CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 21-392/S-002

Trade Name: Cardizem LA

Generic Name(s): (diltiazem hydrochloride)

Sponsor: Biovail Laboratories Inc.,

Agent:

Approval Date: April 9, 2004

Indication: Inhibits the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-392/S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

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Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-392/S-002

Biovail Technologies Limited
Attention: Mr. Stefan Olchaski
700 Route 202-206 North
Bridgewater, New Jersey 08807-0980

Dear Mr. Olchaski:

Please refer to your new drug application (NDA) dated June 6, 2003, submitted under section 505 (b) (1) of the Federal Food, Drug, and Cosmetic Act for Cardizem LA (diltiazem hydrochloride) 120, 180, 240, 300, 360 and 420 mg Extended Release Tablets.

We acknowledge receipt of your submissions dated June 12, August 21 (two), September 5, 2003, February 23 and March 10, 2004.

This supplemental new drug application provides for the use of Cardizem LA (diltiazem hydrochloride) 120, 180, 240, 300, 360 and 420 mg for the management of chronic stable angina.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert) submitted March 10, 2004.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-392/S-002." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Ms. Denise M. Hinton
Regulatory Project Manager
(301) 594-5333

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Biovail Laboratories Incorporated
Attention: John B. Dubeck
c/o Keller and Heckman
1001 G Street, N.W., Suite 500 West
Washington, D.C. 20001

Enclosure (Draft labeling)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-392/S-002

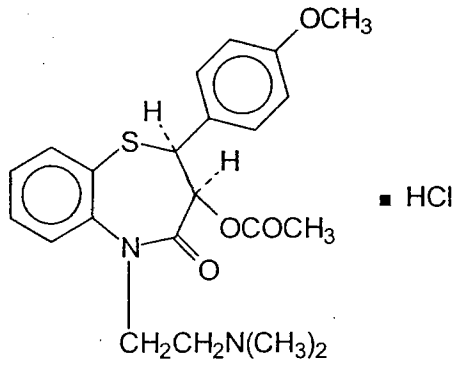
Approved Labeling

CARDIZEM® LA
(Diltiazem Hydrochloride) Extended Release Tablets

Once-a-day dosage
Rx only

DESCRIPTION

Diltiazem hydrochloride is a calcium ion cellular influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2, 3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-.
The structural formula is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform. It has a molecular weight of 450.99. CARDIZEM® LA Tablets, for oral administration, are formulated as a once-a-day extended release tablet containing either 120 mg,
180 mg, 240 mg, 300 mg, 360 mg or 420 mg of diltiazem hydrochloride.

Also contains: Carnauba Wax NF, Colloidal Silicon Dioxide NF, Croscarmellose Sodium NF, Hydrogenated Vegetable Oil NF, Hypromellose USP, Magnesium Stearate NF, Microcrystalline Cellulose NF, Microcrystalline Wax NF, Pregelatinized Starch NF, Polyacrylate Dispersion 30%, Polyethylene Glycol NF, Polydextrose, Polysorbate NF, Povidone USP, Simethicone USP, Sucrose Stearate, Talc USP, Titanium Dioxide USP, Triacetin USP.

CLINICAL PHARMACOLOGY

The therapeutic effects of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action

Hypertension. Diltiazem produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.
Angina. Diltiazem has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in

heart rate and systemic blood pressure at submaximal and maximal work loads. Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergovine-induced coronary artery spasms are inhibited by diltiazem.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissues. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem causes relaxation of coronary smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and non-ischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Pharmacokinetics and Metabolism
Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. Diltiazem undergoes extensive metabolism in which only 2% to 4% of the unchanged drug appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites, which attain higher concentrations than those of diltiazem and are more slowly eliminated; half-life of total radioactivity is about 20 hours compared to 2 to 5 hours for diltiazem.

In vitro binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive in vitro ligand binding studies have also shown diltiazem hydrochloride binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Minimum therapeutic plasma diltiazem concentrations appear to be in the range of 50 to 200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single study in patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

CARDIZEM LA Tablets. A single 360 mg dose of CARDIZEM LA results in detectable plasma levels within 3 to 4 hours and peak plasma levels between 11 and 18 hours; absorption occurs throughout the dosing interval. The apparent elimination half-life for CARDIZEM LA Tablets after single or multiple dosing is 6 to 9 hours. When CARDIZEM LA Tablets were coadministered with a high fat content breakfast, diltiazem peak and systemic exposures were not affected indicating that the tablet can be administered without regard to food. As the dose of CARDIZEM LA Tablets is increased from 120 to 240 mg, area-under-the-curve increases 2.5-fold.

Pharmacodynamics and Clinical Studies

Like other calcium channel antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Such data has no predictive value with respect to effects in patients with poor ventricular function, and increased heart failure has been reported in patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem. Diltiazem decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate.

During dynamic exercise, increases in diastolic pressure are inhibited, while maximum achievable systolic pressure is usually reduced. Chronic therapy with diltiazem produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem reduces the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

Intravenous diltiazem hydrochloride in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of diltiazem hydrochloride in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of diltiazem hydrochloride to patients in doses of up to 540 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation (See WARNINGS).

Hypertension. In a randomized, double-blind, parallel-group, dose-response study involving 478 patients with essential hypertension, evening doses of CARDIZEM LA 120, 240, 360, and 540 mg were compared to placebo and to 360 mg administered in the morning. The mean reductions in diastolic blood pressure by ABPM at roughly 24 hours after the morning (4 AM - 8AM) or evening (6 PM -10 PM) administration (i.e., the time corresponding to expected trough serum concentrations) are shown in the table below:

Mean Change in Trough Diastolic Pressure by ABPM

Evening Dosing				Morning Dosing 360 mg
120 mg	240 mg	360 mg	540 mg	
-2.0	-4.4	-4.4	-8.1	-6.4

A second randomized, double-blind, parallel-group, dose-response study (N=258) evaluated CARDIZEM LA following morning doses of placebo or 120, 180, 300, or 540 mg. Diastolic blood pressure measured by supine office cuff sphygmomanometer at trough (7 AM to 9 AM) decreased in an apparently linear manner over the dosage range studied. Group mean changes for placebo, 120 mg, 180 mg, 300 mg and 540 mg were -2.6, -1.9, -5.4, -6.1 and -8.6 mm Hg respectively.

Whether the time of administration impacts the clinical benefits of antihypertensive treatment is not known.

Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects.

Angina. The effects of Cardizem LA on angina were evaluated in a randomized, double-blind, parallel-group, dose-response trial of 311 patients with chronic stable angina. Evening doses of 180, 360 and 420 mg were compared to placebo and to 360 mg administered in the morning. All doses of Cardizem LA administered at night increased exercise tolerance when compared with placebo after 21 hours. The mean effect, placebo-subtracted, was 20 to 28 seconds for all three doses, and no dose-response was demonstrated. Cardizem LA, 360 mg, given in the morning, also improved exercise tolerance when measured 25 hours later. As expected, the effect was smaller than the effects measured only 21 hours following nighttime administration. Cardizem LA had a larger effect to increase exercise tolerance at peak serum concentrations than at trough.

INDICATIONS AND USAGE

CARDIZEM LA is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.
CARDIZEM LA is indicated for the management of chronic stable angina.

CONTRAINDICATIONS

Diltiazem is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction**. Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may

result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem (see ADVERSE REACTIONS section).

2. **Congestive Heart Failure**. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. **Hypotension** Decreases in blood pressure associated with diltiazem therapy may occasionally result in symptomatic hypotension.

4. **Acute Hepatic Injury** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some (See PRECAUTIONS).

PRECAUTIONS

General. Diltiazem hydrochloride is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem concomitantly with other agents known to affect cardiac contractility and/or conduction (See WARNINGS). Pharmacologic studies indicate that

there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem (See WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of this enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels.

Beta-Blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of diltiazem concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (See WARNINGS).

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis. Administration of diltiazem with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem therapy to avoid possible over- or under-digitalization (See WARNINGS).

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Benzodiazepines. Studies showed that diltiazem increased the AUC of midazolam and triazolam by 3- to 4-fold and the C_{max} by 2-fold, compared to placebo. The elimination half-life of midazolam and triazolam also increase (1.5 to 2.5 fold) during coadministration with diltiazem. These pharmacokinetic effects seen during diltiazem coadministration can result in increased clinical effects (e.g., prolonged sedation) of both midazolam and triazolam.

Cyclosporine. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.

The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Lovastatin. In a ten-subject study, coadministration of diltiazem (120 mg bid diltiazem SR) with lovastatin resulted in a 3 – 4 times increase in mean lovastatin AUC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

Rifampin. Coadministration of rifampin with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with rifampin or any known CYP 3A4 inducer should be avoided when possible, and alternative therapy considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) resulted in embryo and fetal lethality. These studies revealed, in one species or another, a propensity to cause fetal abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights, pup survival, as well as prolonged delivery times and an increased incidence of stillbirths.
There are no well-controlled studies in pregnant women; therefore, use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in pediatric patients have not been established.

Geriatric Use. Clinical studies of diltiazem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.
In the hypertension study, the following table presents adverse reactions more common on diltiazem than on placebo (but excluding events with no plausible relationship to treatment), as reported in placebo-controlled hypertension trials in patients receiving a diltiazem hydrochloride extended-release formulation (once-a-day dosing) up to 540 mg.

Adverse Reactions (MedDRA Term)	Placebo	Diltiazem hydrochloride extended-release	
	n= 120 # pts (%)	120-360 mg n= 501 # pts (%)	540 mg n= 123 # pts (%)
Oedema lower limb	4 (3)	24 (5)	10 (8)
Sinus congestion	0 (0)	2 (1)	2 (2)
Rash NOS	0 (0)	3 (1)	2 (2)

In the angina study, the adverse event profile of CARDIZEM LA was consistent with what has been previously described for CARDIZEM LA and other formulations of diltiazem HCl. The most frequent adverse effects experienced by CARDIZEM LA-treated patients were edema lower-limb (6.8%), dizziness (6.4%), fatigue (4.8%), bradycardia (3.6%), first-degree atrioventricular block (3.2%), and cough (2%).

In clinical trials of other diltiazem formulations involving over 3200 patients, the most common events (i.e. greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%) and rash (1.2%).
In addition, the following events have been reported infrequently (less than 2%) in hypertension trials with other diltiazem products:

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), nausea, thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus.

Other: Albuminuria, allergic reaction, amblyopia, asthenia, CPK increase, crystalluria, dyspnea, ecchymosis, edema, epistaxis, eye irritation, headache, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, neck rigidity, nocturia, osteoarticular pain, pain, polyuria, rhinitis, sexual difficulties, gynecomastia.

The following postmarketing events have been reported infrequently in patients receiving diltiazem: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, some characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem therapy is yet to be established.

OVERDOSAGE

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg.

The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases.

There have been 29 reports of diltiazem overdose in doses ranging from less than 1 g to 10.8 g. Sixteen of these reports involved multiple drug ingestions.

Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 g to 10.8 g. There were seven reports with a fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure, and in cases of cardiac failure, inotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Limited data suggest that plasmapheresis or charcoal

hemoperfusion may hasten diltiazem eliminiation following overdose. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences, the following measures may be considered:

Bradycardia: Administer atropine (0.60 to 1 mg). If there is no response to vagal blockage, administer isoproterenol cautiously.
High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g., dopamine or norepinephrine).
Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION
CARDIZEM LA Tablets are an extended release formulation intended for once-a-day administration.

Patients controlled on diltiazem alone or in combination with other medications may be switched to CARDIZEM LA Tablets once-a-day at the nearest equivalent total daily dose. Higher doses of CARDIZEM LA Tablets once-a-day dosage may be needed in some patients. Patients should be closely monitored. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. There is limited general clinical experience with doses above 360 mg, but the safety and efficacy of doses as high as 540 mg have been studied in clinical trials. The incidence of side effects increases as the dose increases with first-degree AV block, dizziness, and sinus bradycardia bearing the strongest relationship to dose.

The tablet should be swallowed whole and not chewed or crushed.

Hypertension:
Dosage needs to be adjusted by titration to individual patient needs. When used as monotherapy, reasonable starting doses are 180 to 240 mg once daily, although some patients may respond to lower doses. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. The dosage range studied in clinical trials was 120 to 540 mg once daily. The dosage may be titrated to a maximum of 540 mg daily.

CARDIZEM LA Tablets should be taken about the same time once each day either in the morning or at bedtime. The time of dosing should be considered when making dose adjustments based on trough effects.

Angina
Dosage for the treatment of angina should be individualized based on response. The initial dose of 180 mg once daily may be increased at intervals of 7 – 14 days if adequate response is not obtained. CARDIZEM LA doses above 360 mg appear to confer no additional benefit. CARDIZEM LA can be given once daily, either in the evening or in the morning.

Concomitant Use with Other Cardiovascular Agents

1. **Sublingual NTG.** May be taken as required to abort acute anginal attacks during Diltiazem Hydrochloride Extended-release therapy.
2. **Prophylactic Nitrate Therapy.** Diltiazem Hydrochloride Extended Release Tablets may be safely coadministered with short-and long-acting nitrates.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)
4. **Antihypertensives.** CARDIZEM LA has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of Diltiazem Hydrochloride Extended Release Tablets or the concomitant antihypertensives may need to be adjusted when adding one to the other.

HOW SUPPLIED
CARDIZEM LA is supplied as white, capsule-shaped tablets debossed with "B" on one side and the diltiazem content (mg) on the other.

Strength	NDC # 64455-xxx-yy			
	Qty 7	QTY 30	Qty 90	Qty 1000
120 mg	100-07	100-30	100-90	100-10
180 mg	101-07	101-30	101-90	101-10
240 mg	102-07	102-30	102-90	102-10
300 mg	103-07	103-30	103-90	103-10
360 mg	104-07	104-30	104-90	104-10
420 mg	105-07	105-30	105-90	105-10

Storage conditions: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Avoid excessive humidity and temperatures above 30°C (86°F).

Dispense in tight, light resistant container as defined in USP.
Rx Only.
® Cardizem is a registered trademark of Biovail Laboratories, Inc.

BIOVAIL
Pharmaceuticals, Inc.

Distributed by:
Biovail Pharmaceuticals, Inc.
Bridgewater, New Jersey 08807
Made in Canada

Rev. March 2004 LB-0024-00

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/s/

Doug Throckmorton
4/2/04 12:46:45 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-392/S-002

Medical Review(s)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Clinical Review

NDA: 21-392

Sponsor: Biovail Technologies, Ltd.

Submission: SE-002 ((9 June 2003) a request to approve Cardizem LA (extended-release diltiazem) for use in chronic stable angina

Review date: 29 December 2003

Reviewers: John Lawrence, Ph.D., HFD-710
N. Stockbridge, M.D., Ph.D., HFD-110

Summary: This is a review of Study B00.CT3.012.DIL G99, a randomized, parallel, 3-week comparison of placebo and once-daily diltiazem 180, 360, and 420 mg in the treatment of chronic stable angina. The sponsor's proposed labeling makes a claim for use in chronic stable angina and vasospastic angina, and it makes an implied claim regarding nighttime vs. daytime use.

Distribution: NDA 21-392

HFD-110/Project Manager

There are no new pharmacokinetic data and no new formulation issues.

The sponsor categorically denies inappropriate financial arrangements as defined under 21CFR 54.2(a), (b), or (f).

The supplement is supported by a single new clinical study report. This study report was supplied in paper only. No electronic data are available. The description below is based on the final study report (volumes 4-20).

