CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 75135

Trade Name Pacerone 200mg Tablets

Generic Name Amiodarone Hydrochloride Tablets 200mg

Sponsor Upsher-Smith Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 75135

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75135

APPROVAL LETTER

ANDA 75-135

APR 2 0

Upsher-Smith Laboratories, Inc.
Attention: Mark B. Halvorsen
14905 23rd Avenue North
Minneapolis, MN 55447-4709

Dear Sir:

This is in reference to your abbreviated new drug application dated May 19, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Pacerone™ (Amiodarone Hydrochloride Tablets), 200 mg.

Reference is also made to your amendments dated December 31, 1997; and January 30, March 30, and April 24, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Amiodarone Hydrochloride Tablets, 200 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Cordarone® Tablets, 200 mg of Wyeth Ayerst Laboratories Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-040). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-040) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research

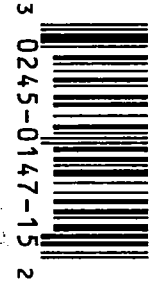
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75135

FINAL PRINTED LABELING

Pacerone™ (Amiodarone HCl) Tablets, 200 mg

Bottle Label for 500 Tablets



NDC 0245-0147-15
500 Tablets

PACERONE™

(Amiodarone HCl)

200 mg

UPSHER-SMITH

Each tablet contains: Amiodarone HCl 200 mg

Usual adult dosage: See package insert for full prescribing information.

Store at room temperature, approximately 25°C (77°F). Keep tightly closed. Protect from light and moisture. Dispense in a tight, light-resistant container with a child-resistant closure.

Keep out of reach of children.

CAUTION: Federal law prohibits dispensing without prescription.

SEALED FOR YOUR PROTECTION.

Manufactured by
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447

Certain manufacturing operations have been performed by other firms.

Rev. 1297

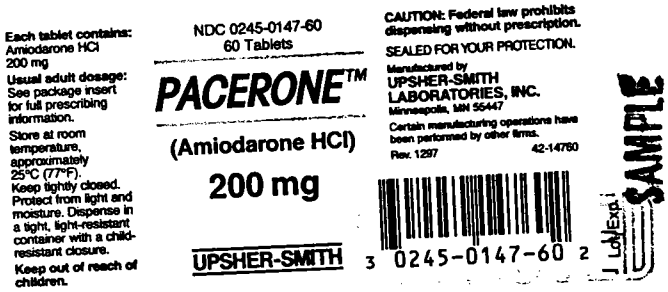
42-14715

Lot/Exp.

SAMPLE

Pacerone™ (Amiodarone HCl) Tablets, 200 mg

Bottle Label for 60 Tablets



Pacerone™ (Amiodarone HCl) Tablets, 200 mg

Unit Dose Card for 10 Tablets (Blister Text)

NOTE: Blister text, including the specific lot number and expiration date, are printed on the paper-backed foil during the unit-dose packaging operation.

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APPROVED

245-147 PACERONE ™ (Amiodarone HCl) 200mg Tablet Rev. 0197 Lot	Upsher-Smith Minneapolis, MN 55447 Certain manufacturing operations have been performed by other firms. Exp.	245-147 PACERONE ™ (Amiodarone HCl) 200mg Tablet Rev. 0197 Lot	Upsher-Smith Minneapolis, MN 55447 Certain manufacturing operations have been performed by other firms. Exp.
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SAMPLE

UPSHER-SMITH

200 mg

(Amiodarone HCl)

PACERONE™

Unit Dose, 100 Tablets

NDC 0245-0147-01

N 3 0245-0147-01 5

PACERONE 200 mg

Store at room temperature, approximately 25°C (77°F).

Protect from light and moisture. This carton may be used to help protect contents from light.

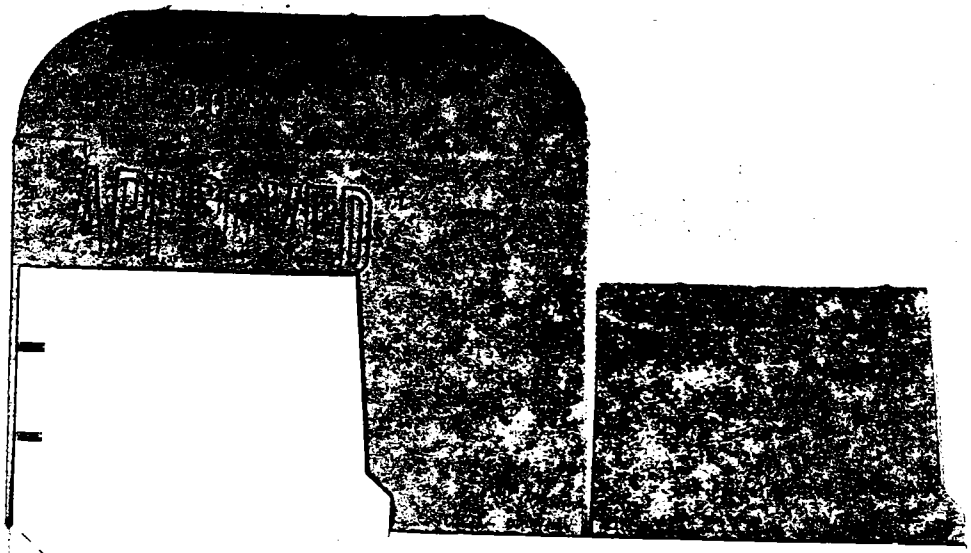
Multiple dispensing package. This unit-dose package is not child-resistant and, therefore, is not for household use. If dispensed for outpatient use, a child-resistant container should be utilized.

Keep out of reach of children.

Manufactured by
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447

Certain manufacturing operations have been performed by other firms.

Rev. 1297 49-14701



NDC 0245-0147-01
Unit Dose, 100 Tablets

PACERONE™

Each tablet contains:
Amiodarone HCl 200 mg

Usual adult dosage: See package insert for full prescribing information.

CAUTION: Federal law prohibits dispensing without prescription.

