figures for other adverse effects are based on a multicenter efficacy study utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table 1

Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

		Incidence by Dose During Upward Titration		
Adverse Effect	Incidence in All 429 Patients at Any Dose	200 mg/Day (N=426)	300 mg/Day (N=293)	400 mg/Day (N=100)
Dizziness*	18.9%	11.0%	[illegible]%	13.0%
Visual Disturbance†	15.9%	5.4%	12.[illegible]%	18.0%
Dyspnea	10.3%	5.2%	7.[illegible]%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.

†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400-600 mg/day, the incidence of these adverse experiences was similar, except for dizziness (32%) and visual disturbances (28%).

The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies: *Body as a Whole* – malaise, fever; *Cardiovascular* – tachycardia, sinus pause or arrest; *Gastrointestinal* – vomiting, diarrhea, dyspepsia, anorexia; *Skin* – rash; *Visual* – diplopia; *Nervous System* – hypothesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus; *Psychiatric* – anxiety, insomnia, depression.

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients: *Body as a Whole* – swollen lips, tongue and mouth, arthralgia, bronchospasm, myalgia; *Cardiovascular* – angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension; *Gastrointestinal* – flatulence; *Urinary System* – polyuria, urinary retention; *Hematologic* – leukopenia, thrombocytopenia; *Skin* – urticaria, exfoliative dermatitis, pruritis; *Visual* – eye pain or irritation, photophobia, nystagmus; *Nervous System* – twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor; *Psychiatric* – amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the T wave, a reduction in myocardial rate and contractility, conduction disturbances, hypotension, and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol, mechanically assisted respiration, circulatory assists such as intra-aortic balloon pump[illegible]

OVERDOSAGE:

No specific antidote has been identified for the treatment of TAMBOCOR overdosage. Animal studies suggest that the following events might occur with overdosage: lengthening of the PR interval, increase in the QRS duration, QT interval and amplitude of the T-wave, a reduction in myocardial rate and contractility, conduction disturbances, hypotension, and death from respiratory failure or asystole. Treatment of overdosage should be supportive and may include the following: administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol, mechanically assisted respiration, circulatory assists such as intra-aortic balloon pumping, and transvenous pacing in the event of conduction block. Because of the long plasma half-life of flecainide (12 to 27 hours in patients receiving usual doses), and the possibility of markedly non-linear elimination kinetics at very high doses, these supportive treatments may need to be continued for extended periods of time. Hemodialysis is not an effective means of removing flecainide from the body.

DOSAGE AND ADMINISTRATION:

For patients with sustained ventricular tachycardia, no matter what their cardiac status, TAMBOCOR, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring. Hospitalization is also recommended for patients with symptomatic congestive heart failure or sinus node dysfunction, even if there is no history of sustained ventricular tachycardia, and should be considered in compensated patients with significant myocardial dysfunction, e.g., low ejection fractions (see Warnings).

Flecainide has a long half-life (12 to 27 hours in patients). Steady-state plasma levels, in patients with normal renal and hepatic function, may not be achieved until the patient has received 3 to 5 days of therapy at a given dose. Therefore, **increases in dosage should be made no more frequently than once every four days**, since during the first 2 to 3 days of therapy the optimal effect of a given dose may not be achieved.

For sustained ventricular tachycardia, patients the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most such patients do not require more than 150 mg every 12 hours (300 mg/day), and the maximum dose is 400 mg/day.

For patients with symptomatic nonsustained ventricular tachycardia, couplets, or premature ventricular complexes the recommended starting dose is also 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every four days until efficacy is achieved. Most of these patients do not require more than 200 mg every 12 hours (400 mg/day). If such a patient is still symptomatic due to the arrhythmia at 400 mg/day, and the plasma level is below 0.6 µg/ml, the dosage may be cautiously increased to a maximum of 600 mg/day.

Use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and congestive heart failure, particularly during the first few days of dosing (see Warnings). Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients efficacy at the lower dose should be evaluated.

TAMBOCOR should be used cautiously in patients with a history of congestive heart failure or myocardial dysfunction (see Warnings). The initial dose should be no more than 100 mg every 12 hours. If needed to achieve efficacy, the dosage may be increased cautiously in increments of 50 mg bid every four days. The maximum dosage should not exceed 200 mg every 12 hours (400 mg/day) because higher doses are associated with a greater incidence of worsened CHF.

In patients with renal impairment, the initial dosage should be 100 mg every 12 hours. Dosage increases should be made cautiously at intervals greater than 4 days, observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than four days before a new steady state plasma level is reached following a dosage change. It is recommended that plasma level monitoring be used to guide dosage adjustments (see below).

Based on theoretical considerations, rather than experimental data, the following suggestion is made when transferring patients from another antiarrhythmic drug to TAMBOCOR: allow at least two to four plasma half-lives to elapse for the drug being discontinued before starting TAMBOCOR at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 µg/ml. The probability of adverse experiences, especially cardiac

Plasma Level Monitoring: The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 0.2 and 1.0 μg/ml. The probability of adverse experiences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 μg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Because elimination of flecainide from plasma may be slower in patients with severe chronic renal failure or severe congestive heart failure, plasma level monitoring may be especially helpful in these patients.

HOW SUPPLIED:

TAMBOCOR is supplied as white, round, scored tablets containing either 100 or 200 mg of flecainide acetate and embossed with RIKER on one side and TR 100 or TR 200 on the other side.

Tambocor 100 mg/tablet is available in:
Bottles of 100 – NDC #0089-0307-10
Bottles of 500 – NDC #0089-0307-50, and
Bottles of 1000 – NDC #0089-0307-80

Tambocor 200 mg/tablet is available in:
Bottles of 100 – NDC #0089-0317-10
Bottles of 500 – NDC #0089-0317-50, and
Bottles of 1000 – NDC #0089-0317-80

Store at controlled room temperature 15°-30°C (59°-86°F) in a tight, light-resistant container.

TR-1 OCTOBER 1985

Manufactured by
Riker Laboratories, Inc./3M
St. Paul, Minnesota 55144

61

DEC 26 1985

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST REVIEW NO. 3

Completed: November 13, 1985

A. 1. NDA: 18-830 ORIGINAL NEW DRUG APPLICATION - AS FURTHER AMENDED

Applicant: Riker Laboratories, Inc.
3M Center, Building 270, 3A01
St. Paul, Minnesota 55144
(612)736-2636 Dr. Florence Wong - Regulatory Specialist

2. Product Names: Proprietary : Tambocor (R) Tablets
Non-proprietary : Flecainide Acetate
Chemical: Benzamide, N-(2-piperidinylmethyl)-2,5-bis (2,2,2,-trifluoroethoxy)-, monoacetate.