Study B00.CT3.012.DIL G99, entitled "A double-blind, randomized, parallel-group, dose-response, multicenter study of the safety and efficacy of diltiazem HCl extended release capsules (G99) compared to placebo dosed at bedtime and to G99 dosed in the morning, in the treatment of chronic, stable, exercise-induced angina" is described by the fully amended protocol, dated 22 November 2000.

Amendments were as follows. Amendment 1 (date?) revised the number of sites, altered the efficacy parameters and inclusion criteria, and made numerous procedural changes. Amendment 2 (date?) added a list of CYP 3A4 substrates, inhibitors, and inducers. Amendment 3 (22 November 2000) amended requirements for pregnancy testing. This last amendment was only 3 months after the initial enrollment, so the nature of the earlier amendments is not critical to the interpretation of the final study.

Subjects were to be adult males and females with a low likelihood of becoming pregnant. They had to have angina triggered by physical effort, relieved by rest or nitroglycerin, and stable over 2 months. Subjects had to have coronary artery disease documented by angiography, thallium scintigram, radionuclide angiogram, myocardial

infarction 3 months prior, or CABG or PTCA 6 months prior. Subjects had to have treadmill exercise times between 3 and 7 minutes (standard Bruce protocol) on two or three baseline assessments, demonstrating angina and ST depression, and 2 of these 3 tests had to agree within 15%. Subjects were excluded for other mechanical or electrical cardiac abnormalities, blood pressure outside <180/90-104 mmHg, other chronic illness by history or screening, or obesity. HCTZ, ACE inhibitors, ARBs and low-dose atenolol were allowed for treatment of hypertension.

Qualified subjects were randomized evenly to placebo, or diltiazem 180 (evening), 360 (evening), 360 (morning), or 420 (evening) mg. Subjects in the 360- and 420-mg groups received 240 mg for the first 7 days. Evening dosing was to be between 2100 and 2300 and morning dosing was 0700 to 0900. Double-blind treatment was a total of 3 weeks.

Exercise assessments were to be conducted between 0700 and 1100 (morning) and 1800 to 2000 (evening). Qualification for the study was based on ETTs conducted in the evening. On the day after qualification, and prior to randomization, the morning baseline ETT was obtained. Subjects were seen at the end of 7 and 14 days, but no ETTs were conducted. The final ETTs were on day 21 (evening) and day 22 (morning).

Total enrollment was supposed to be 290 subjects (58 per arm) recruited from 40 centers.

The primary analysis was a comparison between groups of changes from baseline in total exercise time assessed at "trough". Baseline times were to be compared among groups by ANOVA. Changes from baseline were to be compared by ANCOVA with baseline, study site, and concomitant use of ACEI, ARB or BB as covariates. Multiple comparisons with placebo were handled by Dunnett's test. It appears that the primary analysis was to include all randomized subjects with baseline and final assessments, i.e., completers with at least one post-baseline measurement. Moreover, based on non-normally distributed residuals, the primary analysis was changed to a non-parametric analog of the originally planned ANCOVA using ranks. Both the parametric analysis and the nonparametric analysis were performed and gave similar results (according to the study report). However, only the nonparametric analysis results are shown in the main study report and in this review.

The study was conducted between August 2000 and June 2002. Seventy-eight sites in the US and Canada screened subjects, but only 46 sites enrolled 1 to 30 subjects, for a total enrollment of 311.

Fifteen subjects (5%) were withdrawn prematurely, 11 for adverse events (6 from the 420-mg group), 2 for protocol violations, and 2 for "other" reasons.

Thirty-two subjects were considered to have had significant protocol violations, 25 for compliance failure and 7 for concomitant medications.

Subjects ranged from 33 to 80 years old, 85% were Caucasian, and 79% were male. The treatment groups were similar with respect to demographic characteristics.

The most common concomitant medications were nitrates (70%), beta-blockers (44%), and calcium channel blockers (36%), similarly distributed in the various arms. Only about 2% of subjects were on an ACE inhibitor and no one received an ARB.

Baseline exercise times were similar among groups, as shown in Table 1.

Table 1. Baseline exercise times (seconds ± SD).

		Pcbo N=61	180PM N=65	360AM N=62	360PM N=60	420PM N=62
Total time	PM	344±70	348±75	*	328±77	349±82
	AM	354±81	363±78	379±81	336±85	362±89
Onset angina	PM	270±85	271±92	*	258±76	273±98
	AM	279±92	292±93	297±95	269±91	289±111
Onset ST dep	PM	269±78	260±90	*	247±86	267±88
	AM	283±89	289±94	289±112	269±99	293±98
* Not computed						

The median change from baseline and placebo in total exercise time was 20 s on 180 mg, 28 s on 360 mg (evening), 25 s on 420 mg, and 8 s on 360 mg (morning). By the sponsor's analyses, the evening effects were statistically significant (p=0.0057 to 0.0201), but not for morning dosing (p=0.0555). Using the original primary analysis (parametric ANOVA), both the low and medium evening doses are significantly different from placebo, but the high dose is not. These results were confirmed by the FDA statistical reviewer.

Similar results were obtained with time to onset of angina. The placebo-subtracted median changes were 41 s on 180 mg, 23 s on 360 mg (evening), 22 s on 420 mg (p=0.0029 to 0.0114), and 21 s on 360 mg (morning; p=0.2333). However, some subjects never experienced angina pain at the final assessment (12% on placebo to 30% on 420 mg; orders by dose). An analysis that excluded such subjects showed nominally statistically significant results for comparisons other than the 360-mg (evening).

Similar results were obtained with onset of ST depression, but the median changes were statistically significantly different from zero only for the two 360-mg groups—30 s (evening) and 27 s (morning). Again 12-24% of subjects did not have ischemia on the final assessment, but this time three is no obvious ordering by dose.

There was one death from myocardial infarction in one of the 360-mg arms. Treatment-emergent adverse events were much as one would expect, the most common being lower limb edema, dizziness, bradycardia, and first-degree AV block. The only serious adverse events with any likelihood of being treatment-related were one case of AV block, one sinus arrest, and two cases of bradycardia.

The one study provides adequate confirmation that the formulation is an effective anti-anginal agent when used once per day, largely because one can rely upon anti-anginal effects established with other formulations of diltiazem. Extension to a population with vasospastic angina, as proposed by the sponsor, is only supported by data from other formulations, as this trial did not enroll any such subjects.

The duration of the study—only 3 weeks—is less than one expects with studies of nitrates, but, in this case, there is no prior expectation of loss of effectiveness over time.

The most benign description of the dose-response data is that there is no relationship between dose and effect. Any support for an additional benefit of the 420-mg dose over the 360-mg dose would also have to come from studies of other formulations. If the other data were to look similar to the data in the current study, then the label should not encourage use above 360 mg.

Nighttime administration and daytime administration did not appear to be equivalent in this study. Several explanations are possible. One possibility is that the trial design favored evening dosing. The schedule of dosing and ETT assessments favored evening dosing as shown in Table 2.

Table 2. Dosing and ETT schedules

	Dose	ETT	Mid	Range
AM	0700-0900	0700-1100	25 h	23-28 h
PM	2100-2300	1800-2000	21 h	19-23 h

One cannot even explore the possibility that time between 19 and 28 hours after dosing matters, because the two groups do not even overlap in the acceptable ranges for timing the ETTs.

Second, morning ETTs always followed evening ETTs, and this could easily have introduced a bias. In each of the four evening-dosing groups, the mean baseline ETT was about 10 s shorter in the evening than in the morning.

Third, the standard deviation of the baseline was 3 to 12 s greater for the morning ETT, giving this comparison less power for detecting a difference.

Like the blood pressure study previously reviewed, the present study is adequate to conclude that Cardizem LA has antianginal activity, that use once-daily is appropriate, and that the timing of that dose can be guided by personal preference. This study provides little cause to approve a dose above 360 mg.

In the marked-up labeling that follows, the approved label appears in normal type. Sponsor-proposed changes appear with yellow highlighting. There are no sponsor-proposed deletions. Reviewer-proposed deletions are struck through and reviewer-proposed insertions appear in the margin.

The description of the angina trial has been revised to reflect the similarities in responses to the various evening doses, to show the overall modest treatment effect size, and to attribute differences in morning-evening dosing to trial design. The claim for vasospastic angina can only be sustained using data from another formulation, so it has been struck. Dosing instructions were revised to discourage use above 360 mg.

21 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-392/S-002

Administrative/Correspondence

United States Patent [19]
Deboeck et al.

[11] Patent Number: 5,529,791
[45] Date of Patent: Jun. 25, 1996

[54] EXTENDED RELEASE FORM OF DILTIAZEM

[75] Inventors: Arthur M. Deboeck, Guaibo, Puerto Rico; Philippe R. Bandiet, Waterloo, Belgium

[73] Assignee: Galephar P.R., Inc., Ltd., Carolina, Puerto Rico

[21] Appl. No.: 311,722

[22] Filed: Sep. 23, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 62,951, May 28, 1993, abandoned, which is a continuation of Ser. No. 721,396, Jun. 26, 1991, Pat. No. 5,288,505.

[51] Int. Cl.[6] A61K 9/16; A61K 9/58; A61K 9/62

[52] U.S. Cl. 424/494; 424/490; 424/497; 514/777; 514/785; 514/786; 514/970

[58] Field of Search 424/457, 451, 424/452, 490, 493, 497, 498, 499, 494

[56] References Cited

U.S. PATENT DOCUMENTS

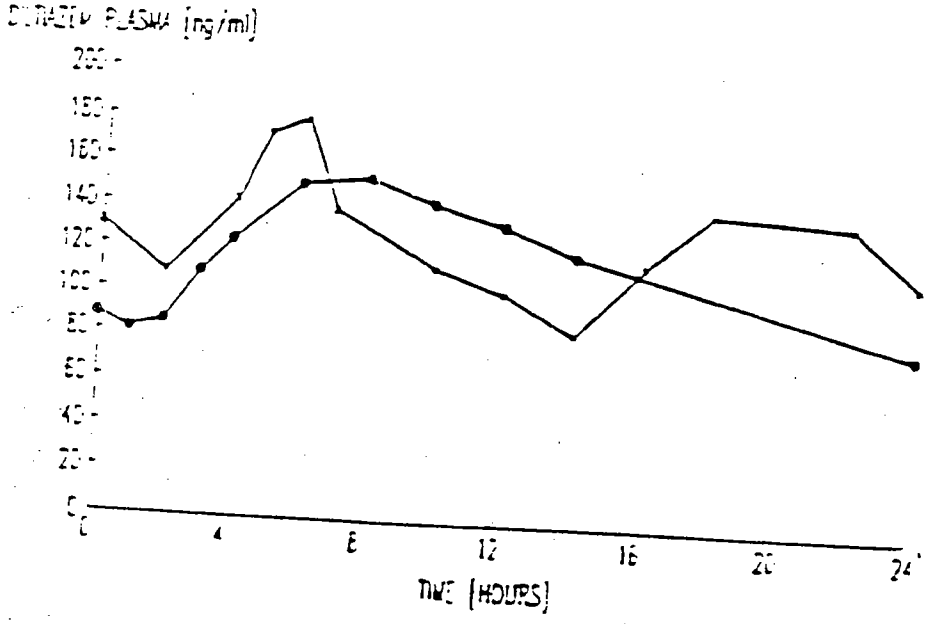
5,110,611 5/1992 Sowden et al. 424/497
5,275,824 1/1994 Oshlack et al. 424/490

Primary Examiner—Thurman K. Page
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] ABSTRACT

An extended-release galenical form of Diltiazem or a pharmaceutically acceptable salt thereof, which comprises beads containing said Diltiazem or a pharmaceutically acceptable salt thereof as an active ingredient and a wetting agent, said beads being coated with a microporous membrane consisting at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.

4 Claims, 2 Drawing Sheets



EXTENDED RELEASE FORM OF DILTIAZEM

This application is a continuation of application Ser. No. 08/068,951, filed on May 28, 1993, now abandoned, which is a continuation of application Ser. No. 07/721,396 filed Jun. 26, 1991, now U.S. Pat. No. 5,288,505.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an extended release form of Diltiazem, a process for the manufacture thereof and pharmaceutical compositions containing the same.

2. Description of the Background

Diltiazem hydrochloride is used in medicine principally for its calcium channel blocking properties and, therefore, finds application in the treatment of angina pectoris and hypertension, either alone or in combination with other medications.

Although the mechanism for calcium channel blocking is not completely understood, calcium ion entry is believed to be inhibited through select voltage, with the sensitive areas termed "slow channels", across cell membranes. By reducing intracellular calcium concentration in cardiac and vascular smooth muscle cells, coronary arterial, peripheral arterial and arteriolar are dilated and heart rate may be reduced. Also, myocardial contractability may be decreased and atrioventricular nodal conduction may be slowed. The activity of diltiazem in humans is directly related to its blood or plasma concentration.

For diseases which require continuous and constant control, such as hypertension and angina pectoris, Diltiazem must be administered every 6 to 8 hours as it has a very short half-life in blood of only about 3 to 4 hours. However, such frequent administration makes control of the treatment very annoying or even impossible to effect, particularly during the night. Further, after each administration of an immediate release galenic form of Diltiazem, which generally is necessary four times per day, a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established. Thus, the organism being treated and the target organ, more particularly the heart, are alternatively subjected to overdoses and to underdoses of medicine.

In order to alleviate these drawbacks a first galenic form of sustained release of Diltiazem known under the trade name CARDIZEM SR® was developed and presented in the form of "coated pellets", U.S. Pat. No. 4,721,619. Although this form affords a reduction in peak concentration and in the number of daily intakes from 4 to 2, it does not eliminate night Diltiazem blood concentration between successive medicine intakes. Hence, the patient is still obliged to take the medication twice daily. The products as described in U.S. Pat. No. 4,721,619 are prepared by a building up process which requires, as described therein, between 50 and 200 layers so as to obtain a core which therefore requires between 20 and 40 layers of coating so as to obtain the resistant. Moreover, the solvent of the polymer solution used to coat the medicament is constituted by organic solvents such as isopropanol, methanol, acetone, and methylene chloride which are dangerous to use due to their flammability and toxicity. Such solvents are also environmentally hazardous. Particular care must be taken to avoid any traces of solvent in the final product because these solvents are toxic and are undesirable in the product which is administered orally.

Thus, a need continues to exist for a multiple unit extended-release diltiazem hydrochloride galenical form which need be administered only once daily, and from which blood Diltiazem concentrations are not affected by the concomitant intake of food, and further, which can be made by a process not using organic solvents.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide galenic forms of Diltiazem with extended release of the active substance.

It is also an object of this invention to provide galenic forms of Diltiazem having excellent bioavailability while avoiding plasmatic concentration peaks.

The above objects and others which will become more apparent in view of the following disclosure are provided by an extended-release galenical form of a pharmaceutically acceptable salt of Diltiazem, which comprises beads containing the pharmaceutically acceptable salt of Diltiazem as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the effect of the present invention in gradually releasing Diltiazem in a relatively uniform manner over a period of about one day after the 8th once daily administration in comparison with the effect of a conventional product after the 8th day of administration twice daily.

FIG. 2 illustrates in the solid curve, the mean plasma levels obtained when the product of the present invention is taken without food. The dotted curve represents mean plasma levels obtained when the product is taken with food.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Diltiazem or (2S-cis)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H) has been known for more than 20 years. The synthesis thereof is described in German patent 1,805,714, corresponding to U.S. Pat. No. 3,562,257.

The present invention relates to novel galenic forms of Diltiazem being characterized by having an extended-release of the above substance. These galenic forms afford excellent bioavailability while avoiding plasmatic concentration peaks, so that it is now possible to maintain diltiazem plasmatic concentrations in a desired effective range while simplifying the administration of the medicament to only once daily.