(Amiodarone HCl)

200 mg

UPSHER-SMITH

PACERONE™
(Amiodarone HCl)
Tablets, 200 mg

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APPROVED

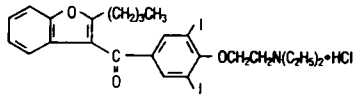
47001297
PACERONE™
(Amiodarone HCl)
Tablets, 200mg

Description

Pacerone™ (Amiodarone HCl) is a member of a new class of antiarrhythmic drugs with predominantly Class III (Vaughan Williams' classification) effects, available for oral administration as pink, scored tablets containing 200 mg of amiodarone hydrochloride. The inactive ingredients present are lactose monohydrate, magnesium stearate, povidone, pregelatinized corn starch, sodium starch glycolate, stearic acid, FD&C Red 40 and FD&C Yellow 6.

Amiodarone hydrochloride, the active ingredient in Pacerone™, is a benzofuran derivative: 2-butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone, hydrochloride. It is not chemically related to any other available antiarrhythmic drug.

The structural formula is as follows:



$C_{25}H_{29}I_2NO_3 \cdot HCl$ Molecular Weight: 681.8

Amiodarone HCl is a white to cream-colored crystalline powder. It is slightly soluble in water, soluble in alcohol, and freely soluble in chloroform. It contains 37.3% iodine by weight.

Clinical Pharmacology

ELECTROPHYSIOLOGY/MECHANISMS OF ACTION

In animals, amiodarone HCl is effective in the prevention or suppression of experimentally induced arrhythmias. The antiarrhythmic effect of amiodarone may be due to at least two major properties: 1) a prolongation of the myocardial cell-action potential duration and refractory period and 2) noncompetitive alpha- and beta-adrenergic inhibition.

Amiodarone prolongs the duration of the action potential of all cardiac fibers while causing minimal reduction of dV/dt (maximal upstroke velocity of the action potential). The refractory period is prolonged in all cardiac tissues. Amiodarone increases the cardiac refractory period without influencing resting membrane potential, except in automatic cells where the slope of the prepotential is reduced, generally reducing automaticity. These electrophysiologic effects are reflected in a decreased sinus rate of 15 to 20%, increased PR and QT intervals of about 10%, the development of U-waves, and changes in T-wave contour. These changes should not require discontinuation of Pacerone™ as they are evidence of its pharmacological action, although amiodarone can cause marked sinus bradycardia or sinus arrest and heart block. On rare occasions, QT prolongation has been associated with worsening of arrhythmia (see **"Warnings"**).

HEMODYNAMICS

In animal studies and after intravenous administration in man, amiodarone relaxes vascular smooth muscle, reduces peripheral vascular resistance (afterload), and slightly increases cardiac index. After oral dosing, however, amiodarone produces no significant change in left ventricular ejection fraction (LVEF), even in patients with depressed LVEF. After acute intravenous dosing in man, amiodarone may have a mild negative inotropic effect.

PHARMACOKINETICS

Following oral administration in man, amiodarone is slowly and variably absorbed. The bioavailability of amiodarone is approximately 50%, but has varied between 35 and 65% in various studies. Maximum plasma concentrations are attained 3 to 7 hours after a single dose. Despite this, the onset of action may occur in 2 to 3 days, but more commonly takes 1 to 3 weeks, even with loading doses. Plasma concentrations with chronic dosing at 100 to 600 mg/day are approximately dose proportional, with a mean 0.5 mg/L increase for each 100 mg/day. These means, however, include considerable individual variability.

Amiodarone has a very large but variable volume of distribution, averaging about 60 L/kg, because of extensive accumulation in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. One major metabolite of amiodarone, desethylamiodarone, has been identified in man; it accumulates to an even greater extent in almost all tissues. The pharmacological activity of this metabolite, however, is not known. During chronic treatment, the plasma ratio of metabolite to parent compound is approximately one.

The main route of elimination is via hepatic excretion into bile, and some enterohepatic recirculation may occur. However, its kinetics in patients with hepatic insufficiency have not been elucidated. Amiodarone has a very low plasma clearance with negligible renal excretion, so that it does not appear necessary to modify the dose in patients with renal failure. In patients with renal impairment, the plasma concentration of amiodarone is not elevated. Neither amiodarone nor its metabolite is dialyzable.

In patients, following discontinuation of chronic oral therapy, amiodarone has been shown to have a biphasic elimination with an initial one-half reduction of plasma levels after 2.5 to 10 days. A much slower terminal plasma-elimination phase shows a half-life of the parent compound ranging from 26 to 107 days, with a mean of approximately 53 days and most patients in the 40- to 55-day range. In the absence of a loading-dose period, steady-state plasma concentrations, at constant oral dosing, would therefore be reached between 130 and 535 days, with an average of 265 days. For the metabolite, the mean plasma-elimination half-life was approximately 61 days. These data probably reflect an initial elimination of drug from well-perfused tissue (the 2.5- to 10-day half-life phase), followed by a terminal phase representing extremely slow elimination from poorly perfused tissue compartments such as fat.

The considerable intersubject variation in both phases of elimination, as well as uncertainty as to what compartment is critical to drug effect, requires attention to individual responses once arrhythmia control is achieved with loading doses because the correct maintenance dose is determined, in part, by the elimination rates. Daily maintenance doses of Pacerone™ should be based on individual patient requirements (see **"Dosage and Administration"**).

Amiodarone and its metabolite have a limited transplacental transfer of approximately 10 to 50%. The parent drug and its metabolite have been detected in breast milk.

Amiodarone is highly protein-bound (approximately 96%).

Although electrophysiologic effects, such as prolongation of QTc, can be seen within hours after a parenteral dose of amiodarone, effects on abnormal rhythms are not seen before 2 to 3 days and usually require 1 to 3 weeks, even when a loading dose is used. There may be a continued increase in effect for longer periods still. There is evidence that the time to effect is shorter when a loading-dose regimen is used.

Consistent with the slow rate of elimination, antiarrhythmic effects persist for weeks or months after Pacerone™ is discontinued, but the time of recurrence is variable and unpredictable. In general, when the drug is resumed after recurrence of the arrhythmia, control is established relatively rapidly compared to the initial response, presumably because tissue stores were not wholly depleted at the time of recurrence.

PHARMACODYNAMICS

There is no well-established relationship of plasma concentration to effectiveness, but it does appear that concentrations much below 1 mg/L are often ineffective and that levels above 2.5 mg/L are generally not needed. Within individuals, dose reductions and ensuing decreased plasma concentrations can result in loss of arrhythmia control. Plasma-concentration measurements can be used to identify patients whose levels are unusually low, and who might benefit from a dose increase, or unusually high, and who might have dosage reduction in the hope of minimizing side effects. Some observations have suggested a plasma concentration, dose, or dose/duration relationship for side effects such as pulmonary fibrosis, liver-enzyme elevations, corneal deposits and facial pigmentation, peripheral neuropathy, gastrointestinal and central nervous system effects.