3. Dosage Form: Tablets either 100 mg or 200 mg strength supplied as white, round, scored tablets embossed RIKER on one side and either TR 100 or TR 200 on the other side.

4. Route of Administration: Oral

5. Structural Formula: Please refer to Chemist Review No. 1 dated July 21, 1983 or the USAN

B. 1. Initial Submission: Dated December 21, 1982

2. Amendments: Please refer to Chemist Review No. 2 dated April 24, 1984 and the latest submission dated October 14, 1984 which is the subject of this Chemist Review.

C. Remarks:

This original new drug application, as amended through the date of Chemist Review No. 2, was approved October 31, 1985.

D. Conclusion:

The technical parts of the amended proposed package insert submitted October 14, 1985 have been reviewed and the following recommendations are presented for the applicant to use at the next printing.

1. Under DESCRIPTION the structural formula of the drug substance should be rotated to make it appear exactly as it is shown in the USAN 1985, page 215.

2. The missing methylene group and carbonyl carbon atom should be added for completeness.

The chemist will telephone the applicant on these matters as soon as this review is endorsed by the supervisory chemist.

Note: The telephone call was made November 14, 1985.

Nathan R. Rosenthal

Nathan R. Rosenthal, Ph.D.

cc:
Orig. NDA 18-830
HFN-83
HFN-110
HFN-110/CSO
HFN-110/NRosenthal/11-15-85
klb/12-12-85/03591
R/D Init.: RWolters/11-4-85

16.1

JUL 9 1984

Divison of Cardio-Renal Drug Products
Chemist Review No 2

Completed: April 24, 1984

A. 1. NDA 18-830 ORIGINAL NEW DRUG APPLICATION - AS AMENDED

Applicant: Riker Laboratories, Inc.
3M Center, Building 270, 3A-01
St. Paul, Minnesota 55144
Florence Wong, Pharm D.
Regulatory Specialist
(612) 736-2636

2. Product Names:

Proprietary: Tambocor(R) Tablets
Non-proprietary: Flecainide Acetate
Chemical: Benzamide, N-(2-piperidinylmethyl)-2,5-bis (2,2,2-trifluoroethoxy)-,monoacetate
Code: R-818
USAN: 20th Edition, page 238

3. Dosage Form: Tablet 100 mg or 200 mg strengths
Route of Administration: Mouth
Availability: Rx only

4. Pharmacological Category: Cardiac depressant (anti-arrhythmic)

5. Structural Formula: Please refer to Chemist Review No. 1 .

B. 1. Initial Submission: Dated December 21, 1982
Chemistry Review No. 1 completed July 21, 1983.

2. Amendments:

*August 29, 1983	- samples for methods validation
*November 11, 1983	- chemistry and labeling
December 7, 1983	- no chemistry
January 3, 1984	-
January 25, 1984	- no chemistry
February 14, 1984	- pharmacology and labeling
*February 15, 1984	- revised draft package insert: chemical name change
*March 19, 1984	- re meeting originally scheduled for 4-20-84; changed to 4-25-84.
March 19, 1984	- for Dr. David Zucker HFN 713
June 15, 1984	- no chemistry

3. Supporting Documents - Please refer to Chemist Review No. 1 .

4. Related Documents - Please refer to Chemist Review No. 1

C. Remarks: This Chemist Review is limited to those amendments, listed above, marked with an asterisk (*), that pertain to chemistry and technical labeling.

When Dr. Florence Wong of Riker Laboratories telephoned me December 30, 1983, I suggested that the November 11, 1983, submission be withdrawn without prejudice, and following approval of the application, Riker could submit the identical correspondence as a supplemental application. Dr. Wong replied that her firm prefers the submission to be regarded as an amendment to the original application. So be it.

Methods validation is being run by FDA Los Angeles District Office, and also by Division of Drug Chemistry HFN-420.

D. Conclusions:

When methods validation, establishment inspections and the small labeling deficiency, noted here are found to be satisfactory, then this application will be approvable from the standpoint of chemistry and technical labeling.

Nathan R. Rosenthal

Nathan R. Rosenthal, Ph.D.

cc:Orig. NDA 18-830
HFN-102 CSKumkumian
HFN-110
HFN-110/CSO
HFN-110/NRosenthal/4/24/84
jg/6/27/94/6894c

RC

7/6/84

Division of Cardio-Renal Drug Products
Chemist Review No. One

AUG 26 1983

Completed: July 21, 1983
(44th day since assignment)

A. 1. NDA 18-830 ORIGINAL NEW DRUG APPLICATION

Applicant: Riker Laboratories, Inc.
3M Center, Building 270, 3A-01
St. Paul, Minnesota 55144
Telephone: (612) 733-3439: Mrs. Deborah A. Weida
Manager,
Regulatory Affairs

2. Product Names:

Proprietary: Tambocor(R) Tablets

Nonproprietary: Flecainide Acetate (USAN name)

Chemical: Benzamide, N-(2-piperidinylmethyl)-2,5-bis (2,2,2-trifluorethoxy)-, monoacetate.

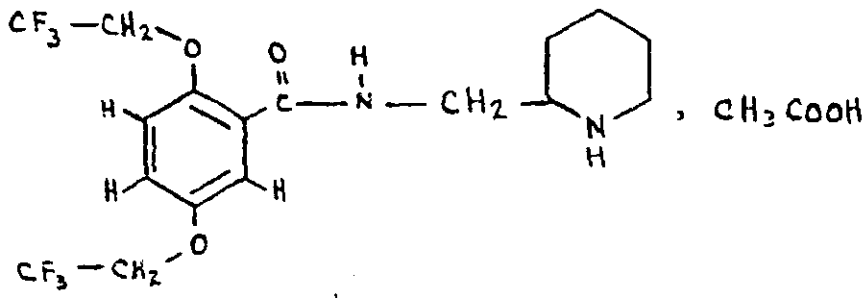
Code: R-818 or S-12697

USAN: 20th Edition, page 238

3. Dosage Form: Tablets 100 mg and 200 mg strength. Rx only. Route of administration: by mouth.

4. Pharmacological Category: Cardiac depressant (anti-arrhythmic) (compared with quinidine)

5. Structural Formula:



6. Classification: 1B "fast track"

B. 1. Initial Submission: Dated December 21, 1982
Received December 29, 1982
Assigned to this Chemist June 7, 1983

2. Amendments: Dated October 28, 1983

3. Supporting:

4. Related:

C. Remarks: On July 8, 1983 Mrs. D.A. Weida visited my office. It was requested that Riker will promptly provide the 3-way commitment pertaining to the submission of additional results of stability studies.