According to the present invention, the Diltiazem extended release galenic forms are substantially characterized by the fact that they are constituted by beads containing a pharmaceutically acceptable salt of Diltiazem as an active substance, associated with at least a wetting agent, the beads being covered with a microporous membrane constituted by at least a water-soluble or water-dispersible polymer or copolymer such as a copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, and a pharmacologically acceptable adjuvant.

In accordance with the present invention, any pharmaceutically acceptable salt of Diltiazem may be prepared in extended release form. For example, such salts may include the hydrochloride, sulfate or phosphate salts. However, they

may also mediate the acetate, citrate or lactate salts, for example. It is preferred however, that the hydrochloride salt be used.

In more detail, the microporous membrane wherein the Diltiazem containing microgranules are covered, is constituted by a mixture of a water-soluble and/or water-dispersible copolymer and including at least one adjuvant which may be plasticizing agents, pigments, fillers, wetting agents, lubricants and antifoam agents.

The active substance containing beads are presented in form of spherules the diameter of which is between about 0.05 mm and 3 mm, preferably between about 0.1 mm and 2 mm.

Among the wetting agents associated with the Diltiazem or salt thereof in the beads, the following compounds may more particularly be exemplified:

saccharose, mannitol, sorbitol;

lecithins;

polyvinylpyrrolidones;

C_{12} to C_{20} fatty acid esters of saccharose, commercialized under the name of sucrosters (Gattefosse, France) or under the name of crodesters (Croda, U.K.).

xylose esters or xylites;

polyoxyethylenic glycerides;

esters of fatty acids and polyoxyethylene (Brijs, Renex and Eumulgines, Henkel, RFA);

sorbitan fatty acid esters (Span, Atlas, U.S.A.);

polyglycerols-glycerides and polyglycerols-alcohols esters (Caloxens, Gattefosse, France).

In addition to at least one of the above named wetting agents the beads may contain excipients or carriers, such as Microcrystalline celluloses, such as Avicel products (FMC, U.S.A.), methylcelluloses, carboxymethylcelluloses, hydroxyethylcelluloses (Natrosol, Hercules, U.S.A.), hydroxypropyl celluloses (Klucels, Hercules, U.S.A.), and starches.

Among the water-soluble and/or dispersible film forming polymers or copolymers constituting the microporous membrane may be mentioned particularly polyacrylates and polymethacrylates of the Eudragit type such as Eudragit E30D, L30D, RS-30 D of Rohm Pharma (RFA), ethylcelluloses such as Ethocels of DOW, U.S.A. and such as AquaCoat of FMC, U.S.A., Hydroxypropyl celluloses and hydroxypropylmethylcelluloses and their derivatives.

These polymers or copolymers may be associated into the microporous membrane with at least one adjuvant as exemplified by the following:

plasticizing agents, such as triacetin, dibutylphthalate, dibutylsebacate, citric acid esters, polyethyleneglycols, polypropyleneglycols and polyvinylpyrrolidone;

pigments, such as iron oxides and titanium oxide;

fillers, such as talcum and silicone;

wetting agents, such as surfactive agents of the Span and Tween types, namely partial esters of fatty acids (lauric, palmitic, stearic and oleic acids) and anhydrides of sorbitol, derived from sorbitol possibly containing polyoxyethylenic chains, preferably surfactive agents of the Tween type, namely Tween 80, as well as polyoxyethyleneglycols;

lubricants, such as magnesium stearate and talc;

antifoaming agents, such as silicone oil.

In addition to the polymer or copolymer, the microporous membrane contains preferably, talc and/or magnesium stearate as a lubricant, polyvinylpyrrolidone as a plasticizing agent, titanium dioxide as a pigment, Tween 80 as an emulsifier, and silicone oil as an antifoaming agent.

Generally, the thickness of the microporous membrane is expressed by the percentage of the coating applied to the uncoated beads.

The weight of the microporous membrane may be 2 to 35%, preferably, 5 to 22%, of the weight of said microgranules. These beads may contain the Diltiazem salt in an amount of 20 to 95% by weight, preferably 30 to 85% by weight. The microporous membrane may contain 5 to 95% and, preferably, 30 to 90% of polymers, polymer mixture or copolymers.

The invention relates also to a medicine containing Diltiazem or salt thereof for extended release, the medicine being constituted by beads containing the Diltiazem or salt, such as the hydrochloride, and at least a wetting agent, coated with at least one polymer-based microporous membrane, the coated beads being contained in capsules, little bags or dosage dispensers.

The present invention relates also to a process for obtaining novel forms of a Diltiazem or salt thereof having extended-release in the gastro-intestinal tracts, said process entailing preparing beads and coating the same with a single microporous membrane.

The beads of the Diltiazem or salt thereof may be prepared using a conventional technique. A first technique consists in mixing the Diltiazem or salt thereof with the wetting agent(s) in a melted or finely divided form, or in solution, in the presence of a solvent, such as water, so as to obtain an extrudable paste or plastic mass. Said paste is thereafter extruded in an extruder and then rendered spherical. Several extruder types are usable, for example the extruder of ALEXANDER WERK (RFA) or the apparatus called X-truder of FUJI-PAUDAL (Japan). For obtaining microspheres or beads from the extruded product provided in the form of spaghetti, an apparatus called "spheronizer" (CALEVA Great-Britain) or MARUMERIZER (FUJI-PAUDAL Japan) type is used.

Another conventional technique for obtaining beads consists in spraying and/or dusting cores obtained through agglomeration of the Diltiazem or salt thereof, such as the chlorohydrate, concurrently mixed to at least a wetting agent, with a dispersion or solution of at least one wetting agent, for example in a known pilling machine or in a granulating apparatus, such as the CF granulator system of FREUND INDUSTRIAL CO. (Japan), or in a known plan-etary granulator such as the column (Belgium) type.

The obtained beads are dried by any means, for example in an oven or by means of a gas in a fluidized bed.

Finally, said beads are calibrated to the necessary diameter by passage through appropriate screens.

A pasty or plastic mixture, appropriate to be granulated by means of anyone of the above described techniques, may contain the following weight proportions of the Diltiazem or salt thereof, wetting agents and carriers or excipients:

20 to 85%, Diltiazem hydrochloride

2 to 20% sucrosters WE 15 (wetting agent),

5 to 25% Avicel PH 101 (microcrystalline cellulose of FMC, U.S.A.),

2 to 10% Metocel E 5 (hydroxypropylmethylcellulose of DOW, U.S.A.),

1 to 15% polyvinylpyrrolidone and

5 to 40% distilled water.

Said microporous membrane may be applied onto said beads by pulverizing an aqueous solution or dispersion of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads. This pul-

...version may be carried out by spray-gunning or by pulverizing the above-named dispersion into a turbine or fluidized bed.

Generally, the present extended release form composition of Diltiazem salt is administered orally. The dosage amount is subject to the response of the individual patient, however, in general, from about 120 mg to about 480 mg per day of Diltiazem salt is administered per day per patient in total.

Additionally, the extended release form composition of the present invention may include other pharmaceutically active ingredients than the Diltiazem salt, provided that the other active ingredient is not pharmaceutically incompatible with the Diltiazem salt.

For example, other pharmaceutically active ingredients, such as β-adrenoceptor blocking agents or diuretics may be used in the present compositions. However, these are only examples and are not intended to be limitative.

As examples of β-adrenoceptor blocking agents, drugs such as Propranolol, Atenolol, Labetalol, Pindolol or Sotalol may be used, for example.

As examples of diuretic agents, drugs such as Hydrochlorothiazides, Furosemide, Ethacrynic Acid or Chlorothiazide, for example.

Further, the additional associated drugs may be present in extended-release form also, if desired, however they need not be.

The present invention will now be further illustrated by reference to certain examples which are provided solely for purposes of illustration and are not intended to be limitative.

According an illustrative embodiment of the present invention, said pharmaceutical medicament may be obtained, starting from an aqueous dispersion which contains by weight:

10 to 70 Eudragit E30D (polymer)
0.5 to 15% talc (lubricant)
0.5 to 15% Titanium dioxide (lubricant)
0.5 to 15% Magnesium stearate (lubricant)
0.5 to 15% polyvinylpyrrolidone (plasticizing agent)
0.01 to 2% silicone oil (antifoaming agent)
0.01 to 5% polysorbate 80 (wetting agent)
10 to 70% water (carrier)

EXAMPLES

The present invention will now be further illustrated by reference to certain examples which are provided solely for purposes of illustration and are not intended to be limitative. In particular examples are provided for: Diltiazem hydrochloride extended release galenic forms, a process for preparing the same, therapeutic applications therefor and pharmaceutical controls using the present galenic forms.

Example 1—beads manufacture

Diltiazem hydrochloride	1120 g
Lactose	119 g
Microcrystalline cellulose (Avicel pH 101)	560 g
Povidone K 30	21 g

After introducing the powders into a planetary mixer and granulating same trough the obtained plastic mass is extruded through a cylinder with 1 mm diameter holes (Alexanderwerk). The small cylinders are rounded so as to obtain beads by means of a spheronizer. After drying at 60° C. for 12 hours the beads are sifted and the fraction with size comprised between 0.7 mm and 1.4 mm are retained. 1.179 g of beads were obtained yield (94%).

Example 2

Diltiazem hydrochloride	560 g
Dicalcium P 160	59.5 g
Microcrystalline cellulose (Avicel pH 101)	70 g
Povidone K 30	10.5 g

The ingredients are introduced in a planetary mixer and dry mixed during approximately 15 minutes. Thereafter 100 ml water USP is added and the mixing is pursued during 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal extruder equipped with a 1 mm screen so as to obtain "spaghettes". A spheronizer type calotte is used so as to transform the extruded product in beads. After drying during 12 hours, on trays, in an oven at 60° C. the beads are sieved so as to eliminate the ones with a size larger than 1.4 mm and with a size smaller than 0.7 mm. The amount of beads obtained with size comprised between 0.7 mm and 1.4 mm was 639.1 g (yield 91.3%).

Example 3

Beads prepared in Example 1 were coated in a STREA-1 (Aeromatic) fluidized bed using the "Top spraying" technic. 440 g of coating suspension of the following composition was applied on 500 g of beads. Thereafter the coated beads were dried at 50° C. during 16 hours.

Coating suspension composition

Magnesium stearate	12.5 g
Titanium dioxide	5.0 g
Povidone K 30	5.0 g
Eudragit NE30D	625.0 g
Talc USP	17.5 g
water	331.0 g
Simethicone	1.0 g
Tween 80	0.1 g

"In vitro" dissolution were obtained using the apparatus #2 as described in the United States Pharmacopoeia. The 900 ml dissolution medium consisted of a phosphate buffer pH 5.8 and the revolution speed 100 rpm.

Sample time (h)	Diltiazem dissolved (%)
1	3
4	36
8	62
12	84

Example 4

The beads as in Example 2 were coated using a fluidized bed coater equipped with a "wurster" system. 1 kg of uncoated beads were introduced in an Aeromatic Aeromatic and 2.77 kg of the following coating suspension was applied at a rate of 30–35 g per minute. Thereafter the coated beads were dried during 15 hours at 45° C.

Coating suspension

Magnesium stearate	0.836 kg
Talc	0.836 kg

-continued

[illegible]	0.0909 g
[illegible]	0.300 g
Povidone K30 ®*	0.057 g
Sorbitan monooleate	0.018 g
Emcapol NE 30 D	12.4 g
purified water	4.7 g

Dissolution "in vitro"

The results were obtained using the same equipment as in Example 3. The dissolution medium was composed of 900 ml of water and the temperature was maintained at 37±0.5° C.

[illegible]	[illegible]
2	9
4	33
6	54
8	81

Pharmacological results

The new galenic form of Example 4 was the object of a pharmacological study in comparison with a form in accordance to the prior art as described in U.S. Pat. No 4,721,619 (Cardizem SR®) therefore 6 healthy subjects received successively in a random order 300 mg of each of the 2 products. The product of Example 4 was administered at a dose of 300 mg once daily while the product on the market was administered twice daily at a dose of 150 mg (300 mg daily total dose) during 7 days. At each of the eight days, 11 samples of blood were withdrawn when product of Example 4 was administered and 15 blood samples when withdrawn after the Cardizem SR® administration. Diltiazem plasma levels were assayed using a specific high pressure liquid chromatographic method. FIG 1 shows the results obtained, the continuous line represents the Diltiazem plasma levels obtained with the product of Example 4 and the broken line the Diltiazem plasma levels of Cardizem SR®.

FIG 1

Pharmacokinetic parameters

	Units	Example 4	Cardizem SR®
[illegible]	ng/ml	270 ± 107	284 ± 101
[illegible]	ng/ml	1163 ± 341	1121 ± 333
Time of maximum concentration	h	8.0 ± 1.8	5.3 ± 2.1
Fluctuation	%	85.7 ± 22.7	109.3 ± 21
Time during the concentration is above 75% of the maximum concentration	h	9.8 ± 2.3	6.7 ± 3.1

From these results the following conclusions can be drawn.

First, FIG 1 shows that the Diltiazem plasma levels obtained after a once daily administration of one of the products of the present invention are comparable to the ones obtained after a twice daily administration of the product of the previous art.

Second, the bioavailability expressed by the area under the curve of the 2 products is equivalent (no statistical significant difference).

Third, the maximal concentration and the fluctuations obtained after a once daily administration of the product of the present invention is lower than the one obtained with Cardizem SR® after a twice daily administration.

Fourth, the time during the concentration is above 75% of the maximum concentration is 46% longer after the once daily administration of the product of the present invention than with product of the previous art when given twice daily.

Food effect study

The product of Example 4 was given to 24 healthy volunteers and the bioavailability was measured after single oral dose of 300 mg given with and without food.

The clinical trial was conducted as an open, single dose, randomized, cross over study. Blood samples were obtained before and until 36 hours after the administration. The experiment was repeated in the same subjects with the other treatment at an interval of 7 days. The plasma concentration of Diltiazem was determined in all available samples using an HPLC method. Pharmacokinetic parameters were derived from the individual plasma concentration versus time profiles and statistically compared for treatment differences and assessment of bioequivalence. FIG. 2 curves shows the mean plasma levels obtained when the product is taken without food and the dotted curve the mean plasma levels obtained when the product is taken with food.

FIG 2

Pharmacokinetic parameters - product of Example 4

	Units	Fasting	Fed
Area under the curve (AUC)	ng/ml	1988 ± 119	1921 ± 105
Mean residence time	h	11.3 ± 0.7	11.9 ± 0.9
k_a	h^{-1}	0.283 ± 0.024	0.300 ± 0.027
Maximum concentration	ng/ml	100 ± 4.1	112 ± 5.9

No statistical difference was detectable. The product of Example 4 given with food is bioequivalent to the administration without food to within less than 20% regarding area under the curve, mean residence time and maximum concentration. The larger interval obtained for k_a was due to the higher variability of this parameter, the difference between the treatment means remaining small (6 %).

From all the results it appears clearly that the product of the present invention can be administered once a day and that the plasma concentration variations are lower than the one obtained with the conventional product given twice a day.

Having described the present invention, it will now be apparent to one skilled in the art that many changes and modifications may be made to the above-described embodiments while remaining within the spirit and the scope of the present invention.

What is claimed as new and desired to be secured by Letters Patent of the United States is:

1. An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient, each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent to admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract

or other adverse conditions whilst the composition will meet internal acid bonds being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid- and base-insoluble polymer and a pharmaceutically-acceptable adjuvant,

and wherein the wetting agent is selected from the group consisting of sugar, C_{12}-C_{20} fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, esters of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycoside esters, glycerol-polyglycosides, lecithins and a combination thereof.

2. The composition of claim 1, wherein the wetting agent is a sugar.

3. The composition of claim 1, wherein the effective amount of the wetting agent is about 2% by weight of the composition.