Indications and Usage

Pacerone™ is indicated for the management of life-threatening recurrent ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients who have not responded to adequate doses of other available antiarrhythmics or when alternative agents could not be tolerated.

1. Recurrent ventricular fibrillation.

2. Recurrent hemodynamically unstable ventricular tachycardia.

As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of amiodarone HCl favorably affects survival.

Pacerone™ (Amiodarone HCl) should be used only by physicians familiar with and with access to (directly or through referral) the use of all available modalities for treating recurrent life-threatening ventricular arrhythmias, and who have access to appropriate monitoring facilities, including in-hospital and ambulatory continuous electrocardiographic monitoring and electrophysiologic techniques.

Because of the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential exacerbation of the arrhythmia, initiation of therapy with Pacerone™ should be carried out in the hospital.

Contraindications

Pacerone™ is contraindicated in severe sinus-node dysfunction, causing marked sinus bradycardia; second- and third-degree atrioventricular block; and when episodes of bradycardia have caused syncope (except when used in conjunction with a pacemaker).

Pacerone™ is contraindicated in patients with a known hypersensitivity to the drug.

Warnings

Pacerone™ is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.

Amiodarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10 to 17% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with amiodarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, amiodarone can exacerbate the arrhythmia, e.g., by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2 to 5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2 to 5%. All of these events should be manageable in the proper clinical setting in most cases. Although the frequency of such proarrhythmic events does not appear greater with amiodarone than with many other agents used in this population, the effects are prolonged when they occur.

Even in patients at high risk of arrhythmic death, in whom the toxicity of amiodarone is an acceptable risk, Pacerone™ poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilize alternative agents first.

The difficulty of using Pacerone™ effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of Pacerone™ is given, and a response generally requires at least one week, usually two or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 required dose reduction and 18 required at least temporary discontinuation because of adverse effects, and several series have reported 15 to 20% overall frequencies of discontinuation due to adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when Pacerone™ must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when amiodarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

MORTALITY

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had had myocardial infarctions 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 encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.

The applicability of these results to other populations (e.g., those without recent myocardial infarctions) or to amiodarone-treated patients is uncertain. While definitive controlled trials with amiodarone are in progress, pooled analysis of small controlled studies in patients with structural heart disease (including post-myocardial infarction) have not shown excess mortality in the amiodarone-treated population.

PULMONARY TOXICITY

Amiodarone may cause a clinical syndrome of cough and progressive dyspnea accompanied by functional, radiographic, gallium-scan, and pathological data consistent with pulmonary toxicity, the frequency of which varies from 2 to 7% in most published reports, but is as high as 10 to 17% in some reports. Therefore, when Pacerone™ therapy is initiated, a baseline chest X-ray and pulmonary-function tests, including diffusion capacity, should be performed. The patient should return for a history, physical exam, and chest X-ray every 3 to 6 months.

Preexisting pulmonary disease does not appear to increase the risk of developing pulmonary toxicity; however, these patients have a poorer prognosis if pulmonary toxicity does develop.

Pulmonary toxicity secondary to amiodarone seems to result from either indirect or direct toxicity as represented by hypersensitivity pneumonitis or interstitial/alveolar pneumonitis, respectively.

Hypersensitivity pneumonitis usually appears earlier in the course of therapy, and rechallenging these patients with Pacerone™ results in a more rapid recurrence of greater severity. Bronchoalveolar lavage is the procedure of choice to confirm this diagnosis, which can be made when a T suppressor/cytotoxic (CD8-positive) lymphocytosis is noted. Steroid therapy should be instituted and Pacerone™ therapy discontinued in these patients.

Interstitial/alveolar pneumonitis may result from the release of oxygen radicals and/or phospholipidosis and is characterized by findings of diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung biopsy specimens. Phospholipidosis (foamy cells, foamy macrophages), due to inhibition of phospholipase, will be present in most cases of amiodarone-induced pulmonary toxicity; however, these changes also are present in approximately 50% of all patients on amiodarone therapy. These cells should be used as markers of therapy, but not as evidence of toxicity. A diagnosis of amiodarone-induced interstitial/alveolar pneumonitis should lead, at a minimum, to dose reduction or, preferably, to withdrawal of the Pacerone™ to establish reversibility, especially if other acceptable antiarrhythmic therapies are available. Where these measures have been instituted, a reduction in symptoms of amiodarone-induced pulmonary toxicity was usually noted within the first week, and a clinical improvement was greatest in the

plasma concentrations, at constant oral dosing, would therefore be reached between 10 and 535 days, with an average of 265 days. For the metabolite, the mean plasma-elimination half-life was approximately 61 days. These data probably reflect an initial elimination of drug from well-perfused tissue (the 2.5- to 10-day half-life phase), followed by a terminal phase representing extremely slow elimination from poorly perfused tissue compartments such as fat.

The considerable intersubject variation in both phases of elimination, as well as uncertainty as to what compartment is critical to drug effect, requires attention to individual responses once arrhythmia control is achieved with loading doses because the correct maintenance dose is determined, in part, by the elimination rates. Daily maintenance doses of Pacerone™ should be based on individual patient requirements (see **"Dosage and Administration"**).

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Consistent with the slow rate of elimination, antiarrhythmic effects persist for weeks or months after Pacerone™ is discontinued, but the time of recurrence is variable and unpredictable. In general, when the drug is resumed after recurrence of the arrhythmia, control is established relatively rapidly compared to the initial response, presumably because tissue stores were not wholly depleted at the time of recurrence.

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MONITORING EFFECTIVENESS

Predicting the effectiveness of any antiarrhythmic agent in long-term prevention of recurrent ventricular tachycardia and ventricular fibrillation is difficult and controversial, with highly qualified investigators recommending use of ambulatory monitoring, programmed electrical stimulation with various stimulation regimens, or a combination of these, to assess response. There is no present consensus on many aspects of how best to assess effectiveness, but there is a reasonable consensus of some aspects:

1. If a patient with a history of cardiac arrest does not manifest a hemodynamically unstable arrhythmia during electrocardiographic monitoring prior to treatment, assessment of the effectiveness of amiodarone requires some provocative approach, either exercise or programmed electrical stimulation (PES).