On July 21, 1983 I telephoned Florence Wong, Pharm D. to discuss the technical corrections needed on the draft labeling. Samples of the drug were requested. It is understood that the FDA may proceed with factory inspection at Northridge, California and Loughborough, England. However, the facility at Decatur, Alabama will be inspected at a later date since it is not now operating in the production of this drug.

D. Conclusion: Pending the firm conforming with our requests and satisfactory EIR and MV this original application is approvable.

Nathan R. Rosenthal

Nathan R. Rosenthal, Ph.D.

cc
Orig.
HFN-102
HFN-110
HFN-110/CSO
HFN-110/NRosenthal/7/21/83
sb/8/3/83/8/22/83/0194c
R/D: JLangston/7/28/83

[redacted]

9.1

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

DATE : AUG 17 1984

TO : Raymond J. Lipicky, M. D.
Acting Director in Division of Cardio-Renal Drug Products
(HFN-110).

FROM : Jerome P. Skelly, Ph. D.
Acting Director in Division of Biopharmaceutics
(HFN-220)

SUBJECT: Biopharmaceutics Recommendation of Approval
Flecainide Acetate
100, 200mg tablets

Riker Laboratories, Inc.
NDA 18-830

BACKGROUND

Flecainide Acetate, an antiarrhythmic drug, chemically is 2,5 - bis - (2,2,2,-trifluoroethoxy) - N - (2-piperidylmethyl) benzamide acetate. It is a white crystalline substance with a pKa of 9.3. The solubility in water at 37 C is 48.4 mg/ml. The following studies were reviewed in the submission:

1. R-818-049-01 (relative bioavailability study)
2. R-818-018-01 (multiple dosing study)
3. R-818-061-01 (single dose dose-proportionality study)
4. Chronic dosing study (Data submitted on January 27, 1984)
5. R-818-050-03 (radioisotope study)
6. Disease State Study
7. R-818-045-01 (interaction study)

OVERALL COMMENTS

1. Pharmacokinetics

For single intravenous dose (0.65 to 1.70 mg/kg) to healthy volunteers, the pharmacokinetics can be deiscribed as follows:

T1/2 = 14 hours (6.9 - 19.1)
Cl = 7.6 ml/min/kg. (4.6 - 12.1)
Vd = 8.7 L/kg (5.0 - 13.4)
Cl_r = 2.4 ml/min/kg
Protein binding = 33% to 41%
Concentration independent over therapeutic levels.

2. Bioavailability / Bioequivalence:

For single oral dose study (0.65 to 3.57 mg/kg), the pharmacokinetic parameters did not deviate from those of intravenous study and the absolute bioavailability was more than 90%. In the bioequivalence study to compare tablet, capsule and oral solution, the time to peak for capsule was 5.1h±26% and those for tablet and solution were 2.8h±39% and 2.2h±37% respectively. In other words, the absorption rate constants for capsule was smaller than those for tablet or solution (0.59 hr^{-1}±49% for capsule; 1.13 hr^{-1}±35% for tablet, 1.83 hr^{-1}±55% for solution). Following administratin of capsule, the peak level (164±48 ng/ml) was significantly lower than either tablet (192±57 ng/ml) or solution (204±49 ng/ml). The availabilities for the three formulations were similar.

3. Dose Proportionality

a. Following multiple oral dosage regimens for 7 days (1.12 to 2.83 mg/kg b.i.d.), 15 out of 16 subjects were able to reach steady-state on day 3. The steady state blood levels for 12 of 16 subjects were predictable by a linear model form single dose data. Subject #15 had steady-state plasma levels lower than values predicted by linear model. Three subjects had higher levels.

b. Single dose dose proportionality study (P-818-061-01) indicated that flecainide followed linear kinetics.

c. Chronic dosing studies indicated that plasma drug levels did not increase with time. However, one out of 84 patients studied had a trend of decreasing plasma levels over 20 months on the drug. The normalized volume decreased stowly from 3.40 ng/ml-mg to 0.31 ng/ml-mg.

4. Metabolism

A substantial amount of the Carbon-14 labeled drug was excreted in the urine as unchanged drug. Cumulative drug excretion varied from 35 to 50% of the dose of unchanged drug administered. The rate of urinary excretion of unchanged flecainide is moderately slow. The urinary excretion of meta-O-dealkylated flecainide (free and conjugated) accounts for about 11 to 16% of the dose. This metabolite is extensively conjugated; the ratio of total conjugated metabolite to metabolite free, in urine ranges from 2.3 to 5.9. The second major metabolite is 5-hydroxy-N-[2-(6-oxopiperidylmethyl)]-2-(2',2',2'-trifluoroethoxy) - benzamide. In one patient study, flecainide under little biliary excretion. There was no information as to enterohepatic recycling.

5. Disease States

Patients with premature ventricular contractions, renal disease, or congestive heart failure have longer flecainide half lives and slower clearance than normal subjects. The volume of distribution remains about the same for both normals and patients.

6. Interactions

a. During multiple oral dosage of flecainide to healthy subjects stabilized on a maintenance dose of digoxin, a 13%±19% (% C.V.) increase in plasma digoxin levels occurred at six hours postdose.

b. During coadministration of flecainide and propranolol, plasma flecainide levels are about 20% higher and propranolol levels are about 30% higher in comparison to control values.

c. Flecainide is not displaced from human plasma proteins in vitro by therapeutic levels of any of ten drugs (digoxin, propranolol, quinidine, procainamide, disopyramide, diazepam, and furosemide) which may be administered concomitantly with flecainide.

d. Food And/or Aluminum Hydroxide antacid do not affect pharmacokinetic parameters

7. Concentration & Effect

a. The minimal effective (greater than 90% suppression) concentration range was 245 to 980 ng/ml. After the final dose of flecainide, the meantime of arrhythmia recurrence to greater than 10% of control frequency was 14.8±5 hours.

b. Concentration - related prolongations of P.R. QRS and Q-Tc intervals were observed in all 11 patients of a study. Prior to abolition of ventricular arrhythmia, there was a progressive prolongation in the coupling interval (R-R') of the predominant ectopic focus. The degree of coupling interval prolongation was linearly related (r=0.61) to the plasma flecainide concentration. The extent of antiarrhythmic effect of flecainide was linearly related to both the extent of QRS prolongation (r=0.68) and to the plasma concentration (r=0.70).