4. The composition of claim 1, wherein the wetting agent is sucrose stearate, the water-soluble or water-dispersible polymer or copolymer is hydroxypropylmethyl-cellulose and the water, acid- and base- insoluble polymer is an acrylic polymer.

* * * * *

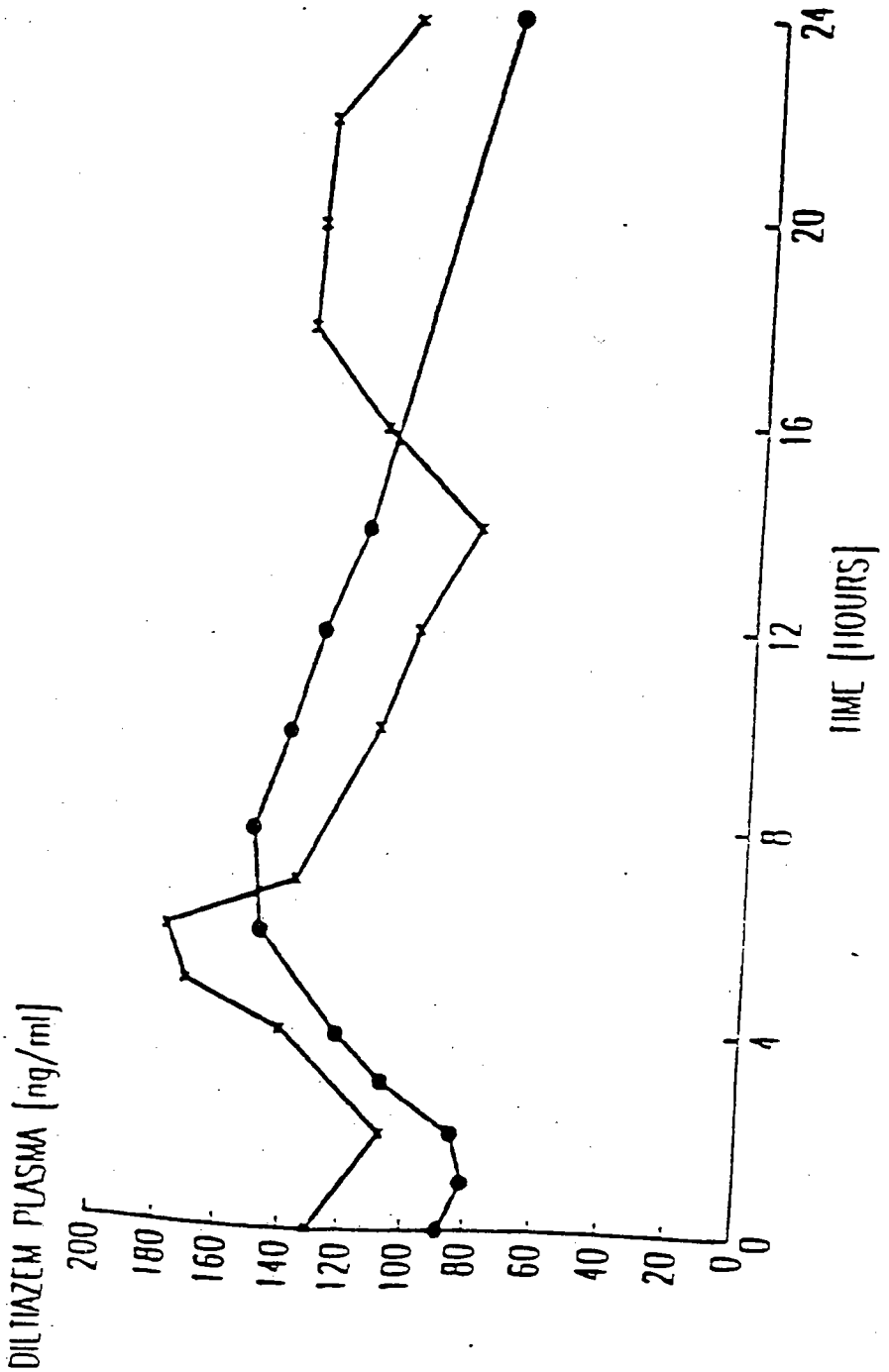

DILTIAZEM PLASMA [ng/ml]
200
180
160
140
120
100
80
60
40
20
0
0
4
8
12
16
20
24
TIME [HOURS]

FIG. 1

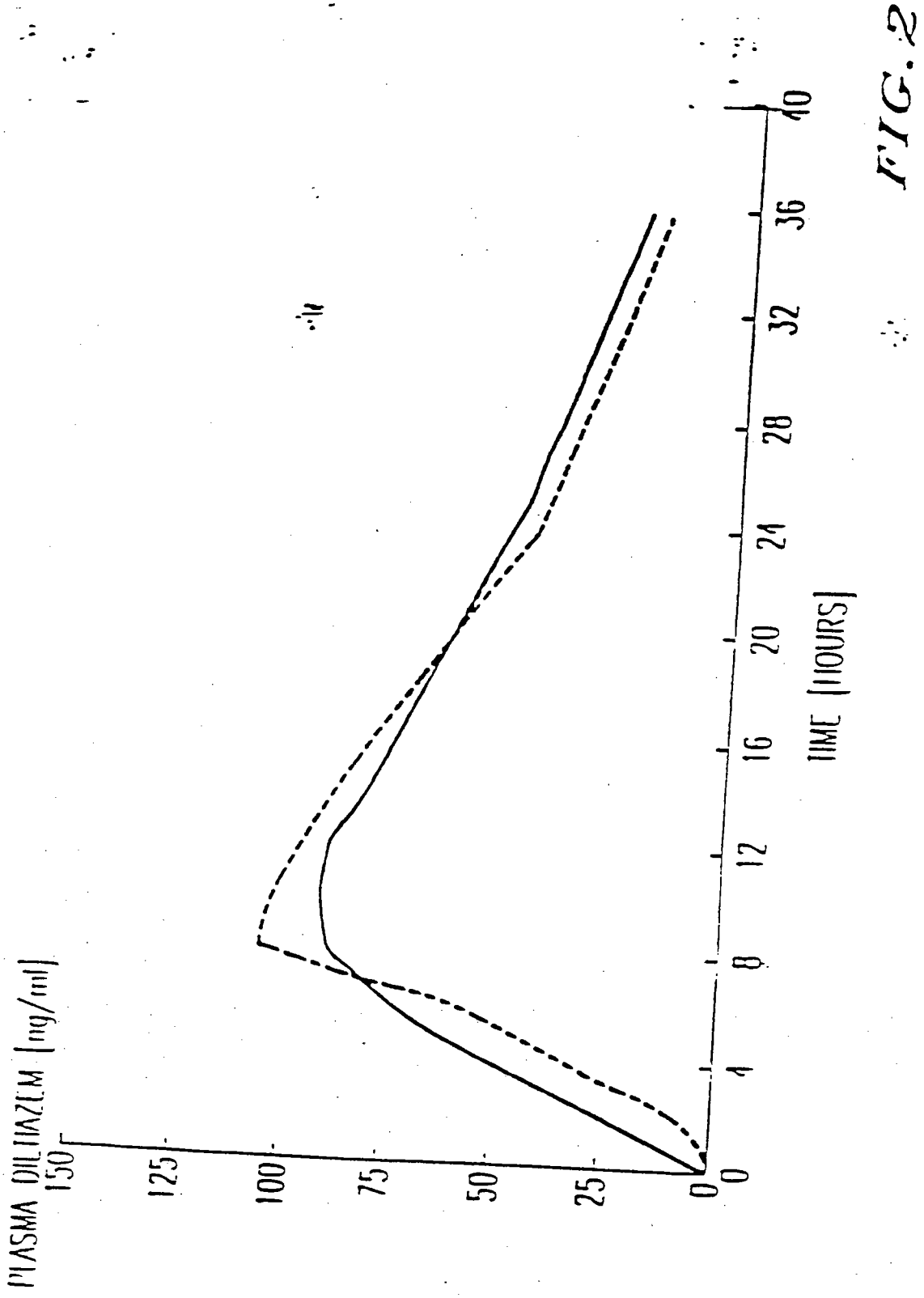

PLASMA DILTIAZEM [ng/ml]
150
125
100
75
50
25
0
0
4
8
12
16
20
24
28
32
36
40
TIME [HOURS]

FIG. 2

[54] EXTENDED RELEASE FORM OF DILTIAZEM

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[73] Assignee: Galephar P.R., Inc., Ltd., Carolina, P.R.

[21] Appl. No.: 721,396

[22] Filed: Jun. 26, 1991

[51] Int. Cl.[5] A61K 9/16; A61K 9/58

[52] U.S. Cl. 424/497; 424/457; 424/451; 424/462; 424/490; 424/499; 424/502

[58] Field of Search 424/499, 457, 451, 462, 424/490, 493, 498, 497

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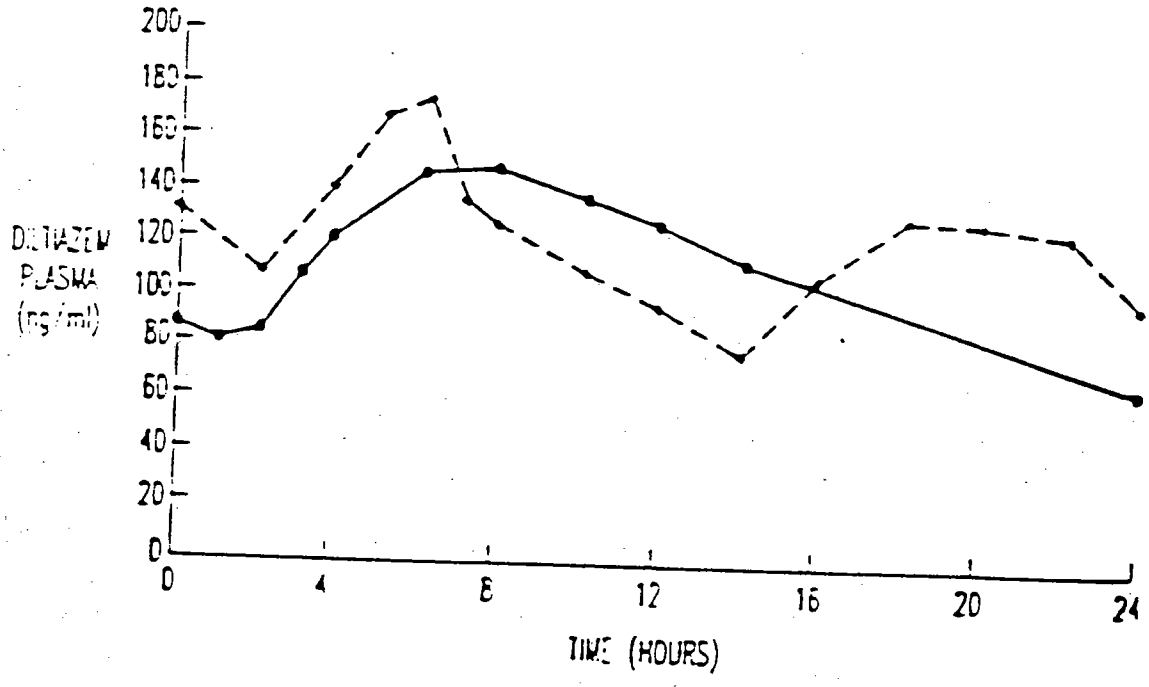
Primary Examiner—Thurman K. Page
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] ABSTRACT

An extended-release galenical form of Diltiazem or a pharmaceutically acceptable salt thereof, which comprises beads containing said Diltiazem or a pharmaceutically acceptable salt thereof as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.

15 Claims, 2 Drawing Sheets



EXTENDED RELEASE FORM OF DILTIAZEM

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an extended release form of Diltiazem, a process for the manufacture thereof and pharmaceutical compositions containing the same.

2. Description of the Background

Diltiazem hydrochloride is used in medicine principally for its calcium channel blocking properties and, therefore, finds application in the treatment of angina pectoris and hypertension, either alone or in combination with other medicaments.

Although the mechanism for calcium channel blocking is not completely understood, calcium ion entry is believed to be inhibited through select voltage, with the sensitive areas termed "slow channels", across cell membranes. By reducing intracellular calcium concentration in cardiac and vascular smooth muscle cells, coronary arteries, peripheral arteries and arterioles are dilated and heart rate may be reduced. Also, myocardial contractibility may be decreased and atrioventricular nodal conduction may be slowed. The activity of diltiazem in human is directly related to its blood or plasma concentration.

For illnesses which require continuous and constant control, such as hypertension and angina pectoris, Diltiazem must be administered every 6 to 8 hours, as it has a very short half-life in blood of only about 3 to 4 hours. However, such frequent administration times render the treatment very annoying or even impossible to effect, particularly during the night. Further, after each administration of an immediate-release galenic form of Diltiazem, which generally is necessary four times per day, a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established. Thus, the organism being treated and the target organ, more particularly the heart, are alternatively subjected to overdoses and to underdoses of medicine.

In order to alleviate these drawbacks, a first galenic form of sustained-released of Diltiazem known under the trade name CARDIZEM SR ® was developed and presented in the form of "erodible pellets". U.S. Pat. No. 4,721,619. Although this form affords a reduction in peak concentration and in the number of daily intakes from 4 to 2, it does not eliminate high Diltiazem blood concentration between successive medication intakes. Hence, the patient is still obliged to take the medicament twice daily. The products as described in U.S. Pat. No. 4,721,619 are prepared by a building up process which requires, as described therein, between 50 and 200 layers so as to obtain a core which, thereafter, requires between 20 and 40 layers of coating so as to obtain the membrane. Moreover, the solvent of the polymer solution used to make the membrane is constituted by organic solvents such as isopropanol, methanol, acetone and methylene chloride which are dangerous to use due to their flammability and toxicity. Such solvents are also environmentally hazardous. Particular care must be taken to avoid any traces of solvent in the final product because these solvents are toxic and are unsuitable in the product which is administered orally.

Thus, a need continues to exist for a multiple unit extended-release diltiazem hydrochloride galenical form which need be administered only once daily, and from which blood Diltiazem concentrations are not affected by the concomitant intake of food, and further, which can be made by a process not using organic solvents.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide galenic forms of Diltiazem with extended release of the active substance.

It is also an object of this invention to provide galenic forms of Diltiazem having excellent bioavailability while avoiding plasmatic concentration peaks.

The above objects and others which will become more apparent in view of the following disclosure are provided by an extended-release galenical form of a pharmaceutically acceptable salt of Diltiazem, which comprises beads containing the pharmaceutically acceptable salt of Diltiazem as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the effect of the present invention in gradually releasing Diltiazem in a relatively uniform manner over a period of about one day after the 8th once daily administration in comparison with the effect of a conventional product after the 8th day of administration twice daily.

FIG. 2 illustrates in the solid curve, the mean plasma levels obtained when the product of the present invention is taken without food. The dotted curve represents mean plasma levels obtained when the product is taken with food.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Diltiazem or (2S-cis)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H) has been known for more than 20 years. The synthesis thereof is described in German patent 1,805,714, corresponding to U.S. Pat. No. 3,562,257.

The present invention relates to novel galenic forms of Diltiazem being characterized by having an extended-release of the active substance. These galenic forms afford excellent bioavailability while avoiding plasmatic concentrations peaks, so that it is now possible to maintain diltiazem plasmatic concentrations in a desired, effective range while simplifying the administration of the medicine to only once daily.