2. Whether provocation is also needed in patients who do manifest their life-threatening arrhythmia spontaneously is not settled, but there are reasons to consider PES or other provocation in such patients. In the fraction of patients whose PES-inducible arrhythmia can be made noninducible by amiodarone (a fraction that has varied widely in various series from less than 10% to almost 40%, perhaps due to different stimulation criteria), the prognosis has been almost uniformly excellent, with very low recurrence (ventricular tachycardia or sudden death) rates. More controversial is the meaning of continued inducibility. There has been an impression that continued inducibility in amiodarone patients may not foretell a poor prognosis but, in fact, many observers have found greater recurrence rates in patients who remain inducible than in those who do not. A number of criteria have been proposed, however, for identifying patients who remain inducible but who seem likely nonetheless to do well on Pacerone™. These criteria include increased difficulty of induction (more stimuli or more rapid stimuli), which has been reported to predict a lower rate of recurrence, and ability to tolerate the induced ventricular tachycardia without severe symptoms, a finding that has been reported to correlate with better survival but not with lower recurrence rates. While these criteria require confirmation and further study in general, *easier* inducibility or *poorer* tolerance of the induced arrhythmia should suggest consideration of a need to revise treatment.

Several predictors of success not based on PES have also been suggested, including complete elimination of all nonsustained ventricular tachycardia on ambulatory monitoring and very low premature ventricular-beat rates (less than 1 VPB/1,000 normal beats).

While these issues remain unsettled for amiodarone, as for other agents, the prescriber of Pacerone™ should have access to (direct or through referral), and familiarity with, the full range of evaluatory procedures used in the care of patients with life-threatening arrhythmias.

It is difficult to describe the effectiveness rates of Pacerone™, as these depend on the specific arrhythmia treated, the success criteria used, the underlying cardiac disease of the patient, the number of drugs tried before resorting to Pacerone™, the duration of follow-up, the dose of amiodarone HCl, the use of additional antiarrhythmic agents, and many other factors. As amiodarone has been studied principally in patients with refractory life-threatening ventricular arrhythmias, in whom drug therapy must be selected on the basis of response and cannot be assigned arbitrarily, randomized comparisons with other agents or placebo have not been possible. Reports of series of treated patients with a history of cardiac arrest and mean follow-up of one year or more have given mortality (due to arrhythmia) rates that were highly variable, ranging from less than 5% to over 30%, with most series in the range of 10 to 15%. Overall arrhythmia-recurrence rates (fatal and nonfatal) also were highly variable (and, as noted above, depended on response to PES and other measures), and depend on whether patients who do not seem to respond initially are included. In most cases, considering only patients who seemed to respond well enough to be placed on long-term treatment, recurrence rates have ranged from 20 to 40% in series with a mean follow-up of a year or more.

Indications and Usage

Because of the life-threatening side effects and the substantial management difficulties associated with amiodarone use (see **"Warnings"** below), Pacerone™ (Amiodarone HCl) is indicated only for the treatment of the following documented, life-threatening recurrent ventricular

groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.

The applicability of these results to other populations (e.g., those without recent myocardial infarctions) or to amiodarone-treated patients is uncertain. While definitive controlled trials with amiodarone are in progress, pooled analysis of small controlled studies in patients with structural heart disease (including post-myocardial infarction) have not shown excess mortality in the amiodarone-treated population.

PULMONARY TOXICITY

Amiodarone may cause a clinical syndrome of cough and progressive dyspnea accompanied by functional, radiographic, gallium-scan, and pathological data consistent with pulmonary toxicity, the frequency of which varies from 2 to 7% in most published reports, but is as high as 10 to 17% in some reports. Therefore, when Pacerone™ therapy is initiated, a baseline chest X-ray and pulmonary-function tests, including diffusion capacity, should be performed. The patient should return for a history, physical exam, and chest X-ray every 3 to 6 months.

Preexisting pulmonary disease does not appear to increase the risk of developing pulmonary toxicity; however, these patients have a poorer prognosis if pulmonary toxicity does develop.

Pulmonary toxicity secondary to amiodarone seems to result from either indirect or direct toxicity as represented by hypersensitivity pneumonitis or interstitial/alveolar pneumonitis, respectively.

Hypersensitivity pneumonitis usually appears earlier in the course of therapy, and rechallenging these patients with Pacerone™ results in a more rapid recurrence of greater severity. Bronchoalveolar lavage is the procedure of choice to confirm this diagnosis, which can be made when a T suppressor/cytotoxic (CD8-positive) lymphocytosis is noted. Steroid therapy should be instituted and Pacerone™ therapy discontinued in these patients.

Interstitial/alveolar pneumonitis may result from the release of oxygen radicals and/or phospholipidosis and is characterized by findings of diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung biopsy specimens. Phospholipidosis (foamy cells, foamy macrophages), due to inhibition of phospholipase, will be present in most cases of amiodarone-induced pulmonary toxicity; however, these changes also are present in approximately 50% of all patients on amiodarone therapy. These cells should be used as markers of therapy, but not as evidence of toxicity. A diagnosis of amiodarone-induced interstitial/alveolar pneumonitis should lead, at a minimum, to dose reduction or, preferably, to withdrawal of the Pacerone™ to establish reversibility, especially if other acceptable antiarrhythmic therapies are available. Where these measures have been instituted, a reduction in symptoms of amiodarone-induced pulmonary toxicity was usually noted within the first week, and a clinical improvement was greatest in the first two to three weeks. Chest X-ray changes usually resolve within two to four months. According to some experts, steroids may prove beneficial.

Prednisone in doses of 40 to 60 mg/day or equivalent doses of other steroids have been given and tapered over the course of several weeks depending upon the condition of the patient. In some cases rechallenge with amiodarone at a lower dose has not resulted in return of toxicity. Recent reports suggest that the use of lower loading and maintenance doses of amiodarone are associated with a decreased incidence of amiodarone-induced pulmonary toxicity.

In a patient receiving Pacerone™, any new respiratory symptoms should suggest the possibility of pulmonary toxicity, and the history, physical exam, chest X-ray, and pulmonary-function tests (with diffusion capacity) should be repeated and evaluated. A 15% decrease in diffusion capacity has a high sensitivity but only a moderate specificity for pulmonary toxicity; as the decrease in diffusion capacity approaches 30%, the sensitivity decreases but the specificity increases. A gallium scan also may be performed as part of the diagnostic workup.