8. Strengths

The firm intended to market both 100 and 200mg tablets (both strengths are composition proportional), however, the firm only performed 100mg bioavailability study. Since this drug follows linear kinetics, 200mg strength bioavailability study may not be required. The capsule formulation was used in bioequivalence study as well as pivotal therapeutic study, and the final market tablet formulation was used in bioequivalence as well as long term safety study.

CONCLUSION

The studies of NDA 18-830 submitted on March 8, 1983 have been found acceptable by the Division of Biopharmaceutics in regard to bioavailability / bioequivalence requirements. The application has fulfilled every necessary element of bioavailability / bioequivalence requirements provided that the firm agrees dissolution specification to be Q = in 60 minutes using USP method II at 50 rpm in 900 ml 0.075 N HCl.

Jerome P. Skelly
Division of Biopharmaceutics

FT initialed by H. Malinowski, Ph.D.

cc: NDA 18-830 orig., HFN-110, HFN-220(Skelly,Marlene), HFN-225(Huang), Chron, Drug, Review, and Division Files

JPS/kek:#2126x(7-31-84)

Flecainide Acetate
100, 200 mg tablets
NDA 18-830
Reviewer: Mei-Ying Huang, Ph.D.
Wang #2002x

Riker Laboratories, Inc.
St. Paul, Minnesota 53144
Submission Date:
June 12, 1984

AUG 17 1984

Review of a Dissolution Study

Background

1. Flecainide Acetate is an antiarrhythmic drug. It is soluble in water with an aqueous solubility at 37°C of 48.4 mg/ml and a pKa of 9.3. On March 8, 1983, Riker Laboratories, Inc. submitted its originl NDA 18-830 to the Agency. The *in vivo* biopharmaceutics studies were acceptable, yet, the *in vitro* dissolution that the Division of Biopharmaceutics recommended was different from what the firm pursued.

   FDA recommendation :

   Q = in 60 minutes
   USP method II at 50 rpm
   in 900 ml 0.075 N HCl

   Firm's Specification:

   Q = in 45 minutes
   USP method II at rpm
   in 900 ml 0.1N HCl

2. In the current submission, the firm provided 15 lots of dissolution data using FDA recommended method, and firm's own method.

Results

1. The dissolution results using 0.1N HCl, method II at rpm or 0.075 N HCl, method II at 50 rpm are shown in Table 1 and 2 respectively. In the *in vivo* bioavailability study, the Tmax's for capsule and tablet were 5.1 hr. ± 26% and 2.8 hr ± 39% respectively. In the *in vitro* study the capsules and tablets dissolve 53% ± 3.3 (S.D.) and 73% ± 11.4 (S.D.) in 0.075N HCl at 50 rpm in 30 minutes. However, the firm's proposed method was not able to pick up difference.

2. The individual results for the bioavailability study lot using 0.1N HCl at rpm or 0.075 N HCl at 50 rpm are shown in Table 4 and 15 respectively.

Comments

1. The firm should be informed to forward the commercial 100 and 200 mg tablets (300 units each) to Biopharmaceutics Laboratory Branch FOB Rm. 6076, HFD-524 200 C Street S.W. Washington, D.C. 20206

Conclusion -

The dissolution study submitted on June 12, 1984 has been found acceptable by the Divison of Biopharmaceutics. The Divison of Biopharmaceutics recommends dissolution specification be Q= in 60 minutes using USP method II at 50 rpm in 900 ml 0.075 N HCl. The firm should use the USP Acceptance Table criteria for this specification. The above recommendation as well as comment #1 should be forwarded to the firm.

M Y Huang 8/17/84

Mei-Ying Huang, Ph.D.
Pharmacokinetics Evaluation Branch I
(CR/SD) Drug Products

Initialed by H.Malinowski, Ph.D

cc: NDA 18-830 orig., HFN-110 (2), HFN-225 (Huang), Chron, Drug, Division and Review Files

MYH/dea/2002x (7/19/84)

Flecainide Acetate (TAMBOCOR)
100, 200 mg Tablets
NDA 18-830
Reviewer: Mei-Ying Huang, Ph.D.
Wang # 8177e

Riker Laboratories, Inc.
St. Paul, Minnesota 55144
Submission Date: March 8, 1983

9.1

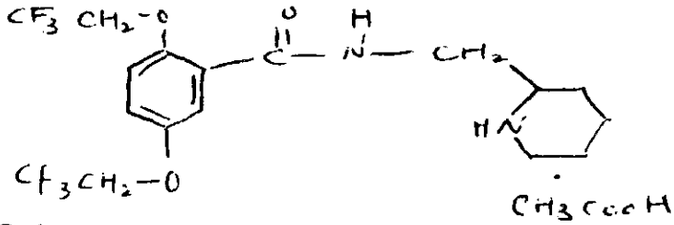
MAY - 4 1984

MAY 30 1984

REVIEW OF BIOAVAILABILITY/DOSE PROPORTIONALITY STUDIES

BACKGROUND

TAMBOCOR, an antiarrhythmic drug, chemically is 2.5-bis-(2, 2, 2, -trifluoroethoxy)-N-(2-piperidylmethyl) benzamide acetate. The structure formula is given below:



TAMBOCOR is a white crystalline substance with a pKa of 9.3. It is soluble in water with an aqueous solubility at 37°C of 48.4 mg/ml.

SUMMARY OF STUDIES

The pharmacokinetic parameters in normal volunteers or patients of the studies are described in Table 1.

(30)

FORMULATION

1. Capsule formulations were used in initial clinical trials.

2. K-1a formulation (Tablet) is the formulation submitted in this NDA.

ASSAY VALIDATION

The firm has validated the method for Flecainide and its metabolite.