According to the present invention, the Diltiazem extended release galenic forms are substantially characterized by the fact that they are constituted by beads containing a pharmaceutically acceptable salt of Diltiazem as an active substance, associated with at least a wetting agent, the beads being covered with a microporous membrane constituted by at least a water-soluble or water-dispersible polymer or copolymer such as a copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, and a pharmacologically acceptable adjuvant.

In accordance with the present invention, any pharmaceutically acceptable salt of Diltiazem may be prepared in extended release form. For example, such salts may include the hydrochloride, sulfate or phosphate salts. However, they may also include the acetate, ci-

... of ... acid, for example. It is preferred however, that the hydrochloride salt be used.

In more detail, the microporous membrane wherewith the Diltiazem containing microgranules are covered, is constituted by a mixture of a water-soluble and/or water-dispersible copolymer and including at least one adjuvant which may be plasticizing agents, pigments, fillers, wetting agent lubricants and antifoam agents.

The above substance containing beads are presented in form of spherules the diameter of which is between about 0.05 mm and 3 mm, preferably between about 0.1 mm and 2 mm.

Among the wetting agents associated with the Diltiazem or salt thereof in the beads, the following compounds may more particularly be exemplified:

sugars, for example saccharose, mannitol, sorbitol and lactose;

lecithins;

C_{12} to C_{20} fatty acid esters of saccharose, commercialized under the name of sucrosters (Gattefosse, France) or under the name of crodesters (Croda, U.K.);

xylose esters or xylites;

polyoxyethylenic glycerides;

esters of fatty acids and polyoxyethylene (Brijs, Renex and Eumulgines, Henkel, RFA);

sorbitan fatty acid esters (Span, Atlas, U.S.A.);

polyglycerides-glycerides and polyglycerides-alcohols esters (Gelucires, Gattefosse, France).

In addition to at least one of the above named wetting agents the beads may contain excipients or carriers, such as Microcrystalline celluloses, such as Avicel products (FMC, U.S.A.), methylcelluloses, carboxymethylcelluloses, hydroxyethylcelluloses (Natrosol, Hercules, U.S.A.), hydroxypropyl celluloses (Klucels, Hercules, U.S.A.), and starches.

Among the water-soluble and/or dispersible film-forming polymers or copolymers constituting the microporous membrane, may be mentioned particularly polyacrylates and polymethacrylates of the Eudragit type, such as Eudragit E30D, L30D, RS - 30 D of Roehm Pharma (RFA), ethylcelluloses, such as Ethocels of DOW, U.S.A. and such as AquaCoat of FMC, U.S.A., Hydroxypropyl cellulose and hydroxypropylmethylcellulose and their derivations.

These polymers or copolymers may be associated into the microporous membrane with at least one adjuvant as exemplified by the following:

plasticying agents, such as triacetin, dibutylphthalate, dibutylsebacate, citric acid esters, polyethyleneglycols, polypropyleneglycols and polyvinylpyrrolidone;

pigments, such as iron oxides and titanium oxide;

fillers, such as lactose and sucrose;

wetting agents, such as surfactive agents of the Span and Tween types, namely partial esters of fatty acids (lauric, palmitic, stearic and oleic acids) and anhydrides of sorbitol possibly containing polyoxyethylenic chains, preferably surfactive agents of the Tween type, namely Tween 80, as well as polyethyleneglycols;

lubricants, such as magnesium stearate and talc;

antifoaming agents, such as silicone oil.

In addition to the polymer or copolymer, the microporous membrane contains preferably talc and/or magnesium stearate as a lubricant, polyvinylpyrrolidone as a plasticying agent, titanium dioxide as a pigment, Tween 80 as an emulsifier, and silicone oil as an antifoam agent.

Generally, the thickness of the microporous membrane is expressed by the percentage of the ... applied to the uncoated beads.

The weight of the microporous membrane may ... to 35%, preferably, 5 to 20%, of the weight of ... microgranules. These beads may contain the Diltiazem salt in an amount of 20 to 95% by weight, preferably ... to 85% by weight. The microporous membrane may contain 5 to 95% and, preferably, 30 to 90% of ... mers, polymer mixture or copolymers.

The invention relates also to a medicine containing Diltiazem or salt thereof for extended release, the ... ceutical being constituted by beads containing the Diltiazem or salt such as the hydrochloride, and at least ... wetting agent, coated with at least one polymer-based microporous membrane, the coated beads being ... used in capsules, brute bags or dosage dispensers.

The present invention relates also to a process for obtaining novel forms of a Diltiazem or salt thereof having extended-release in the gastro-intestinal tract, said process entailing preparing beads and coating said salt with a single microporous membrane.

The beads of the Diltiazem or salt thereof may be prepared using a conventional technique. A first technique consists in mixing the Diltiazem or salt thereof with the wetting agent(s) in a melted or finely divided form, or in solution, in the presence of a solvent, such as water, so as to obtain an extrudable paste or plastic mass. Said paste is thereafter extruded in an extruder and then rendered spherical. Several extruder types are usable, for example the extruder of ALEXANDERWERK (RFA) or the apparatus called X-truder of FUJI-PAUDAL (Japan). For obtaining microspheres or beads from the extruded product provided in the form of spaghetti, an apparatus called "spheronizer" (CALEVA Great-Britain) or MARUMERIZER (FUJIU-PAUDAL Japan) type is used.

Another conventional technique for obtaining beads consists in spraying and/or dusting cores obtained through agglomeration of the Diltiazem or salt thereof, such as the chlorohydrate, contingently mixed to at least a wetting agent, with a dispersion or solution of at least one wetting agent, for example in a known pill turbine or in a granulating apparatus, such as the C... granulator system of FREUND INDUSTRIAL C... (Japan), or in a known planetary granulator such as the collette (Belgium) type.

The obtained beads are dried by any means, for example in an oven or by means of a gas in a fluidized bed.

Finally, said beads are calibrated to the necessary diameter by passage through appropriate screens.

A pasty or plastic mixture, appropriate to be granulated by means of anyone of the above described techniques, may contain the following weight proportions of the Diltiazem or salt thereof, wetting agents and carriers or excipients:

20 to 85%, Diltiazem hydrochloride

2 to 20% sucrosters WE 15 (wetting agent);

5 to 25% Avicel PH 101 (microcrystalline cellulose of FMC, U.S.A.);

2 to 10% Methocel E 5 (hydroxypropylmethyl cellulose of DOW, U.S.A.);

1 to 15% polyvinylpyrrolidone and

5 to 40% distilled water.

Said microporous membrane may be applied onto said beads by pulverizing an aqueous solution or disper...

one of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads. This pulverization may be carried out by spray-granulating or by pulverizing the above-named dispersion into a turbine or fluidized bed.

Generally, the present extended release form composition of Diltiazem salt is administered orally. The dosage amount is subject to the response of the individual patient, however, in general, from about 120 mg to about 480 mg per day of Diltiazem salt is administered per day per patient in total.

Additionally, the extended release form composition of the present invention may include other pharmaceutically active ingredients than the Diltiazem salt, provided that the other active ingredient is not pharmaceutically incompatible with the Diltiazem salt.

For example, other pharmaceutically active ingredients such as β-adrenoceptor blocking agents or diuretics may be used in the present compositions. However, these are only example and are not intended to be limitative.

As examples of β-adrenoceptor blocking agents, drugs such as Propranolol, Atenolol, Labetalol, Pronidolol or Sotalol may be used, for example.

As examples of diuretic agents, drugs such as Hydrochlorothiazide, Furosemide, Ethacrynic Acid or Chlorothiazide, for example.

Further, the additional associated drugs may be present in extended-release form also, if desired, however, they need not be.

The present invention will now be further illustrated by reference to certain examples which are provided solely for purposes of illustration and are not intended to be limitative.

According an illustrative embodiment of the present invention, said microporous membrane may be obtained, starting from an aqueous dispersion which contains by weight:

10 to 70 Eudragit E30D (polymer)
0.5 to 15% talc (lubricant)
0.5 to 15% Titanium dioxide (lubricant)
0.5 to 15% Magnesium stearate (lubricant)
0.5 to 15% polyvinylpyrrolidone (plasticizing agent)
0.0 to 2% silicone oil (antifoaming agent)
0.01 to 5% polysorbate 80 (wetting agent)
10 to 70% water (carrier)

EXAMPLES

The present invention will now be further illustrated by reference to certain examples which are provided solely for purposes of illustration and are not intended to be limitative. In particular, examples are provided for Diltiazem Hydrochloride extended release galenic forms, a process for preparing the same therapeutic applications therefor and pharmacokinetic control using the present galenic forms.

EXAMPLE 1

Beads Manufacture

[illegible]	1120 g
[illegible]	119 g
[illegible] (Avicel pH 101)	840 g
[illegible] K 30	21 g

After introducing the powders into a planetary mixer and granulating water through the obtained plastic mass is extruded through a cylinder with 1 mm diameter holes (Alexanderwerk). The small cylinders are rounded, so as to obtain beads, by means of a spheronizer. After drying at 60° C. for 12 hours the beads are sifted and the fraction with size comprised between 0.7 mm and 1.4 mm are retained. 1.175 g of beads were obtained yield (94%).

EXAMPLE 2

Diltiazem Hydrochloride	840 g
Crospovidone F 100	393.5 g
Microcrystalline cellulose (Avicel pH 101)	70 g
Povidone K 30	105.5 g

The ingredients are introduced in a planetary mixer and dry mixed during approximately 15 minutes. Thereafter 100 ml water USP is added and the mixing is pursued during 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal extruder equipped with a 1 mm screen so as to obtain "spaghettis". A spheronizer type caleva is used so as to transform the extruded product in beads. After drying during 12 hours, on trays, in an oven at 60° C the beads are sieved so as to eliminate the ones with a size larger than 1.4 mm and with a size smaller than 0.7 mm. The amount of beads obtained with size comprised between 0.7 mm and 1.4 mm was 639.1 g (yield 91.3%)

EXAMPLE 3

Beads prepared in Example 1 were a STREA-1 (Aeromatic) fluidized bed using the "Top spraying" technic. 440 g of coating suspension of the following composition was applied on 500 g of beads. Thereafter the coated beads were dried at 50° C. during 16 hours.

Coating suspension composition:	
Magnesium stearate	12.5 g
Titanium dioxide	50 g
Povidone K 30	50 g
Eudragit NE30D	4200 g
Talc USP	175 g
water	3388 g
Simethicone	10 g
Tween 80	0.5 g

"In vitro" dissolution were obtained using the apparatus #2 as described in the United States Pharmacopeia. The 900 ml dissolution medium consisted of a phosphate buffer pH 5.8 and the revolution speed 100 rpm.

[illegible] (h)	[illegible] dissolved (%)
1	5
4	36
8	62
12	84

EXAMPLE 4

The beads as in Example 2 were coated using a fluidized bed coater equipped with a "wurster" system. 8 kg of uncoated beads were introduced in an Aeromatic Aerocoater and 2.77 kg of the following coating suspension was applied at a rate of 30–35 g per minute. Thereafter the coated beads were dried during 15 hours at 45° C.

salts thereof, which comprises beads consisting essentially of in admixture together:

a) an effective amount of Diltiazem or said one or more salts thereof as an active ingredient, and

b) an effective amount of a wetting agent, wherein said wetting agent is selected from the group consisting of a sugar, a C_{12}–C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester, lecithins and a combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl acrylate, and a pharmaceutically-acceptable adjuvant.

2. The extended-release galenical composition of claim 1, wherein said salt is the hydrochloride salt.

3. The extended-release galenical composition of claim 1, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

4. The extended-release galenical composition of claim 3, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

5. The extended-release galenical composition of claim 1, wherein the weight of the Diltiazem salt is about 20 to 95% by weight.

6. A pharmaceutical composition comprising an extended-release galenical composition of Diltiazem or one or more pharmaceutically-acceptable salts thereof, which comprises in capsule form

a) beads consisting essentially of an effective amount of each of Diltiazem or said one or more salts thereof and a wetting agent in admixture together, wherein said wetting agent is selected from the group consisting of a sugar, a C_{12}–C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide ester, an alcohol-polyglycide ester, lecithins and a combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, and

b) one or more other pharmaceutically active ingredients which are pharmaceutically compatible with Diltiazem or said one or more salts thereof.

7. The pharmaceutical composition of claim 6, wherein said one or more other pharmaceutically active ingredients comprise β-adrenoceptor or diuretic compounds or compositions containing the same.

8. The pharmaceutical composition of claim 6, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

9. The pharmaceutical composition of claim 6, wherein said salt is the hydrochloride salt.

10. The pharmaceutical composition of claim 6, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

11. A method for treating angina pectoris or hypertension or both in a mammal which comprises administering to said mammal an effective amount of an extended-release galenical composition consisting essentially of Diltiazem or one or more pharmaceutically-acceptable salts thereof and a wetting agent in admixture together in the form of beads, wherein the wetting agent is selected from the group consisting of a sugar, a C_{12}–C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, an alcohol-polyglycide ester, a glyceride-polyglyceride lecithins and a combination thereof, and

wherein the beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable excipient.

12. The method of claim 11, wherein said administration is orally and once per day.

13. The method of claim 11, wherein said mammal is a human.

14. The method of claim 12, wherein from about 120 mg to about 480 mg of said one or more Diltiazem salts are administered in total per day.

15. The method of claim 11, wherein said salt is the hydrochloride salt.

* * * * *

APPEARS THIS WAY
ON ORIGINAL

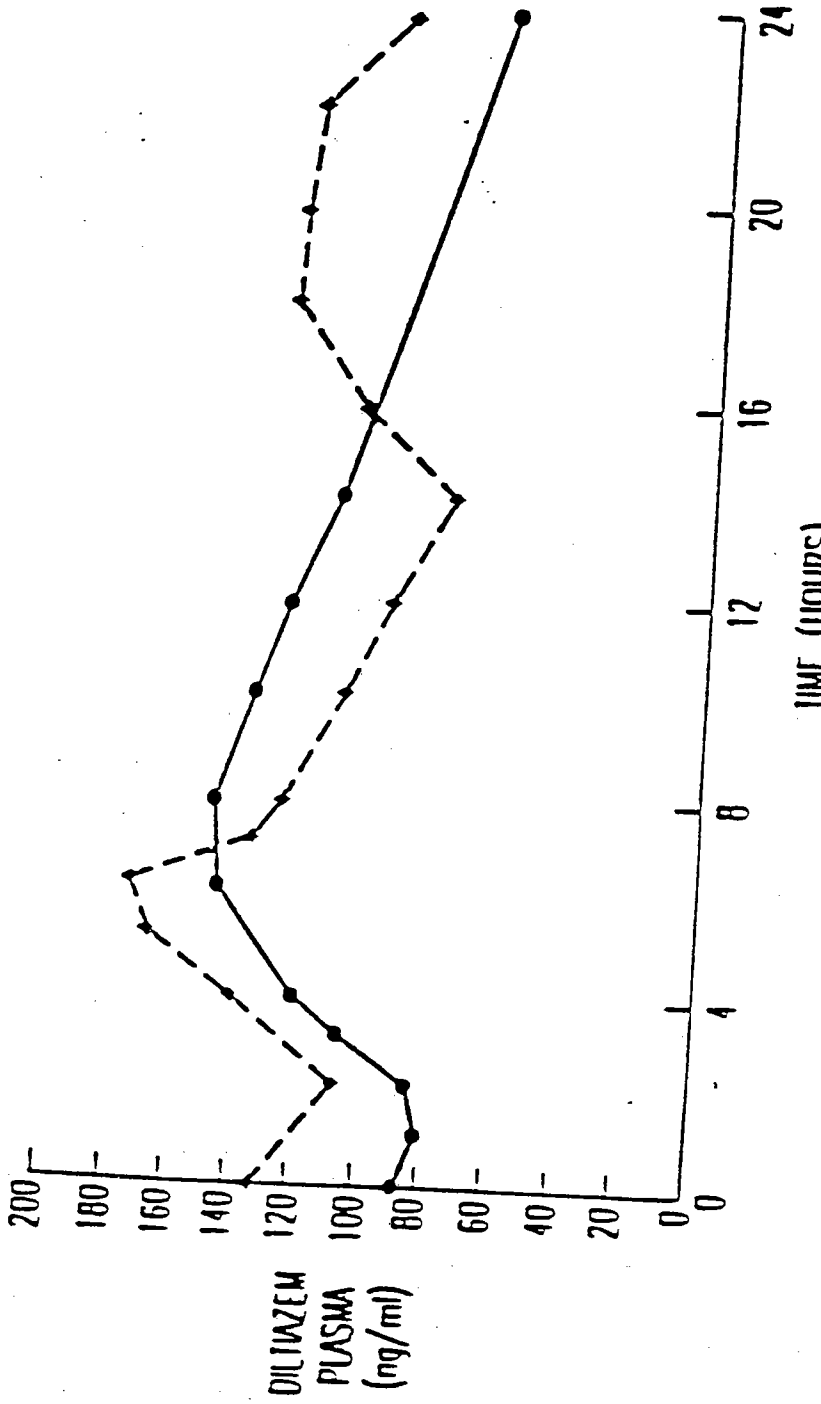

200
180
160
140
120
100
80
60
40
20
0
DILTIAZEM PLASMA (ng/ml)
0
4
8
12
16
20
24
TIME (HOURS)