Fatalities, secondary to pulmonary toxicity, have occurred in approximately 10% of cases. However, in patients with life-threatening arrhythmias, discontinuation of Pacerone™ therapy due to suspected drug-induced pulmonary toxicity should be undertaken with caution, as the most common cause of death in these patients is sudden cardiac death. Therefore, every effort should be made to rule out other causes of respiratory impairment (i.e., congestive heart failure with Swan-Ganz catheterization if necessary, respiratory infection, pulmonary embolism, malignancy, etc.) before discontinuing Pacerone™ in these patients. In addition, bronchoalveolar lavage, trans-bronchial lung biopsy and/or open lung biopsy may be necessary to confirm the diagnosis, especially in those cases where no acceptable alternative therapy is available.

If a diagnosis of amiodarone-induced hypersensitivity pneumonitis is made, Pacerone™ should be discontinued, and treatment with steroids should be instituted. If a diagnosis of amiodarone-induced interstitial/alveolar pneumonitis is made, steroid therapy should be instituted and, preferably, Pacerone™ discontinued or, at a minimum, reduced in dosage. Some cases of amiodarone-induced interstitial/alveolar pneumonitis may resolve following a reduction in Pacerone™ dosage in conjunction with the administration of steroids. In some patients, rechallenge at a lower dose has not resulted in return of interstitial/alveolar pneumonitis; however, in some patients (perhaps because of severe alveolar damage) the pulmonary lesions have not been reversible.

WORSENED ARRHYTHMIA

Amiodarone, like other antiarrhythmics, can cause serious exacerbation of the presenting arrhythmia, a risk that may be enhanced by the presence of concomitant antiarrhythmics. Exacerbation has been reported in about 2 to 5% in most series, and has included new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and polymorphic ventricular tachycardia associated with QT prolongation (Torsade de Pointes). In addition, amiodarone has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2 to 4% of patients.

LIVER INJURY

Elevations of hepatic enzyme levels are seen frequently in patients exposed to amiodarone and in most cases are asymptomatic. If the increase exceeds three times normal, or doubles in a patient with an elevated baseline, discontinuation of Pacerone™ or dosage reduction should be considered. In a few cases in which biopsy has been done, the histology has resembled that of alcoholic hepatitis or cirrhosis. Hepatic failure has been a rare cause of death in patients treated with amiodarone.

PREGNANCY: PREGNANCY CATEGORY D

Amiodarone has been shown to be embryotoxic (increased fetal resorption and growth retardation) in the rat when given orally at a dose of 200 mg/kg/day (18 times the maximum recommended maintenance dose). Similar findings have been noted in one strain of mice at a dose of 5 mg/kg/day (approximately 1/2 the maximum recommended maintenance dose) and higher, but not in a second strain nor in the rabbit at doses up to 100 mg/kg/day (9 times the maximum recommended maintenance dose).

3

Neonatal hypo- or hyperthyroidism
Amiodarone can cause fetal harm when administered to a pregnant woman. Although amiodarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism. If Pacerone™ (Amiodarone HCl) is used during pregnancy, or if the patient becomes pregnant while taking Pacerone™, the patient should be apprised of the potential hazard to the fetus.

In general, Pacerone™ should be used during pregnancy only if the potential benefit to the mother justifies the unknown risk to the fetus.

Precautions

CORNEAL MICRODEPOSITS; IMPAIRMENT OF VISION
Corneal microdeposits appear in the majority of adults treated with amiodarone. They are usually discernible only by slit-lamp examination, but give rise to symptoms such as visual halos or blurred vision in as many as 10% of patients. Corneal microdeposits are reversible upon reduction of dose or termination of treatment. Asymptomatic microdeposits are not a reason to reduce dose or discontinue treatment.

PHOTOSENSITIVITY
Amiodarone has induced photosensitization in about 10% of patients; some protection may be afforded by the use of sun-barrier creams or protective clothing. During long-term treatment, a blue-gray discoloration of the exposed skin may occur. The risk may be increased in patients of fair complexion or those with excessive sun exposure, and may be related to cumulative dose and duration of therapy.

THYROID ABNORMALITIES
Amiodarone inhibits peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause increased thyroxine levels, decreased T_3 levels, and increased levels of inactive reverse T_3 (rT_3) in clinically euthyroid patients. It is also a potential source of large amounts of inorganic iodine. Because of its release of inorganic iodine, or perhaps for other reasons, amiodarone can cause either hypothyroidism or hyperthyroidism. Thyroid function should be monitored prior to treatment and periodically thereafter, particularly in elderly patients, and in any patient with a history of thyroid nodules, goiter, or other thyroid dysfunction. Because of the slow elimination of amiodarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for several weeks or even months following Pacerone™ withdrawal.

Hypothyroidism has been reported in 2 to 4% of patients in most series, but in 8 to 10% in some series. This condition may be identified by relevant clinical symptoms and particularly by elevated serum TSH levels. In some clinically hypothyroid amiodarone-treated patients, free thyroxine index values may be normal. Hypothyroidism is best managed by Pacerone™ dose reduction and/or thyroid hormone supplement. However, therapy must be individualized, and it may be necessary to discontinue Pacerone™ in some patients.

Hyperthyroidism occurs in about 2% of patients receiving amiodarone, but the incidence may be higher among patients with prior inadequate dietary iodine intake. Amiodarone-induced hyperthyroidism usually poses a greater hazard to the patient than hypothyroidism because of the possibility of arrhythmia breakthrough or aggravation. In fact, IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Hyperthyroidism is best identified by relevant clinical symptoms and signs, accompanied usually by abnormally elevated levels of serum T_3 RIA, and further elevations of serum T_4, and a subnormal serum TSH level (using a sufficiently sensitive TSH assay). The finding of a flat TSH response to TRH is confirmatory of hyperthyroidism and may be sought in equivocal cases. Since arrhythmia breakthroughs may accompany amiodarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of Pacerone™. The institution of antithyroid drugs, beta-adrenergic blockers and/or temporary corticosteroid therapy may be necessary. The action of antithyroid drugs may be especially delayed in amiodarone-induced thyrotoxicosis because of substantial quantities of preformed thyroid hormones stored in the gland. Radioactive iodine therapy is contraindicated because of the low radioiodine uptake associated with amiodarone-induced hyperthyroidism. Experience with thyroid surgery in this setting is extremely limited, and this form of therapy runs the theoretical risk of inducing thyroid storm. Amiodarone-induced hyperthyroidism may be followed by a transient period of hypothyroidism.