PHAMACOKINETICS

The firm submitted many intravenous studies in this submission. They are summarized as follows:

STUDY*	n	DOSE	Tl/2 (hr)	Vd (L/kg)	Cl/F (ml/min/kg)	Clr (ml/min/kg)	F	Urinary Excretion %
R-818-001-01	8	0.5-2 i.v. mg/kg	11±0.08	7±0.6	7.7±0.8	------	--------	---------
R-818-005-01	8	60-120mg P.O.	14±1.8	-----	-----	------	0.95±0.07	---------
"	"	" i.v.	14±1.5	-----	-----	------	--------	---------
82-105-FRV-BE-002	5	2mg/kg i.v.	17.5±1.4	7.3±0.5	5.0±0.6	2.4±0.3	--------	38±2.6
81-105-FRO-BE-002	5	200mg P.O.	11.5±0.7	7.8±0.5	7.8±1.2	2.5±0.3	0.91±0.32	29±4.6

*Note that values in the table are mean ± SEM

BIOAVAILABILITY/BIOEQUIVALENCE STUDY

Study Number: R-818-049-01 Phase: I

Drug Name: Flecainide acetate (R-818)
Lot #PD1745 Tablet 100 mg, formulation K-1a
Lot #80-045A Cap 200 mg, formulation U-1p

Investigator:

Study Site:

Study Objectives:

1. To compare the relative rate and extent of flecainide absorption from the final tablet formulation to those from two reference formulations, a capsule and a solution; and

2. To assess the effect of food on flecainide absorption from the final tablet formulation.

Study Population: Eighteen healthy, adult male subjects.

Study Design: Open-label, metabolic and safety study using a randomized three-period crossover design with three formulations of oral flecainide, and a fourth period of tablets with food.

For metabolic evaluations, blood samples were obtained predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours following the 0800 hours drug administration for each study period.

To assess safety, physical examinations, ophthalmologic examinations, clinical laboratory tests, and 12-lead electrocardiograms were performed both prestudy and poststudy. Additional laboratory tests were performed on specimens obtained prior to each study period. A chest radiograph was also obtainded prestudy. Side effects were elicited at times of blood sampling.

Test Dosage: Single dose (200 mg) of flecainide per period as either one 200mg capsule, two 100 mg tablets, or 200mg powder dissolved in sterile water (30 ml).

Route of Drug Administration: Oral dose under fasting conditions for the first three study periods; oral tablets with food for Period 4.

Duration of Administration: Each subject received a single oral dose of flecainide during each study period with a seven-day washout period between doses.

RESULTS

1.	Plasma Profiles	--	See Fig. 2.1 — 2.9.
2.	AUCs	--	See Table 2.1
	AUCs.Beta		See Table 2.2
3.	Cmaxs	--	See Table 2.3
4.	Tmaxs	--	See Table 2.4
5.	T1/2	--	See Table 2.5
6.	75/75 Rule	--	See Table 2.6
7	k_a	--	See Table 2.7

The mean area under the plasma drug level versus time curve (AUC) (time zero to infinity) for the tablet, capsule and solution were 3170±1310 (±SD), 3240±1060 and 3300±873 ng hr/ml, respectively. The small differences in the AUC values were not significant ($p > 0.05$). Thus, the extents of flecainide absorption from the tablet, capsule and solution were comparable. The power of ANOVA to tell a % difference from reference solution at alpha of 0.05 was greater than 90%.

Peak drug levels (mean±SD) of 192±57 and 204±49 ng/ml following administration of the tablet and solution were seen at 2.8±1.1 and 2.2±0.8 hr, respectively. Neither the peak level nor the time to peak level was statistically different ($p > 0.05$). Following administration of the capsule, the peak level (164±48 ng/ml) was significantly lower ($p < 0.05$) and the time to peak level (5.1±1.3 hr) was significantly later ($p < 0.05$) than with either the tablet or solution.

The terminal plasma half-lives of flecainide following administration of the tablet, capsule, and solution averaged 10.2, 10.8, and 11.0 hr, respectively, and were not significantly different ($p > 0.05$) from each other.

When tablets were given with a meal, peak drug levels of 205±41 ng/ml were seen at 3.2±1.1 hr, which were not significantly different ($p > 0.05$) from the corresponding values seen with tablets administered on an empty stomach. The terminal flecainide half-lives averaged 10.2±2.7hr when tablets were given under fasting conditions and 11.3±2.9 hr when tablets were administered with a meal. This half-life difference, although small, was significantly different for the fasting and non-fasting treatment periods, the AUC values were normalized for intrasubject differences in elimination rate by multiplying each AUC by the corresponding terminal elimination rate constant, β. The average AUC·B values were 212±54 (±SD) and 224±56 ng hr/ml 1/hr for the tablets administered under fasting and non-fasting conditions, respectively. The difference in the AUC.B values was not significant ($p > 0.05$). Thus, when tablets were given with food, both the rate and extent of absorption were comparable.

DOSE - PROPORTIONALITY STUDY

Study Number: R-818-018-01 Phase: I

Drug Name: Flecainilde acetate (R-818)

Investigator

Study Site:

Study Objectives: To directly determine the plasma levels of flecainide acetate during multiple oral dosage regimens for seven days, to assess the potential influence of multiple oral dosage on the plasma pharmacokinetics of flecainide (induction or inhibition of drug elimination), and to determine the safety and tolerance of multiple oral doses of flecainide in healthy human subjects.

Study Population: Sixteen healthy, adult male subjects.

Study Design: Open-label, metabolic and safety study with increasing muliptle oral dosage regimens.

To obtain plasma pharmacokinetic data for the first dose (Day 1) and for the final dose (Day 7), blood samples were obtained just prior to, and at 2, 4, 6, 8, 12, and 24 hours following each of these two single doses; to monitor plasma drug levels during the twice daily dosage regimens on Days 2 through 6 of the study, blood samples were also obtained just prior to, and at 2 and 4 hours after the morning doses.

Physical examinations, 12-lead electrocardiograms, ophthalmologic examinations, and clinical laboratory tests were performed both prestudy and poststudy to assess safety. Tolerance was monitored during the seven day dosage period by obtaining vital signs and a 12-lead electrocardiogram prior to each morning dose; in addition, vital signs and a one-minute rhythm strip (lead II) were obtained and side effects were elicited at 4 hours following each morning and evening dose.

Test Dosage: The seven day multiple oral dosage regimen consisted of the following: On Day 1, a single morning dose (0800 hours); on Days 2 through 6, a morning dose (0800 hours) and an evening dose (2000 hours); and on Day 7, a single morning dose (0800 hours). The first four subjects received 80 mg of flecainide acetate per dose; the next four subjects received 120 mg per dose; the last four subjects received 180 mg per dose. Capsule formulations U-1a (40 mg), U-1b (50 mg), and U-1c (60 mg) were used.

Route of Drug Administration:
Oral dosing was under fasting conditions on Days 1 and 7, and under non-fasting conditions on Days 2 through 6.