FIG. 1

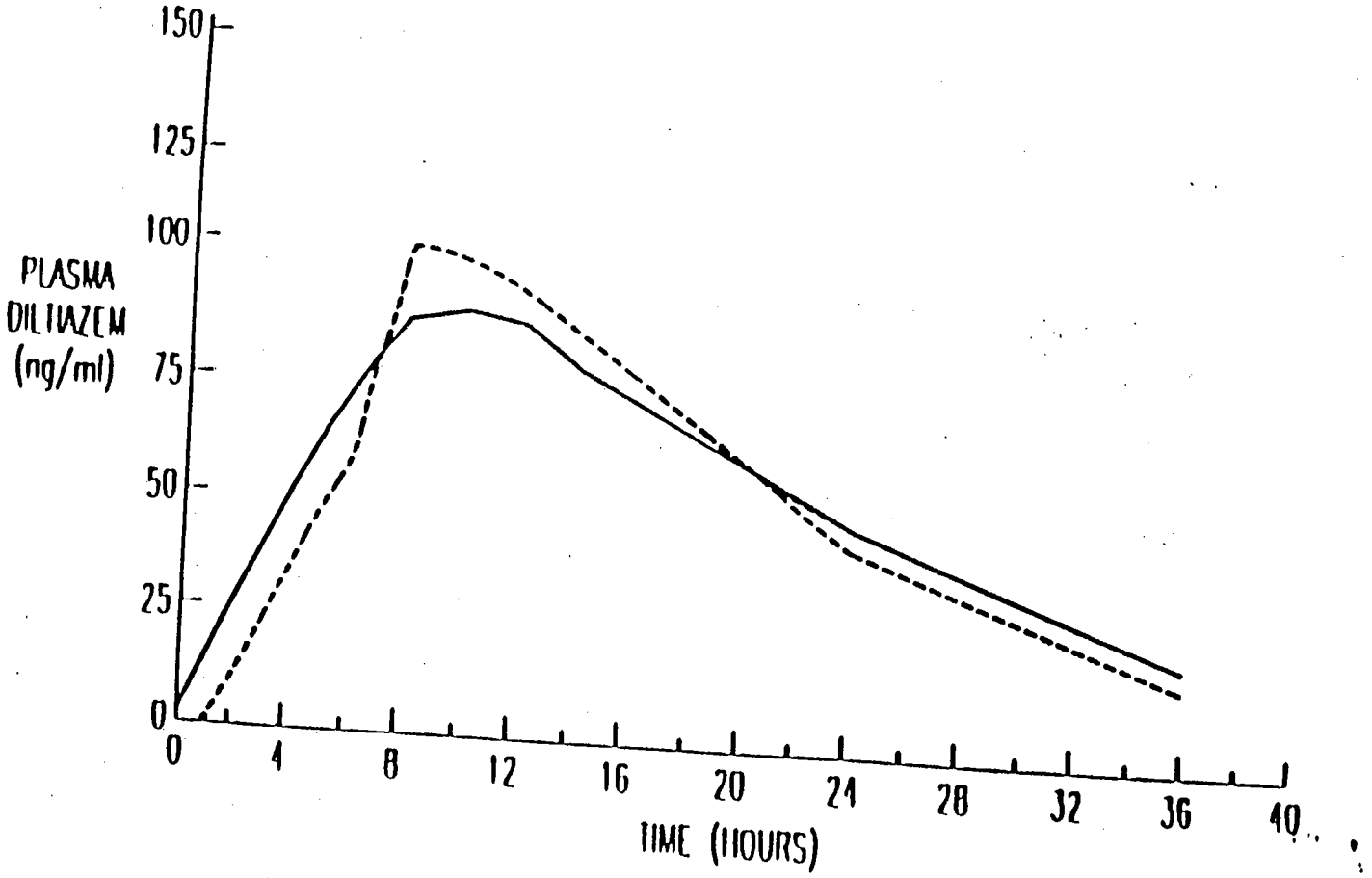


FIG. 2

SECTION 14 – PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

Certification

This section is not applicable to this Supplemental New Drug Application.

EXCLUSIVITY SUMMARY for NDA # 21-392 SUPPL # S-002
Trade Name Cardizem LA Generic Name diltiazem hydrochloride

Applicant Name Biovail Laboratories, Inc. HFD-110
Approval Date April 9, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /X/

   b) Is it an effectiveness supplement? YES /X/ NO /___/

      If yes, what type (SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /X/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity? YES /___/NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

On March 7, 2001, Biovail was granted a full waiver from including pediatric studies for this product.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /X/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 18-602 (Cardizem) NDA# 20-062 (Cardizem CD)

NDA # 19-471 (Cardizem SR) NDA# 20-092 (Dilacor SR)

NDA # 20-027 (Cardizem) NDA# 20-027 (Cardizem)

NDA # 20-401 (Tiazac) NDA# 20-792 (Cardizem)

NDA# 20-939 (Diltiazem HCl)

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO/__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /X/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain:

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #BOO.CT3.012.DIL99 entitled " A double-blind, randomized, parallel-group, dose-response, multicenter study of the safety and efficacy of diltiazem HCl extended release capsules (G99) compared to placebo dosed at bedtime and to G99 dosed in the morning, in the treatment of chronic, stable, exercise-induced angina" was reviewed to support the angina indication.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study #B00.CT3.011.DILG99

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided

substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 51, 711 YES /X/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant

should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

Denise M. Hinton

Signature of Preparer Date: 23Mar04
Title: Regulatory Health Project Manager

Signature of Division Director Date:
Douglas C. Throckmorton, M.D.

cc:
Archival NDA
HFD-110/Division File
HFD-110/RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-392 Supplement Type (e.g. SE5): SE1 Supplement Number: 002

Stamp Date: June 9, 2003 Action Date: April 9, 2004

HFD 110 Trade and generic names/dosage form: Cardizem LA/ Diltiazem Hydrocloride Extended Release Tablets, 120, 240, 300, 360 and 420 mg for once daily administration

Applicant: Biovail Laboratories Inc. Therapeutic Class: Calcium Channel Blocker

Indication(s) previously approved: Hypertension

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Hypertension

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
X Other: This product is not suitable for dosing in the pediatric population.
Application granted under 21 CFR 314.55

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Angina

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
X Other: This product is not suitable for dosing in the pediatric population. Application granted under 21 CFR 314.55

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

BIOVAIL
TECHNOLOGIES LTD.

DEBARMENT CERTIFICATION

Cardizem LA
Diltiazem Hydrochloride Extended Release Tablets, 120, 180, 240, 300, 360 and 420 mg

In accordance with the requirements of Section 306 (k) (1) of the Federal Food Drug and Cosmetic Act, I, the undersigned, certify that, Biovail Laboratories Incorporated did not and will not use in any capacity the services of any person debarred under Section 306 (k) of the Federal Food, Drug and Cosmetic Act connection with this application.

Furthermore, I certify that neither the applicant, nor its employees nor any affiliated company or its employees has been convicted within the last five years for acts described in subsections (a) and (b) of Section 306.

On behalf of Biovail Laboratories Incorporated

Paul Desjardins, Ph.D
Vice President
BIOVAIL TECHNOLOGIES LIMITED

5/30/2003
Date

Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel (301) 594-5365, FAX (301) 594-5494

Memorandum

DATE: 4.04

FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

SUBJECT: NDA 21-392/SE-1, S-002,
NAME OF DRUG: Cardiazem LA
SPONSOR: Biovail Laboratories, Inc.

DOCUMENTS USED FOR MEMO:

1. Project Management Overview, by Denise M. Hinton, date 3.18.04
2. Medical/ Statistical Review by Norman Stockbridge, M.D., Ph.D., and John Lawrence, Ph.D., dated 12.29.03.
3. Debarment Certification, signed by Paul Desjardins, dated 5.30.03.
4. NDA 21-392 submissions by sponsor.

CONCLUSIONS

This memorandum constitutes the secondary review for the named supplement as well as the Divisional memorandum for the approval of Cardiazem LA for the treatment of angina, whether administered in the morning or at night before bedtime.

CHEMISTRY

There was no formal Chemistry review and no Chemistry issues identified.

Environmental Impact Analysis Statement

The sponsor submitted a proposal for an exemption from the Environmental Assessment, dated 8.21.03, that is satisfactory.

PHARMACOLOGY TOXICOLOGY

There was no Pharmacology Toxicology review of this supplement and no issues identified.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

There was no Clinical Pharmacology review of this supplement and no issues identified.

MEDICAL/STATISTICAL REVIEW

Both Dr. Stockbridge and Dr. Lawrence concluded that Cardiazem LA demonstrated antianginal efficacy for both the low and medium doses of Cardiazem LA. The highest dose studied in the trial (420 mg) showed no greater efficacy than the middle dose(360 mg, see primary review page 3). These data are sufficient to demonstrate anti-anginal efficacy for this formulation, although there is no evidence for greater efficacy for the highest dose.

In another analysis, the sponsor sought to compare the effects of am and pm administration of Cardiazem LA, but the design of the studied was flawed (see primary review for discussion). Nothing can be concluded about this comparison; certainly the data do not support any claim that the pm dosing was more or less effective than the am dosing.

Labeling

The sponsor and FDA have come to agreement on the wording of the proposed labeling, including a description of the doses recommended for use. DDMAC has been involved to assure that the labeling does not imply a difference between am and pm dosing, as no clinically relevant difference was demonstrated.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Doug Throckmorton
4/5/04 02:42:19 PM
MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(908) 927-1552
Attention:	Mr. Stefan Ochalski
Company Name:	Biovail Pharmaceuticals Incorporated
Phone:	(908) 927-1752
Subject:	**NDA 21-392/S-002**
Date:	April 2, 2004
Pages including this sheet:	15

From: **Denise M. Hinton**
Phone: **301-594-5333**
Fax: **301-594-5494**

RHPM Overview
March 18, 2004

NDA 21-392	Cardizem LA (diltiazem hydrochloride) Extended Release Tablets
Sponsor:	Biovail Technologies
Classification:	SE1
Date of Application:	June 6, 2003
Date of Receipt:	June 9, 2003
User Fee Goal Date:	April 9, 2004
Date of review:	March 18, 2004

Background:

Diltiazem hydrochloride, a calcium ion cellular influx inhibitor intended for use as an antihypertensive, is currently marketed as once-a-day extended release capsules for daytime administration. Cardizem LA (diltiazem hydrochloride) was approved on February 6, 2003 for the treatment of hypertension, the basis of approval was a double blind clinical study demonstrating the efficacy of 120 mg to 420 mg diltiazem capsules administered at nighttime compared to placebo and 360 mg daytime administration. The related IND is 51,711.

Biovail submitted clinical and labeling information in this efficacy supplement for approval of the angina indication. The study is entitled "A double-blind, randomized, parallel-group, dose-response, multi-center study of the safety and efficacy of diltiazem HCl extended release capsules (G99) compared to placebo dosed at bedtime and to G99 dosed in the morning, in the treatment of chronic, stable, exercise-induced angina." Reference is made to hypertension studies contained in the approved NDA which used diltiazem hydrochloride extended-release capsules in the angina clinical trial. Pharmacokinetic data from nine studies were reviewed in the original NDA and demonstrated that Cardizem LA (diltiazem hydrochloride) extended release tablets are bioequivalent to diltiazem hydrochloride extended release capsules.

Reviews

Medical Review

Reviewer:	Norman Stockbridge, M.D., Ph.D.
Labeling:	Dr. Stockbridge recommended revisions be made to the CLINICAL PHARMACOLOGY/Mechanisms of Action/Angina, Pharmacodynamics and Clinical Studies/Angina, INDICATIONS AND USAGE, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION/Angina sections of the label (See review dated December 29, 2003).
Conclusion:	The study (a randomized, parallel, 3-week comparison of placebo and once daily diltiazem 180, 360 and 420 in the treatment of chronic stable angina) confirmed that the formulation is an effective anti-anginal agent when used once daily. There are no clinical barriers to the approval of the angina indication for Cardizem LA for use once daily in the morning or evening.

Statistical Review:

Reviewer:	John Lawrence, Ph.D. (HFD-710)
Labeling:	In the CLINICAL PHARMACOLOGY/Pharmacodynamics and Clinical Studies/Angina section, Drs. Lawrence and Stockbridge revised the description of the angina trial to reflect the similarities in responses to the various evening

doses, to show the overall modest treatment effect size, and to attribute differences in morning-evening dosing to trial design. The DOSAGE AND ADMINISTRATION/Angina section was revised to discourage use above 360 mg (See review dated December 29, 2003).

Conclusion: Dr. Lawrence reviewed the primary nonparametric analysis that compared groups of changes from baseline in total exercise time assessed at trough to baseline times compared among groups by ANOVA. Dr. Lawrence confirmed that the evening effects were statistically significant at p=o.oo57 to 0.0201, as the low and medium evening doses are significantly different from placebo, but the high dose is not.

Chemistry Review

Reviewer: Ramsharam Mittal, Ph.D.

Labeling: Under the DESCRIPTION section, Dr. Mittal recommended that Hydroxypropylmethylcellulose USP be changed to Hypromellose USP.

Conclusion: Dr. Mittal stated that the Environmental Impact Analysis Statement claiming Categorical Exclusion as per 21 CFR 25.31 is acceptable.

Environmental Assessment: Biovail has filed for categorical exclusion for 120, 180, 240, 300, 360 and 420 mg diltiazem hydrochloride extended release tablets.

Safety Update: No safety concerns were identified.

Patent Information: Patent information is included in the package.

Pediatric Information: Waiver granted.

EER: The overall EER recommendation, dated July 19, 2001, is acceptable. No further inspections are required.

Methods Validation: Methods validation was not requested.

DSI: No DSI audits conducted.

Debarment Certification: Certification is included in the package.

RHPM Summary

To my knowledge, there are no issues that might prevent action on this supplement.