SURGERY
Hypotension Postbypass: Rare occurrences of hypotension upon discontinuation of cardiopulmonary bypass during open-heart surgery in patients receiving amiodarone have been reported. The relationship of this event to Pacerone™ therapy is unknown.

Adult Respiratory Distress Syndrome (ARDS): Postoperatively, rare occurrences of ARDS have been reported in patients receiving amiodarone therapy who have undergone either cardiac or noncardiac surgery. Although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. Until further studies have been performed, it is recommended that FiO_2 and the determinants of oxygen delivery to the tissues (e.g., SaO_2, PaO_2) be closely monitored in patients on amiodarone.

LABORATORY TESTS
Elevations in liver enzymes (SGOT and SGPT) can occur. Liver enzymes in patients on relatively high maintenance doses should be monitored on a regular basis. Persistent significant elevations in the liver enzymes or hepatomegaly should alert the physician to consider reducing the maintenance dose of Pacerone™ or discontinuing therapy.

Amiodarone alters the results of thyroid-function tests, causing an increase in serum T_4 and serum reverse T_3, and a decline in serum T_3 levels. Despite these biochemical changes, most patients remain clinically euthyroid.

DRUG INTERACTIONS
Although only a small number of drug-drug interactions with amiodarone have been explored formally, most of these have shown such an interaction. The potential for other interactions should be anticipated, particularly for drugs with potentially serious toxicity, such as other antiarrhythmics. If such drugs are needed, their dose should be reassessed and, where appropriate, plasma concentration measured.

In view of the long and variable half-life of amiodarone, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of Pacerone™.

Cyclosporine
Concomitant use of amiodarone and cyclosporine has been reported to produce persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.

Digitalis
Administration of amiodarone to patients receiving digoxin therapy regularly results in an increase in the serum digoxin concentration that may reach toxic levels with resultant clinical toxicity. **On initiation of Pacerone™, the need for digitalis therapy should be reviewed and the dose reduced by approximately 50% or discontinued.** If digitalis treatment is continued, serum levels should be closely monitored and patients observed for clinical evidence of toxicity. These precautions probably should apply to digitoxin administration as well.

Anticoagulants
Potentiation of warfarin-type anticoagulant response is almost always seen in patients receiving amiodarone and can result in serious or fatal bleeding. **The dose of the anticoagulant should be reduced by one-third to one-half, and prothrombin times should be monitored closely.**

Antiarrhythmic Agents
Other antiarrhythmic drugs, such as quinidine, procainamide, disopyramide, and phenytoin

LABOR AND DELIVERY
It is not known whether the use of Pacerone™ during labor or delivery has any immediate or delayed adverse effects. Preclinical studies in rodents have not shown any effect of amiodarone on the duration of gestation or on parturition.

NURSING MOTHERS
Amiodarone is excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug. Nursing offspring of lactating rats administered amiodarone have been shown to be less viable and have reduced body-weight gains. Therefore, when Pacerone™ therapy is indicated, the mother should be advised to discontinue nursing.

PEDIATRIC USE
The safety and effectiveness of Pacerone™ in pediatric patients have not been established.

Adverse Reactions
Adverse reactions have been very common in virtually all series of patients treated with amiodarone HCl for ventricular arrhythmias with relatively large doses of drug (400 mg/day and above), occurring in about three-fourths of all patients and causing discontinuation in 7 to 18%. The most serious reactions are pulmonary toxicity, exacerbation of arrhythmia, and rare serious liver injury (see "**Warnings**"), but other adverse effects constitute important problems. They are often reversible with dose reduction and virtually always reversible with cessation of amiodarone treatment. Most of the adverse effects appear to become more frequent with continued treatment beyond six months, although rates appear to remain relatively constant beyond one year. The time and dose relationships of adverse effects are under continued study.

Neurologic problems are extremely common, occurring in 20 to 40% of patients and including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy; they are rarely a reason to stop therapy and may respond to dose reductions.

Gastrointestinal complaints, most commonly nausea, vomiting, constipation, and anorexia, occur in about 25% of patients but rarely require discontinuation of drug. These commonly occur during high-dose administration (i.e., loading dose) and usually respond to dose reduction or divided doses.

Asymptomatic corneal microdeposits are present in virtually all adult patients who have been on drug for more than 6 months. Some patients develop eye symptoms of halos, photophobia, and dry eyes. Vision is rarely affected and drug discontinuation is rarely needed.

Dermatological adverse reactions occur in about 15% of patients, with photosensitivity being most common (about 10%). Sunscreen and protection from sun exposure may be helpful, and drug discontinuation is not usually necessary. Prolonged exposure to amiodarone occasionally results in a blue-gray pigmentation. This is slowly and occasionally incompletely reversible on discontinuation of drug but is of cosmetic importance only.

Cardiovascular adverse reactions, other than exacerbation of the arrhythmias, include the uncommon occurrence of congestive heart failure (3%) and bradycardia. Bradycardia usually responds to dosage reduction but may require a pacemaker for control. CHF rarely requires drug discontinuation. Cardiac conduction abnormalities occur infrequently and are reversible on discontinuation of drug.

The following side-effect rates are based on a retrospective study of 241 patients treated for 2 to 1,515 days (mean 441.3 days).

The following side effects were each reported in 10 to 33% of patients:
Gastrointestinal: Nausea and vomiting.

The following side effects were each reported in 4 to 9% of patients:
Dermatologic: Solar dermatitis/photosensitivity.
Neurologic: Malaise and fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias.
Gastrointestinal: Constipation, anorexia.
Ophthalmologic: Visual disturbances.
Hepatic: Abnormal liver-function tests.
Respiratory: Pulmonary inflammation or fibrosis.

The following side effects were each reported in 1 to 3% of patients:
Thyroid: Hypothyroidism, hyperthyroidism.
Neurologic: Decreased libido, insomnia, headache, sleep disturbances.
Cardiovascular: Congestive heart failure, cardiac arrhythmias, SA node dysfunction.
Gastrointestinal: Abdominal pain.
Hepatic: Nonspecific hepatic disorders.
Other: Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities.