Duration of Administration:
Each subject received a total oral doses over a seven day period.

RESULTS

The individual data and predicted plasma levels were shown in Fig. 3.1 ~ 3.16.

Following the first oral dose (Day 1), the plasma half-life of flecainide during the terminal elimination phase was found to range from 9.1 to 19.1 hours (mean, 12.9 hours) for the 16 subjects; after the final dose (Day 7), the plasma half-life was found to range from 9.5 to 23.1 hours (mean, 16.2 hours, see Table 3.1). The plasma levels at steady-state for subjects #7, #10 and #11 were higher than predicted values. The AUC ratio (first dose/final dose) for the subject #7 was 1.2 yet those for subjects #10 and #11 were 0.6 and 0.7 respectively (see Table 3.2). It was worth noticing that the plasma levels for these 3 subjects reached steady-state on day 3. The plasma levels at steady-state for subject #15 were lower than predicted values. The firm demonstrated that a significant correlation (r=0.715, two-sided p=0.002) between dose (mg/kg) and the area after the final dose was found for the 16 subjects and concluded that plasma levels were reasonably proportional to dose at steady-state over a range in multiple oral dosage regimens of 1.1 to 2.8 mg/kg bid (see Fig. 3.17).

In study R-818-026-01, renal clearance of unchanged flecainide was found to average about 170 ml/min in the 16 healthy subjects. In comparison to plasma clearance (mean, 730 ml/min), renal clearance of flecainide accounts for about 25% of total body clearance. Fig. 3.18 indicated the renal clearance was constant over the plasma levels of 0 - 250 ng/ml.

STUDY R-818-061-01

Objective

Single dose dose-proportionality study

Procedure

This was an open-label study included four periods using a randomized four-period crossover design with a seven day washout period between each singel dose. each subject received the following dose/route treatments under fasting conditions:

1. intravenous dose of 100 mg over 10 minutes
2. oral dose of 100 mg (1 tablet, formulation K-1a)
3. oral dose of 200 mg (2 tablets)
4. oral dose of 300 mg (3 tablets).

Results

1. The AUCs and AUC ratios for each individual are found in Table 3.3. Mean (±SD) plasma AUC values (zero to infinity) were 1441 ± 497, 3225 ± 1052, and 5355 ± 1660 ng. hours/ml for the 100, 200, and 300 mg doses, respectively. The mean AUC ratios (200/100 mg doses and 300/100 mg doses, respectively) were 2.29 ± 0.38 and 3.81 ± 0.61. The mean AUC ratios for the 300/200 mg doses were 1.67 ± 0.15.

2. Peak plasma levels and time to peak level of flecainide acetate following oral administration of singel 100, 200 or 300 mg doses are shown in Table 3.4. The peak plasma levels are 91 ± 26 ng/ml, 189 ± 56 ng/ml and 286 ± 61 ng/ml for 100 mg, 200 mg and 300 mg doses respectively.

3. Plasma half-life, plasma clearance and volume of distribution are shown in Table 3.5. The terminal plasma half-life or flecainide following administration of 100, 200, and 300 mg doses averaged (± SD) 10.1 ± 3.2, 10.9 ± 3.4, and 11.7 ± 3.4 hours, respectively. The trend of slower drug elimination from plasma with increasing dose was also apparent in the plasma clearance results. Mean (± SD) plasma clearance values following administration of 100, 200, and 300 mg doses were 17.02 ± 6.70, 14.75 ± 4.28, and 13.25 ± 3.76 ml/min/kg respectively and were significantly different ($p < 0.05$) from each other.

CHRONIC DOSING STUDY (Data submitted on January 27, 1984)

Objective

To determine whether plasma flecainide levels increase with time on drug

Database

The study population consisted of patients from the following study groups:

R-818-030-02,	(dose ranging)
R-818-031-02,	(long-term followup to 030-02)
R-818-030-02,	(dose ranging)
R-818-031-02,	(long-term followup to 030-03)
R-818-030-02,	(quinidine comparison)
R-818-031-02,	(long-term followup to 032-02)
R-818-035,	(long-term open-labels)

To best determine long term effects patients were chosen who were on drug three months or longer and had plasma level data available

Method

The SAS procedure REG was used to fit a linear model with time (months on drug) as the independent variable and plasma flecainide level (adjusted for 12 hour trough and total daily dose) as the dependent variable. The slope in this model indicates the rate of change of the adjusted plasma levels over time. Separate regression analysis were done for each patient within a study group.. A weighted average slope was calculated for each study group. Individual patient slopes were weighted by the number of observations that were used in the particular regression. Greater number of observations gave a better estimate of the slope. For each study group the average slopes were tested. Using a t-test to determine if they were significantly different from zero. The length of time a given patient was followed is also important in estimating the slope.

Results

1. The results of the analysis are summarized in Table 3.6 ~Table 3.8. For each study group the average slope was not significantly different from zero as indicated by the large p values. Based on analysis of the studies, plasma levels do not increase with time on drug.

2. There was a trend in decreasing plasma levels over 20 months of drug administration in the patient #5 of study 035-01 (see Table 3.9)

METABOLISM

Study Number: R-818-050-03 Phase: I

Drug Name: Flecainide acetate (R-818)

Investigator:

Study Site:

Study Objectives: Following a single oral dose of carbon-14 labelled flecainide, the objectives were to determine the rate and extent of excretion for flecainide and/or it metabolites in urine and feces, to determine the concentrations and time course of elimination from plasma for flecainide and/or its metabolites, and to obtain urine specimens containing carbon-14 labelled metabolites of flecainide for isolation and identification.

Study Population: Four subjects (three males and one female) completed this study. All subjects were judged to be in good health.

Study Design: Open-label, special metabolic and safety study with a single oral dose.

For metabolic evaluations, blood samples were obtained predose and periodically during the 144 hours following dosage. Complete urine and fecal collections were obtained predose (24 hours) and until on-line monitoring of urinary radioactivity indicated that levels of carbon-14 had returned to near background concentrations.

Test Dosage: Single, 200 mg (91.8 uCi) dose of carbon-14 labelled flecainide acetate in a capsule (formulation U-lo).

Route of Drug Administration:
Oral dosage under fasting conditions.

Duration of Administration
Each subject received a single, oral dose of carbon-14 labelled flecainide.