Denise M. Hinton
Regulatory Health Project Manager, HFD-110

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Denise Hinton
4/6/04 04:45:07 PM
CSO

Denise Hinton
4/6/04 04:45:47 PM
CSO

RHPM Labeling Review

NDA:	21-392/SE1-002
Drug:	Cardizem LA
Sponsor:	Biovail Laboratories Inc.
Date of Original Submission:	June 6, 2003
Date of Receipt:	June 9, 2003
Date of Review:	March 10, 2004

Background:
Cardizem LA (diltiazem hydrochloride) 120, 180, 240, 360 and 420 mg Extended Release Tablets was approved on February 6, 2003 for the treatment of hypertension, the basis of approval was a double blind clinical study demonstrating the efficacy of 120 mg to 420 mg diltiazem capsules administered at nighttime compared to placebo and 360 mg daytime administration. The related IND is 51,711. Final printed labeling for this product was approved on January 8, 2004.

Biovail submitted this supplemental application for approval of the new indication, the treatment of angina.

Review:
This supplemental application proposes the following changes to the package insert:

1. Under **CLINICAL PHARMACOLOGY/Mechanisms of Action, Hypertension** was added as a subtitle.

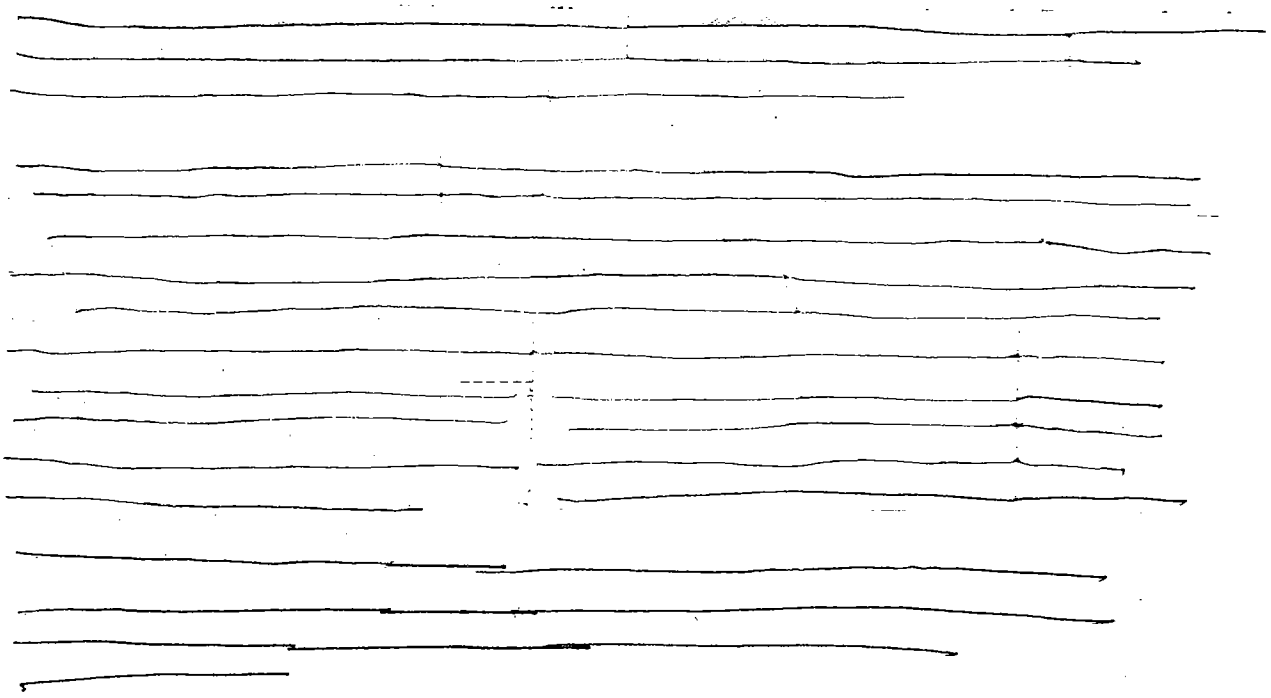
2. Under **CLINICAL PHARMACOLOGY/Mechanisms of Action, Angina** was added as a subtitle with the addition of the following paragraph:

Angina. Diltiazem has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal work loads. Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine induced coronary artery spasms are inhibited by diltiazem.

3. Under **CLINICAL PHARMACOLOGY/Pharmacodynamics in Clinical Studies,** the Hypertension subtitle was added before the 6th paragraph.

4. Under **CLINICAL PHARMACOLOGY/Pharmacodynamics in Clinical Studies,** the Angina subtitle was added along with the following paragraph:

Angina.



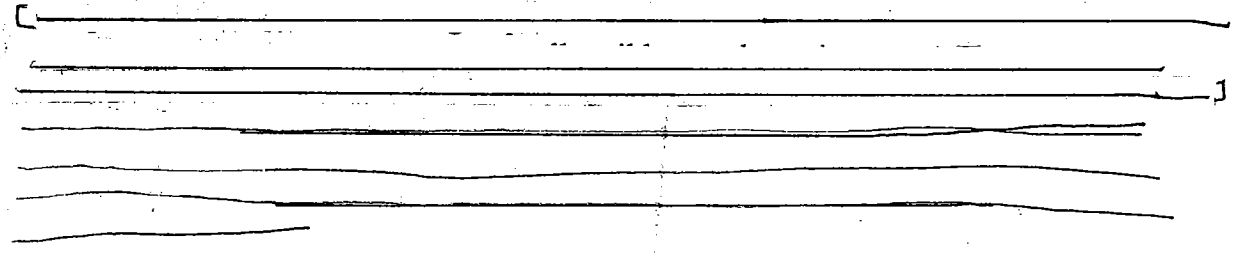
Median Change in Exercise Tolerance Time (sec)
$p \leq 0.05$

6. Under **INDICATIONS AND USAGE**, the following sentence was added after the first sentence:

7. Under **ADVERSE REACTIONS** the words, in the hypertension study, were added at the beginning of the second paragraph.

8. Under **ADVERSE REACTIONS**, the following paragraph was added after the second paragraph:

In the angina study, the adverse event profile of CARDIZEM LA was consistent with what has been previously described for CARDIZEM LA and other formulations of dilitiazem HCl.



9. Under **DOSAGE AND ADMINISTRATION**, the **Angina** subtitle was added after the second paragraph of the Hypertension subsection and reads as follows:

Angina. [redacted]

10. The distribution address was updated and changed from Morrisville, NC, 27560 to Bridgewater, New Jersey 08807.

The Division requested that revisions be made to the label as follows:

1. Under the **DESCRIPTION** section, [redacted] should be changed to Hypromellose USP.

2. Under **Pharmacodynamics and Clinical Studies, Precautions/Beta-Blockers/Carcinogenesis, Mutagenesis Impairment of Fertility,** in vivo and in vitro should not be italicized.

3. Under **Pharmacodynamics and Clinical Studies,** revise the Angina section to read as follows:

Angina. The effects of Cardizem LA on angina were evaluated in a randomized, double-blind, parallel-group, dose-response trial of 311 patients with chronic stable angina. Evening doses of 180, 360 and 420 mg were compared to placebo and to 360 mg administered in the morning. All doses of Cardizem LA administered at night increased exercise tolerance when compared with placebo after 21 hours. The mean effect, placebo-subtracted, was 20 to 28 seconds for all three doses, and no dose-response was demonstrated. Cardizem LA, 360 mg, given in the morning, also improved exercise tolerance when measured 25 hours later. As expected, the effect was smaller than the effects measured only 21 hours following nighttime administration. Cardizem LA had a larger effect to increase exercise tolerance at peak serum concentrations than at trough.

4. Under **INDICATIONS AND USAGE**, revise the second sentence to read as follows:

[redacted]

5. Under **PRECAUTIONS,** revise the **Pregnancy** paragraph to read as follows:

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) resulted in embryo and fetal lethality. These studies revealed, in one species or another, a propensity to cause fetal abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights and pup survival, as well as prolonged delivery times and an increased incidence of stillbirths.

6. Under **ADVERSE REACTIONS**, revise the revise the second paragraph to read as follows:

In the hypertension study, the following table presents adverse reactions more common on diltiazem than on placebo (but excluding events with no plausible relationship to treatment), as reported in placebo-controlled hypertension trials in patients receiving a diltiazem hydrochloride extended-release formulation (once-a-day dosing) up to 540 mg.

Adverse Reactions (MedDRA Term)	Placebo	Diltiazem hydrochloride extended-release	
	n= 120 # pts (%)	120-360 mg n= 501 # pts (%)	540 mg n= 123 # pts (%)
Oedema lower limb	4 (3)	24 (5)	10 (8)
Sinus congestion	0 (0)	2 (1)	2 (2)
Rash NOS	0 (0)	3 (1)	2 (2)

In the angina study, the adverse event profile of CARDIZEM LA was consistent with what has been previously described for CARDIZEM LA and other formulations of diltiazem HCl. The most frequent adverse effects experienced by CARDIZEM LA-treated patients were edema lower-limb (6.8%), dizziness (6.4%), fatigue (4.8%), bradycardia (3.6%), first-degree atrioventricular block (3.2%), and cough (2%).

7. Under **DOSAGE AND ADMINISTRATION,** revise the **Angina** paragraph to read as follows:

Angina.

Dosage for the treatment of angina should be individualized based on response. The initial dose of 180 mg once daily may be increased at intervals of 7 – 14 days if adequate response is not obtained. CARDIZEM LA doses above 360 mg confer no additional benefit.

CARDIZEM LA can be given once daily, either in the evening or in the morning.

Recommendation:
Biovail submitted draft labeling on March 10, 2004 revised as recommended by the Division. An approval letter will be drafted for Dr. Throckmorton's signature.

Denise M. Hinton
Regulatory Health Project Manager, HFD-110

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Denise Hinton
4/6/04 04:50:37 PM
CSO

2 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

78 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

Hinton, Denise

From: Hinton, Denise
Sent: Tuesday, February 10, 2004 11:00 AM
To: Throckmorton, Douglas C; Stockbridge, Norman L
Subject: FW: Cardizem LA S/NDA # 21-392 for the angina indication

-----Original Message-----
From: Thuy Chau [mailto:Thuy.Chau@biovail.com]
Sent: Tuesday, February 10, 2004 10:52 AM
To: Denise Hinton (E-mail)
Subject: Cardizem LA S/NDA # 21-392 for the angina indication

Dear Denise:

Thank you very much for your phone call inquiring whether the comments made by the Division at the April 21, 2000 and May 7, 2003 meetings were addressed. As per your instruction, I am sending you the reply via this e-mail.

* As stated in the Reviewer's guide (Section 8- Clinical Data, Volume 1), Section 2H Clinical Data Summary (Volume 1), and in Section 8B Background and/Overview of Clinical Investigations (Volume 3), the objective of the study was to compare the trough effects of G99 in patients dosed with G99 or placebo, in the morning or in the evening, as recommended by the Division at the April 21, 2000 meeting.

* The collection of data at through, as well as the AM/PM difference and the lack of dose-related effect which were the 2 issues raised at the May 7, 2003 meeting with the Division, were addressed in the following subsections of Section 8G (Integrated Summary of Efficacy) of the submission:

Under 2.0 Study Design and Patient selection
(a) subsection 2.1.1 - Selection of Treadmill Stress Test Times
(b) subsection 2.1.2 - Pharmacokinetic Justification for Treadmill Stress Test Times
Under 3.0 Discussions & Conclusions
(c) subsection 3.1.1 - Lack of a Dose-response
(d) subsection 3.1.2 - Lack of Statistical Significance of the Effect of the G99 360 mg AM Dose

I would appreciate receiving a call from you, or an email, at your convenience regarding the status of the review of our Cardizem LA S/NDA for angina, and any other questions the reviewers might have. Please feel free to call me at 908-927 1754 or email or Fax at 908-927-1554. You can also reach Dr. John Weet, VP Regulatory Affairs by telephone at 908-927-1748 or by Fax at 908-927-1548.

Thank you and with best regards
Thuy

Thuy T. Chau, Ph.D
Director, Regulatory Affairs
Biovail Pharmaceuticals, Inc.
700 202/206 North
Bridgewater, NJ 08807
Tel: 1-908-927-1754
Fax: 1-908-927-1554
Thuy.Chau@biovail.com

ORIGINAL

BIOVAIL
Technologies Ltd.

AMENDMENT TO SUPPLEMENT 002
VIA OVERNIGHT COURIER

August 21, 2003

SUPPL NEW CORRESP
~~A~~
BE1-002(C)

Douglas C. Throckmorton, M.D.
Director, Division of Cardio-Renal Drug Products (HFD-110)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Office Complex II
1451 Rockville Pike
Rockville, MD, USA
20852

Re: NDA 21-392 Cardizem LA, S-002 Amendment
120 mg, 180 mg, 240 mg, 300 mg, 360 mg and 420 mg

Dear Dr. Throckmorton,

Biovail Laboratories Incorporated wishes to amend its supplement application for Cardizem LA 120 mg, 180 mg, 240 mg, 300 mg, 360 mg and 420 mg (Diltiazem Hydrochloride Extended Release Tablets) in response to a telephone request from the Agency on August 20, 2003.

Biovail Laboratories Incorporated is herewith attaching an Environmental Impact Analysis Statement claiming a Categorical Exclusion as per 21 CFR 25.31 for Biovail's new formulation for Cardizem LA (Diltiazem Hydrochloride) for the treatment of Angina. Because Diltiazem Hydrochloride is already an established drug for the treatment of Angina, the Cardizem LA formulation will not be used to expand the patient pool but will be used to acquire only a larger share of the existing patient pool for Diltiazem Hydrochloride.

We trust this amendment is complete and satisfactory for filing. If you have any questions or comments, please contact the undersigned at telephone number (703) 480-6000 or fax number (703) 480-5944.

Sincerely,
On Behalf of Biovail Laboratories Incorporated

Beth Ferguson
Manager, Regulatory Affairs
Biovail Technologies Limited

Biovail Technologies Ltd.
3701 Concorde Parkway
Chantilly, Virginia USA
20151

T 703 480.6000
F 703 480.5990
www.biovail.com

4 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Environmental Impact Analysis Statement

Cardizem LA, 120, 180, 240, 300, 360 and 420 mg

Biovail Laboratories Incorporated claims a Categorical Exclusion
as per 21 CFR 25.31

> "The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or and EIS:
>
> > (a) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety."

Bth Ferguson

08/21/03

Beth Ferguson
Manager, Regulatory Affairs
Biovail Technologies Limited
ON BEHALF OF BIOVAIL LABORATORIES INC.