The following side effects were each reported in less than 1% of patients:
Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension, and cardiac conduction abnormalities.

Rare occurrences of hepatitis, cholestatic hepatitis, cirrhosis, optic neuritis, epididymitis, vasculitis, pseudotumor cerebri, and thrombocytopenia have been reported in patients receiving amiodarone.

In surveys of almost 5,000 patients treated in open U.S. studies and in published reports of treatment with amiodarone HCl, the adverse reactions most frequently requiring discontinuation of drug included pulmonary infiltrates of fibrosis, paroxysmal ventricular tachycardia, congestive heart failure, and elevation of liver enzymes. Other symptoms causing discontinuations less often included visual disturbances, solar dermatitis, blue skin discoloration, hyperthyroidism, and hypothyroidism.

Overdosage
There have been a few reported cases of amiodarone HCl overdose in which 3 to 8 grams were taken. There were no deaths or permanent sequelae. Animal studies indicate that amiodarone HCl has a high oral LD_{50} (>3,000 mg/kg).

In addition to general supportive measures, the patient's cardiac rhythm and blood pressure should be monitored and if bradycardia ensues, a B-adrenergic agonist or a pacemaker may be used. Hypotension with inadequate tissue perfusion should be treated with positive inotropic and/or vasopressor agents. Neither amiodarone nor its metabolite is dialyzable.

Dosage and Administration
BECAUSE OF THE UNIQUE PHARMACOKINETIC PROPERTIES, DIFFICULT DOSING SCHEDULE, AND SEVERITY OF THE SIDE EFFECTS IF PATIENTS ARE IMPROPERLY MONITORED, PACERONE™ SHOULD BE ADMINISTERED ONLY BY PHYSICIANS WHO ARE EXPERIENCED IN THE TREATMENT OF LIFE-THREATENING ARRHYTHMIAS WHO ARE THOROUGHLY FAMILIAR WITH THE RISKS AND BENEFITS OF AMIODARONE THERAPY, AND WHO HAVE ACCESS TO LABORATORY FACILITIES CAPABLE OF ADEQUATELY MONITORING THE EFFECTIVENESS AND SIDE EFFECTS OF TREATMENT.

In order to insure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for administration of Pacerone™ has not been determined. Individual patient titration is suggested according to the following guidelines.

For life-threatening ventricular arrhythmias, such as ventricular fibrillation or hemodynamically unstable ventricular tachycardia: Close monitoring of the patients is indicated during the loading phase, particularly until risk of recurrent ventricular tachycardia or fibrillation has abated. Because of the serious nature of the arrhythmia and the lack of predictable time course of effect, loading should be performed in a hospital setting. Loading doses of 800 to 1,600 mg/day are required for 1 to 3 weeks (occasionally longer) until initial therapeutic

Concomitant use of amiodarone and cyclosporine has been reported to produce persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.

Digitalis

Administration of amiodarone to patients receiving digoxin therapy regularly results in an increase in the serum digoxin concentration that may reach toxic levels with resultant clinical toxicity. **On initiation of Pacerone™, the need for digitalis therapy should be reviewed and the dose reduced by approximately 50% or discontinued.** If digitalis treatment is continued, serum levels should be closely monitored and patients observed for clinical evidence of toxicity. These precautions probably should apply to digitoxin administration as well.

Anticoagulants

Potentiation of warfarin-type anticoagulant response is almost always seen in patients receiving amiodarone and can result in serious or fatal bleeding. **The dose of the anticoagulant should be reduced by one-third to one-half, and prothrombin times should be monitored closely.**

Antiarrhythmic Agents

Other antiarrhythmic drugs, such as quinidine, procainamide, disopyramide, and phenytoin, have been used concurrently with amiodarone.

There have been case reports of increased steady-state levels of quinidine, procainamide, and phenytoin during concomitant therapy with amiodarone. In general, any added antiarrhythmic drug should be initiated at a lower than usual dose with careful monitoring.

In general, combination of Pacerone™ with other antiarrhythmic therapy should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to amiodarone. During transfer to Pacerone™, the dose levels of previously administered agents should be reduced by 30 to 50% several days after the addition of Pacerone™, when arrhythmia suppression should be beginning. The continued need for the other antiarrhythmic agent should be reviewed after the effects of amiodarone have been established, and discontinuation ordinarily should be attempted. If the treatment is continued, these patients should be particularly carefully monitored for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias, as Pacerone™ is continued. In Pacerone™ treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

Pacerone™ should be used with caution in patients receiving beta-blocking agents or calcium antagonists because of the possible potentiation of bradycardia, sinus arrest, and AV block; if necessary, Pacerone™ can continue to be used after insertion of a pacemaker in patients with severe bradycardia or sinus arrest.

SUMMARY OF DRUG INTERACTIONS WITH PACERONE™

Concomitant Drug	Interaction: Onset (days)	Interaction: Magnitude	Recommended Dose Reduction of Concomitant Drug
Warfarin	3 to 4	Increases prothrombin time by 100%	↓ 1/3 to 1/2
Digoxin	1	Increases serum concentration by 70%	↓ 1/2
Quinidine	2	Increases serum concentration by 33%	↓ 1/3 to 1/2 (or discontinue)
Procainamide	<7	Increases plasma concentration by 55%; NAPA* concentration by 33%	↓ 1/3 (or discontinue)

*NAPA = n-acetyl procainamide.

ELECTROLYTE DISTURBANCES

Since antiarrhythmic drugs may be ineffective or may be arrhythmogenic in patients with hypokalemia, any potassium or magnesium deficiency should be corrected before instituting Pacerone™ therapy.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Amiodarone HCl reduced fertility of male and female rats at a dose level of 90 mg/kg/day (8 times highest recommended human maintenance dose).

Amiodarone caused a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors was greater than control even at the lowest dose level of amiodarone HCl tested, i.e., 5 mg/kg/day or approximately equal to 1/2 the highest recommended human maintenance dose.

Mutagenicity studies (Ames, micronucleus, and lysogenic tests) with amiodarone were negative.

PREGNANCY: PREGNANCY CATEGORY D

See **"Warnings"**.