RESULTS

1. Individual comulative urinary excretions-see Fig 4.1-4.4.

2. Individual fecal and urinary excretions-see Fig.4.5.

3. Individual plasma profiles - See Fig. 4.6-4.9.

There was about 90% of radioactivity recovered in urine of which about 30% to 40% of dose administered was unchanged drug. The study with a T-tube inserted into the common bile duct indicated that there was little bile secretion as parent compound. However, there was no information as to enterohepatic recycling.

DISEASE STATE

1. Patients with premature ventricular contractions T 1/2:longer than normals (20.3 hrs vs 14 hrs).
Vd:similar to normals
Overall, the rate of flecainide elimination from plasma of patients with PVC's was slower than that for healthy subjects.

2. Patients with renal failures
T 1/2:longer than normals (16.8 hrs for moderate renal failure, 26 hrs. for end stage renal failure).
Vd:Similar to normals
Overall, the rate of flecainide elimination from plasma was somewhat slower in patients with moderate renal failure and was markedly slower in some patients with end-stage disease.

Disease State, cont.

3. Patients with congestive heart failure The rate of flecainide elimination from plasma of CHF patients was somewhat slower than that for healthy subjects.

For all comparisons, see Table 5.1 and 5.2.

INTERACTIONS

Study Number: R-818-045-01 Phase: I

Drug Name: Flecainide acetate (R-818)

Investigator

Study Site:

Study Objective: To determine the possible effect of flecainide acetate on steady-state plasma digoxin concentrations in healthy, male subjects on a maintenance dose of digoxin.

Study Population: Fifteen healthy, adult male subjects. Two other subjects (Nos. 4 and 15) entered the study, but were discontinued.

Study Design: Open-label, metabolic and safety study with multiple oral dosage (digoxin and flecainide).

For metabolic evaluations, blood samples were obtained predose and at 6 hours following the 0800 hours drug (flecainide and/or digoxin) dose on Days 9, 10, 13, 15, 19, and 22 for digoxin level determination and on Days 13, 15, 19, and 22 for flecainide measurement.

To assess safety, physical examinations, ophthalmologic examinations, clinical laboratory tests, and 12-lead electrocardiograms were performed both prestudy and poststudy. Tolerance was monitored by periodically obtaining vital signs and one-minute ECG rhythm strips; side effects were also elicited.

Test Dosage: Multiple, 0.25 mg doses of digoxin (Lanoxin^{R} tablets) once daily (0800 hours) and multiple, 200 mg doses of flecainide acetate (100 mg/tablet, formulation U-1e) twice daily (0800 and 2000 hours).

Route of Drug Administration:
Oral dosage under non-fasting conditions.

Duration of Administration:

Each subject received a single daily oral dose of digoxin for 22 consecutive days and twice daily oral doses of flecainide for 5 days (Days 11 through 15).

Results

During coadministration of flecainide to healthy, adult male subjects stabilized on a maintenance dose of digoxin, only a small, but at sometimes statistically significant, increase in plasma digoxin levels occurred. See Fig. 6.1.

Plasma flecainide levels were found to be within the range associated with suppression of PVCs.

DISSOLUTION

1. The data for dissolutions in different media -water, 0.05 M HCl or 0.1 M HCl was shown in Fig. 7.1. Also see Table 7.1

2. The dissolution results (in 0.1N HCl at 50 rpm rpm) for the bioavailability study lots were shown in Table 7.2 and 7.5.

3. The dissolution results for 100mg tablet, 200mg tablet, and 200mg capsule using 0.075N HCl at 50 rpm are shown in table 7.6.

4. The proposed dissolution specification by the firm is as follows:

   USP Method II at rpm in 0.1 N HCl with Q= in 45 minutes.

EFFECT VS CONCENTRATIONS

See two literatures attached

I. Suppression of Resistant Ventricular Arrhythmias by Twice Daily Dosing with Flecainide (Am. J. Cardial 48 (#6): 1133-1140, 1981).

II. Relationship between Plasma Concentrations and Suppression of Ventricular Extrasystoles by Flecainide Acetate. A New Antiarrlythmic, in Patients. (Arzeniem-Forsch/Drug Res. 32(1), 2, 155-159 1982).

LABELING

The pharmacokinetics portion of the labeling is acceptable, however, precaution should be taken in patients with liver dysfunction since about 60% of the drug will be eliminated through metabolism.

OVERALL COMMENTS

1. Pharmacokinetics:

For single intravenous dose (0.65 to 1.70 mg/kg) to healthy volunteers, the pharmacokinetics can be deiscribed as follows:

T1/2 = 14 hours (6.9 - 19.1)
Cl = 7.6 ml/min/kg. (4.6 -12.1)
Vd = 8.7 L/kg (5.0 - 13.4)
Cl_r = 2.4 ml/min/kg
Protein binding = 33% to 41%
Concentration independent over therapeutic levels.

2. Bioavailability/Bioequivalence:

For single oral dose study (0.65 to 3.57 mg/kg), the pharmacokinetic parameters did not deviate from those of intravenous study and the absolute bioavailability was more than 90%. In the bioequivalence study to compare tablet, capsule and oral solution, the time to peak for capsule was 5.1h±26% and those for tablet and solution were 2.8h±39% and 2.2h± 37% respectively. In other words, the absorption rate constants for capsule was smaller than those for tablet or solution (0.59 hr^{-1}±49% for capsule; 1.13 hr^{-1}±35% for tablet, 1.83 hr^{-1}±55% for solution). Following administratin of capsule, the peak level (164±48 ng/ml) was significantly lower than either tablet (192±57 ng/ml) or solution (204±49 ng/ml). The availabilities for the three formulations were similar.

3. Dose Proportionality

a. Following multiple oral dosage regimens for 7 days (1.12 to 2.83 mg/kg b.i.d.), 15 out of 16 subjects were able to reach steady-state on day 3. Subject #15 had steady-state plasma levels lower than values predicted by linear model.

b. Single dose dose proportionality study (P-818-061-01) indicated that flecainide followed linear kinetics.

c. Chronic dosing studies indicated that plasma levels did not increase with time on drug. However, one out of 84 patients studied had a trend of decreasing plasma levels over 20 months on drug (see Table 3.9).

4. Metabolism

A substantial amount of the Carbon-14 excreted in urine is accounted for as unchanged drug: the cumulative percent of dose excreted in urine as unchanged drug ranges from 35% to 50%. The rate of urinary excretion of unchanged flecainide is moderately slow. The urinary excretion of meta-O-dealkylated flecainide (free and conjugated) acccunts for about 11 to 16% of the dose. This metabolite is extensively conjugated; the ratio of total conjugated metabolite to metabolite free, in urine ranges from 2.3 to 5.9. The second major metabolite is 5-hydroxy-N-[2-(6-oxopiperidylmethyl)]-2-(2', 2', 2'-trifluoroethoxy) - benzamide. In one patient study, flecainide undergoes little biliary excretion. There was no information as to enterohepatic recycling.

5. Disease States

Patients with premature ventricular contractions or renal disease, or congestive heart failure will have longer half lives of flecainide than in normal subjects.

6. Interactions

a. During multiple oral dosage of flecainide to healthy subjects stabilized on a maintenance dose of digoxin, a 13%±19% (% C.V.) increase in plasma digoxin levels occurred at six hours postdose.

b. During coadministration of flecainide and propranolol, plasma flecainide levels are about 20% higher and propranolol levels are about 30% higher in comparison to control values.

c. Flecainide is not displaced from human plasma proteins in vitro by therapeutic levels of any of ten drugs (digoxin, propranol, quinidine, procainamide, disopyramide, diazepam, and furosemide) which may be administered concomitantly with flecainide.

d. Food or Aluminum Hydroxide antacid do not affect pharmacokinetic parameters.

7. Concentration & Effect

a. The minimal effective (greater than 90% suppression) concentration range was 245 to 980 ng/ml. After the final dose of flecainide, the meantime of arrhythmia recurrence to greater than 10% of control frequency was 14.8±5 hours.

Concentration & Effect, cont.

b. Concentration - related prolongations of P.R. QRS and Q-Tc intervals were observed in all 11 patients of a study. Prior to abolition of ventricular arrhythmia, there was a progressive prolongation in the coupling interval (R-R') of the predominant ectopic focus. The degree of Coupling interval prolongation was linearly related (r=0.61) to the plasma flecainide concentration. The extent of antiarrhythmic effect of flecainide was linearly related to both the extent of QRS prolongation (r=0.68) and to the plasma concentration (r=0.70).

8. Strengths

The firm intended to market both 100 and 200 mg tablets (both strengths are composition proportional, however, the firm only performed 100 mg bioavailability study. Since this drug follows linear kinetics, 200 mg strength bioavailability study may not be required. The capsule formulation was used in bioequivalence study as well as pivotal therapeutic study, and the final market tablet formulation was used in bioequivalence as well as long term safety study.

CONCLUSION - Studies - Acceptable
Application - Acceptable

The studies of NDA 18-830 submitted on March 8, 1983 have been found acceptable by the Division of Biopharmaceutics in regard to bioavailability/bioequivalence requirements. The application has fufilled every necessary element of bioavailability/bioequivalence requirements provided that the firm agrees regulatory dissolution specification to be Q= in 60 minutes using USP method II at 50 rpm in 900 ml 0.075 N HCl. The firm should use the USP Acceptance Table criteria for this specification. However, the firm can of course continue using its own specification (USP method II in 0.1 N HCl at rpm with Q= at 45 min) as the firm's in-house dissolution specification. The above recommendation should be forwarded to the firm.

M. Y. Huang 5/1/84

Mei-Ying Huang, Ph.D.
Pharmacokinetics Branch

RD INITIALED BY H. MALINOWSKI, Ph.D.
FT INITIALED BY H. MALINOWSKI, Ph.D. HCM

cc: Orig., HFN-110 (2 copies), HFN-525 (Huang), Drug, Chron, Division and Review Files.

MYH:cas:11-17-83:dea:3/28/84:8177e:

NDA 18830

w/D

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

32.1

6-7-96

Food and Drug Administration
Rockville MD 20857

NDA 18-830

JUL 11 1996

3M Pharmaceuticals
Attention: Ms. Mary L. Mathisen
3M Center, Bldg. 270-3A-01
St. Paul, MN 55144-1000

Dear Ms. Mathisen:

We acknowledge the receipt of your communication dated June 7, 1996 requesting withdrawal of the 200 mg tablet in your approved new drug application (NDA) for Tambocor (flecainide acetate) 50, 100, 150 and 200 mg Tablets.

As you requested, we have initiated withdrawal of the 200 mg tablet strength of Tambocor as provided under 21 CFR 314.152. We will publish a notice in the Federal Register withdrawing the approval of the 200 mg tablet strength of Tambocor. The notice will state that you have voluntarily requested withdrawal of this tablet strength because you have not manufactured or distributed this dosage strength under the NDA.

Because you have voluntarily requested the withdrawal of the 200 mg tablet strength of Tambocor, we consider you to have waived your opportunity for a hearing concerning this product in accord with 21 CFR 314.150(c).

To avoid being billed under the Prescription Drug User Fee Act of 1992 (PDUFA) for a listed drug, we suggest that you notify the Product Information Management Branch to remove your product from the approved products list by October of this year. You may contact them at:

Food and Drug Administration
Product Information Management Branch, HFD-058
5600 Fishers Lane
Rockville, MD 20857
(301) 594-1086

If you decide to resubmit your application at a future time, under section 736(a)(1)(c) of the Prescription Drug User Fee Act of 1992 (PDUFA), the submission will be subject to a fee.

Sincerely yours,

7/11/96
Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-7/Regulatory Policy Staff
HFD-80/DDIR
HFD-110
HFD-110/DWillard/6/20/96;6/24/96 D. Willard 7/1/96
sb/6/20/96;7/9/96
R/D: JShort/6/24/96
RWolters/6/26/96
SChun/6/24/96
NMorgenstern/7/5/96

WITHDRAWAL OF APPROVAL INITIATED (WI)

(200 mg tablet only)

3M Pharmaceuticals

3M Center, Building 270-3A-01
St. Paul, MN 55144-1000

(612) 733-9125

3M

CORRESP
SNC

June 7, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products HFD-110
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Document Control Room 16B-30

Subject: **NDA 18-830 Tambocor™ (flecainide acetate) tablets**
Discontinuation of 200 mg tablet

ORIGINAL

Dear Sir/Madam:

In accordance with 21 CFR 314.150(c), 3M Pharmaceuticals, the sponsor, hereby withdraws the 200 mg tablet strength under NDA 18-830 without prejudice to refiling. This product has not been marketed by 3M Pharmaceuticals.

The Tambocor 200 mg tablets have not been manufactured or distributed by 3M Pharmaceuticals.

We trust that this withdrawal of the 200 mg strength tablet under NDA 18-830 will be kept confidential under the provisions of 21 CFR 314.430.

Sincerely,

Mary L Mathisen

Mary L. Mathisen
Regulatory Affairs