BECAUSE OF THE UNIQUE PHARMACOKINETIC PROPERTIES OF AMIODARONE, ITS TOXICITY PROFILE, AND SEVERITY OF THE SIDE EFFECTS IF PATIENTS ARE IMPROPERLY MONITORED, PACERONE™ SHOULD BE ADMINISTERED ONLY BY PHYSICIANS WHO ARE EXPERIENCED IN THE TREATMENT OF LIFE-THREATENING ARRHYTHMIAS WHO ARE THOROUGHLY FAMILIAR WITH THE RISKS AND BENEFITS OF AMIODARONE THERAPY, AND WHO HAVE ACCESS TO LABORATORY FACILITIES CAPABLE OF ADEQUATELY MONITORING THE EFFECTIVENESS AND SIDE EFFECTS OF TREATMENT.

In order to insure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for administration of Pacerone™ has not been determined. Individual patient titration is suggested according to the following guidelines.

For life-threatening ventricular arrhythmias, such as ventricular fibrillation or hemodynamically unstable ventricular tachycardia: Close monitoring of the patients is indicated during the loading phase, particularly until risk of recurrent ventricular tachycardia or fibrillation has abated. Because of the serious nature of the arrhythmia and the lack of predictable time course of effect, loading should be performed in a hospital setting. Loading doses of 800 to 1,600 mg/day are required for 1 to 3 weeks (occasionally longer) until initial therapeutic response occurs. (Administration of Pacerone™ in divided doses with meals is suggested for total daily doses of 1,000 mg or higher, or when gastrointestinal intolerance occurs.) If side effects become excessive, the dose should be reduced. Elimination of recurrence of ventricular fibrillation and tachycardia usually occurs within 1 to 3 weeks, along with reduction in complex and total ventricular ectopic beats.

Upon starting Pacerone™ therapy, an attempt should be made to gradually discontinue prior antiarrhythmic drugs (see **"Precautions**, DRUG INTERACTIONS"). When adequate arrhythmia control is achieved, or if side effects become prominent, Pacerone™ dose should be reduced to 600 to 800 mg/day for one month and then to the maintenance dose, usually 400 mg/day (see **"Clinical Pharmacology**, MONITORING EFFECTIVENESS"). Some patients may require larger maintenance doses, up to 600 mg/day, and some can be controlled on lower doses. Pacerone™ may be administered as a single daily dose, or in patients with severe gastrointestinal intolerance, as a b.i.d. dose. In each patient, the chronic maintenance dose should be determined according to antiarrhythmic effect as assessed by symptoms, Holter recordings, and/or programmed electrical stimulation and by patient tolerance. Plasma concentrations may be helpful in evaluating nonresponsiveness or unexpectedly severe toxicity (see **"Clinical Pharmacology"**).

The lowest effective dose should be used to prevent the occurrence of side effects. In all instances, the physician must be guided by the severity of the individual patient's arrhythmia and response to therapy.

When dosage adjustments are necessary, the patient should be closely monitored for an extended period of time because of the long and variable half-life of amiodarone and the difficulty in predicting the time required to attain a new steady-state level of drug. Dosage suggestions are summarized below:

	Loading Dose (Daily)	Adjustment and Maintenance Dose (Daily)	
Ventricular Arrhythmias	1 to 3 weeks	~1 month	usual maintenance
	800 to 1,600 mg	600 to 800 mg	400 mg

How Supplied

Pacerone™ (Amiodarone HCl) Tablets, 200 mg, are available in bottles of 60 tablets (NDC 0245-0147-60), bottles of 500 tablets (NDC 0245-0147-15), and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each) (NDC 0245-0147-01).

Pacerone™ Tablets are pink, round, flat-faced, scored, uncoated tablets, debossed with "P_{200}" on the unscored side, and "U-S" above and "0147" below the score on the reverse side.

Storage

Store at room temperature, approximately 25°C (77°F). Protect from light and moisture.

Dispense in a tight, light-resistant container with a child-resistant closure.

Caution: Federal law prohibits dispensing without prescription.

Manufactured by
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
Certain manufacturing operations have been performed by other firms.
Rev. 1297
40-14700

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75135

CHEMISTRY REVIEW(S)

9/J

1. CHEMISTRY REVIEW NO. 2

2. ANDA 75-135

3. NAME AND ADDRESS OF APPLICANT
Upsher-Smith Laboratories, Inc.
14905 23rd Avenue North
Minneapolis, MN 55447-4709

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies that the patent for the reference listed drug has expired, and is not entitled to a period of marketing exclusivity.
Innovator: Wyeth-Ayerst Laboratories, Inc. - Cordarone®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Pacerone™

7. NONPROPRIETARY NAME
Amiodarone Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm: 5/19/97 - Original.
12/31/97 - Response to 1st def. facsimile (chem. & labeling). Subject of this review.

FDA: 6/16/97 - Acknowledgment.
12/4/97- 1st def. facsimile (chem. & labeling).
12/23/97 - Bio. review, acceptable.

10. PHARMACOLOGICAL CATEGORY
Anti-arrhythmic

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)

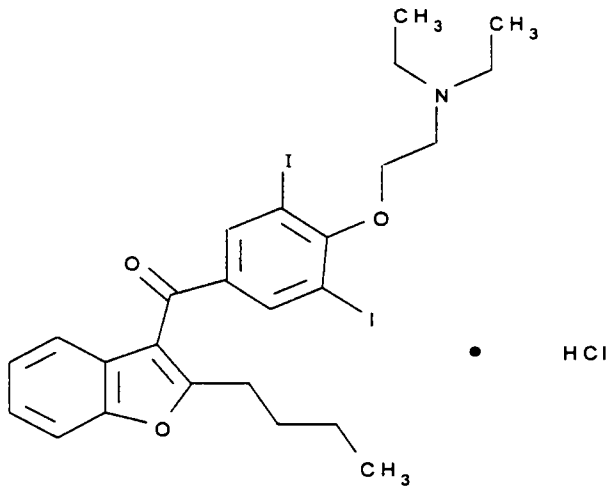
13. DOSAGE FORM
Tablet

14. POTENCIES
200 mg

15. CHEMICAL NAME AND STRUCTURE

Amiodarone Hydrochloride

$C_{25}H_{29}I_2NO_3.HCl$; M.W. = 681.77



2-Butyl-3-benzofuranyl 4-[2-(dimethylamino)ethoxy]-3,5-di-iodophenyl ketone hydrochloride.
CAS [1977-82-4]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
a. Active ingredient and finished product method validation sent to Detroit District Lab on 1/8/98.
b. Labeling **pending review**.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER:
Norman Gregory

DATE COMPLETED:
1/7/98