Date

Hinton, Denise

From: Hinton, Denise
Sent: Thursday, August 14, 2003 9:38 AM
To: 'alexander.rochefort@biovail-btl.com'
Cc: 'beth.ferguson@biovail-btl.com'
Subject: FW: cardizem for angina NDA 21392

Dear Mr. Rochefort,

Below are questions raised by the statistical reviewer regarding the analysis. Please provide me with a response to the following questions:

> A patient could have up to 3 baseline PM exercise measurements. The baseline used in the analysis used a single number that represents the average of the two qualifying measurements.
> In the data set TSMT, the value for the visit # for these baseline pm measurements will be 2.0, 3.0 or 3.1. Let
>
> b1 = exercise time at visit 2.0 in seconds
> b2 = exercise time at visit 3.0 in seconds
> b3 = exercise time at visit 3.1 in seconds
>
> 1a. I can't understand how variability is defined. How would I know if the patient qualified based on their first two measurements (b1 and b2) alone? Do I compare abs(b1-b2) to 15%*b1 or do I compare it to 15%*max{b1, b2}.
>
> 1b. Sometimes, a patient's first two measurements (b1 and b2) appear to qualify them, but they have a b3 anyway. For example, one patient had b1=354, b2= 340, and b3=378. In cases like this, how is the baseline defined?
>
> 1c. Suppose b2=120% * b1, so the patient needed a b3 to qualify. Now, suppose b3=110% *b1. Either the pair {b2,b3} or {b1,b3} appear to qualify them into the study. How is the baseline defined?
>
> 1d. Sometimes the patient does not appear to qualify. For example, Patient S11 at site 2048 had an exercise time of 6 minutes, 58 seconds at visit 2.0 and a time of 10 minutes, 42 seconds at visit 3.0.
>
> 2. Is the following an accurate description of the way that the dichotomous variable for concomitant beta-blocker, ARB, or ACE-I is defined?
> In the data set MEDS, I can find all of the concomitant medications the patient is taking. I look in the variable ATCTEXT2 to see the class of medication the patient is taking. If any of the values are either "AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM" or "BETA BLOCKING AGENTS" then the dichotmous variable is 1 and otherwise it is 0.
>
> 3. Please send me a data set that has one row for each patient containing the following variables:
>
> SITE
> PTNO

> BASEPM (avg. of 2 qualifying baseline exercise time measurements in
> seconds)
> BASEAM
> FINALPM (end of study pm exercise time)
> FINALAM
TRT (1= randomized to placebo, 2=randomized to 180 pm, 3=360 am, 4=360 pm,
> 5=420 pm)
> CON (1= taking concomitant BB, ACEI, or ARB, 0 = not taking any)
>
> 4. The primary analysis starts by ranking the FINALPM measurements among
> the subset of patients with TRT = 1, 2, 4, or 5.
> These ranks are called Y. Then, the pairwise differences for the mean
> response Y among groups 2 vs 1, 4 vs 1, and 5 vs 1 are
> tested using Dunnett's procedure. Is this correct?
>
> 4a. Are the FINALPM ranked or are the changes from baseline
> (FINALPM-BASEPM) ranked to define Y? Was the
> residual normality check, the criteria used to determine if the analysis
> would be changed, and the exact way that
> the analysis would be modified described in the original protocol or any
> amendments?
>
> 5. Some of the tables say "LOCF" and describe that the endpoint is either
> the value at visit #6 or at the final pm visit for patients
> who discontinued early from the study. But, it is impossible to have any
> values carried forward, right? A patient either had a
> measurement at week 3 or had no post-baseline measurements (and was not
> included in the analysis).
>
Thank you,

Denise M. Hinton
Regulatory Health Project Manager
Food and Drug Administration
ivision of Cardio-Renal Drug Products, HFD-110
>

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(908) 927- 1552
Attention:	Mr. Stefan Olchaski
Company Name:	Biovail Laboratories Incorporated
Phone:	(908) 927- 1752
Subject:	**NDA 21-392/S-002** **Teleconference Minutes**
Date:	March 26, 2004
Pages including this sheet:	4

From: **Denise M. Hinton**
Phone: **301-594-5333**
Fax: **301-594-5494**

Teleconference minutes of a meeting between Biovail and the FDA Division of Cardio-Renal Drug Products

NDA:	21-392
Drug:	Diltiazem Hydrochloride Extended Release Tablets
Sponsor:	Biovail Laboratories Incorporated
Date of meeting:	March 10, 2004
Type:	C
Classification:	Labeling Discussion
Meeting chair:	Douglas C. Throckmorton, M.D.
Meeting recorder:	Denise Hinton

FDA Participants:

Douglas C. Throckmorton, M.D.	Division Director Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D.	Team Leader Medical Officer
John Lawrence, Ph.D.	Statistician
Denise Hinton	Project Manager

Biovail Participants:

Stefan Ochalski, MBA	Director,Regulatory Affairs
John Weet, Ph.D.	Vice President Regulatory Affairs
Marie-Louise Jacques, Ph. D., MBA	Vice President Clinical Affairs
Greg Szpunar, Ph. D.	Senior Vice President Research and Development

Background:

Biovail submitted an efficacy supplement for NDA 21-392, Cardizem LA, requesting approval of an angina indication. The Division reviewed the draft label and requested that labeling changes be made to the Description, Clinical Pharmacology/Pharmacokinetics and Metabolism,/Pharmacodynamics and Clinical Studies/Angina, Indications and Usage, Precautions/Beta-Blockers/Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy, Dosage and Administration/Angina sections of the label. The requested revisions were communicated via email on February 10, 18 and 25, 2004. Biovail agreed to all proposed revisions with the exception of the Division's proposed language to the Dosage and Administration/Angina section of the label. The Division requested this teleconference to provide rationale and reach agreement on the proposed text.

In their written correspondence dated February 23, 2004, Biovail recommended that the statement ' [redacted] be deleted from the label. In support of that request, Biovail stated that their angina clinical program has shown that for some patients a dose of 420 mg does provide an efficacious benefit that does not compromise safety. For the primary efficacy analysis, the change from baseline to final visit in total duration of exercise as measured during the CARDIZEM LA trough periods, all nighttime doses (180, 360 and 420 mg) were significantly different from placebo, albeit, the 360 mg dose was better than 180 mg and 420 mg.

Discussion:
Biovail stated that the 420 mg dose was statistically significant and that the design of the trial was not intended to compare doses, but to compare the 420 mg dose against placebo. Patients may get additional benefit with doses above 360 mg, therefore, they request that the sentence be deleted or modified to state such.

The Division stated that the proposed text adequately describes the hypertensive and antianginal effect, as it addresses the initial dose where efficacy was seen as well as describes the upper range of additional benefit of higher

doses. Although the change from baseline differs from placebo, the 420 mg dose is not numerically superior on any metric to show efficacy, and the shape of the curve does not show evidence that 420 mg confers additional benefit over 360 mg.

There was a brief discussion about the exercise tolerance test. Biovail stated that of the 62 patients in the study, only 10 did not benefit from the 420 mg dose, which would support their argument that some patients may benefit from higher doses of Cardizem LA.

The Division needs data demonstrating that there was benefit to taking the higher dose. The argument that 10 patients from a larger randomized trial did have benefit demonstrated is not a strong case. In order to state benefit in the labeling, Biovail should reflect their own data demonstrating that 420 mg beat 360 mg numerically and not rely on data from other similar product labels. The Division is open to modification but will not base the changes on other labels without the requested data.

After some discussion about alternative language, all came to agreement that the sentence would be changed from [redacted] to "Cardizem LA doses above 360 mg appear to confer no additional benefit." Biovail agreed to update the label with the agreed-upon revisions and submit them to the Agency.

Meeting recorder: *{See appended electronic signature page}*
Denise M. Hinton

Meeting concurrence: *{See appended electronic signature page}*
Douglas C. Throckmorton, MD

Draft: 25Mar04
Final: 26Mar04

RD:
Stockbridge 3/26/04
Throckmorton 3/26/04

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Denise Hinton
3/26/04 02:16:13 PM

Doug Throckmorton
3/26/04 02:19:58 PM

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number:	21-392/S-002
Trade Name:	CARDIZEM LA
Generic Name:	(diltiazem hydrochloride) Extended Release Tablets
Strengths:	120, 180, 240, 300, 360 and 420 mg
Applicant:	Biovail Laboratories Inc.
Date of Application:	June 6, 2003
Date of Receipt:	June 9, 2003
Date of Filing Meeting:	July 31, 2003
Filing Date:	August 8, 2003
User Fee Goal date:	April 9, 2004
Indication requested:	Treatment of angina
Type of Application:	Supplement/505(b)(1)
Therapeutic Classification:	Standard

Resubmission after a withdrawal or refuse to file: NO

Chemical Classification: 6S

Other (orphan, OTC, etc.) NA

Has orphan drug exclusivity been granted to another drug for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

NA

If the application is affected by the application integrity policy (AIP), explain. NA

User Fee Status: Paid

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee ID# 4545

Clinical data Referenced to NDA# 21-392 YES

Date clock started after UN June 9, 2003

- Does the submission contain an accurate comprehensive index? YES

- Form 356h included with authorized signature? YES

- Submission complete as required under 21 CFR 314.50? YES

- If electronic NDA, does it follow the Guidance? YES

If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? NA

- Patent information included with authorized signature? YES

- Exclusivity requested? 3 Years YES

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES

  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? NA
  If no, for what ages and/or indications was a waiver and/or deferral requested:

- Field Copy Certification (that it is a true copy of the CMC technical section)? NO
  Submitted with the original NDAs 21-392 and NDA 21-420

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? YES

List referenced IND numbers: IND 51, 711

End-of-Phase 2 Meeting? NO

Pre-NDA Meeting(s)? NO

Project Management

Copy of the labeling (PI) sent to DDMAC? YES

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support? YES

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support? NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? NA

Advisory Committee Meeting needed? NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? Yes
  If no, did sponsor submit a complete environmental assessment?
  If EA submitted, consulted to Nancy Sager (HFD-357)?

- Establishment Evaluation Request (EER) package submitted? NO

- Parenteral Applications Consulted to Sterile Products (HFD-805)? NA

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 30, 2003

BACKGROUND:
Biovail Technologies Ltd. has submitted supplement NDA 21-392/S-002, dated June 6, 2003, for approval of CARDIZEM LA (diltiazem hydrochloride) 240, 300 and 360 mg Extended Release Tablets for the treatment of angina. Cardizem LA was approved on February 6, 2003 for the treatment of hypertension.

Diltiazem Hydrochloride Extended Release capsules were used in the angina clinical investigation in the hypertension trial for NDA 21-392. Information from this placebo controlled double-blind clinical study (B00.CT3.012.DIL G99) that supports the safety and efficacy of Cardizem LA in the treatment of angina is included in the supplement, in addition to the Human Pharmacokinetics and Bioavailability Summary.

ATTENDEES:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products
Ramsharan Mittal, Ph.D.	Chemist
Lydia Velazquez, Pharm. D.	Biopharmaceutist
John Lawrence, Ph.D.	Statistician
Rob Shibuya, Ph.D.	Pharmacologist, Division of Scientific Investigations
Sriram Subramaniam, Ph.D.	Physiologist, Division of Scientific Investigations
Zelda McDonald	Chief of Project Management Staff
Denise Hinton	Regulatory Health Project Manager

ASSIGNED REVIEWERS:

Discipline	Reviewer/Review completion date	
Medical:	Norman Stockbridge, M.D., Ph.D.	1Feb03
Statistical:	John Lawrence, Ph.D.	1Sep03
Chemist:	Ramsharam Mittal, Ph.D.	1Feb03
Biopharmaceutical:	Lydia Velazquez, Pharm.D.	1Feb03
DSI:	Rob Shibuya, Ph.D.	
Project Manager:	Denise M. Hinton	

Per reviewers, all parts in English, or English translation?	YES
CLINICAL –	File
• Clinical site inspection needed:	NO
MICROBIOLOGY CLINICAL –	NA
STATISTICAL –	File

BIOPHARMACEUTICS –	File
• Biopharm. inspection Needed:	NO
PHARMACOLOGY –	File
CHEMISTRY –	File
• Establishment(s) ready for inspection?	YES

REGULATORY CONCLUSIONS:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

Denise M. Hinton
Regulatory Project Manager, HFD-110

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-392/S-002

6/16/03

Biovail Laboratories Incorporated
Attention: Thuy T. Chau, Ph.D.
Director, Regulatory Affairs
3701 Concorde Parkway
Chantilly, VA 20151

Dear Dr. Chau:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cardizem LA (diltiazem hydrochloride) 240, 300, and 360 mg Extended-release Tablets

NDA Number: 21-392

Supplement number: 002

Review Priority Classification: Standard (S)

Date of supplement: June 6, 2003

Date of receipt: June 9, 2003

This supplemental application proposes a new indication for Cardizem LA for the treatment of angina.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 8, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 9, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Ms. Denise Hinton
Regulatory Health Project Manager
(301) 594-5333

Sincerely,

{See appended electronic signature page}

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Mr. John B. Dubeck
U.S. Agent for Biovail Laboratories Inc.
Keller and Heckman
1001 G Street, N.W., Suite 500 West
Washington, D.C. 20001

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zelda McDonald
6/16/03 10:09:54 AM

Minutes of a Teleconference between Biovail and the FDA Division of Cardio-Renal Drug Products

Sponsor:	Biovail Technologies Limited
NDA:	21-392
Drug:	Diltiazem Hydrochloride Extended Release Tablets
Date of meeting request:	April 8, 2003
Date of briefing document:	April 8, 2003
Date of confirmation:	April 16, 2003
Date of meeting:	May 7, 2003
Time:	11:30 AM –12:00 PM
Type:	C
Classification:	Guidance

FDA Participants:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Lydia Velazquez, Pharm.D.	Clinical Pharmacology and Biopharmaceutist, HFD-860
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Biovail Participants:

Alex Rochefort	VP Regulatory Affairs
Thuy Chau Ph.D	Director Regulatory Affairs
Paul Desjardins	VP Product Development Operations
Kenneth Albert Ph.D	VP Clinical Development
Theo Gana, M.D., Ph.D.	Director Clinical Development

Background:
Biovail requested a teleconference to discuss their planned supplemental NDA in support of a new Angina indication and labeling text for Cardizem LA. An angina study has already been performed in which diltiazem extended release capsules were used instead of the extended release tablet formulation. Bioequivalence was previously established in NDA 21-392 for Cardizem LA, currently approved for a hypertension indication.

Discussions:
The Division asked the Sponsor if the study was conducted under the IND. The Sponsor confirmed that the study was conducted under [redacted] sites would be available for inspection and they have all primary data sets.

1. Does the Agency concur that the clinical data outlined in this briefing package provides adequate efficacy and safety information to support the approval of a Cardizem-LA angina labeling indication?

FDA response: Subject to review of the clinical data, an indication for angina could be supported.

2. Does the Agency concur that the clinical data outlined in the briefing package adequately supports the approval of the following Cardizem-LA angina labeling text for "Indications" section of the P.I.:
   "Cardizem-LA is indicated for the management of chronic stable angina [redacted]

   FDA response: The labeling text is a review issue and is dependent on data, and the population studied will certainly be described.

3. Does the Agency concur that the clinical data outlined in this briefing package adequately supports the approval of the Cardizem-LA P.I. "Dosage & Administration" text statement that,
   [redacted]

   FDA response: The labeling text for the Dosage and Administration section is a review issue but it is not clear that the proposed labeling will be accepted. The timing of trough measure shows a difference between morning (AM) and evening (PM) administration with AM administration being measured 25 hours later and effect for PM administration being 21 hours later. The sponsor will need to make a strong case that the observed difference is not simply a difference that is predicted based on the pharmacokinetics of the drug.

   The Sponsor stated that in a previous meeting with the Division, the timing of measurement and selections were found acceptable.

   The Division asked the Sponsor to include the agreement and provide the rationale for the differences with AM/PM administration in the supplemental NDA.

   The Sponsor asked if they make a cogent argument and convince the Division that the timing is not an issue but a difference in AM versus PM administration, could the proposed labeling statement be supported if 21 hour versus 25 hour does not prove to effect the results.

   The Division stated that the decision would be based on the robustness of their single study and whether we were convinced that the value findings would be seen if the trial was repeated. Unless the Sponsor is able to convince the Division that the difference could be reproduced, the proposed labeling text for the Dosage and Administration section could not be supported since there would be difficulty in knowing how to develop confidence from the single trial. There is also concern about including the difference in labeling because the trial has several surprises such as the AM/PM difference and lack of dose related effect.

   The Sponsor stated that the dose remains consistent for all variables evaluated thus supporting that there is a lack of dose related effect.

Conclusion/Recommendations

- The proposed data could support an angina indication for Cardiazem LA. A description of the trial data, including the populations studied would be included in the label under those circumstances.

- Regarding the AM/PM difference, the Sponsor needs to justify the finding as more than simply a pharmacokinetic difference. Review issues in this regard will include the apparent lack of dose-response relationship in the trial.

- The Biometricians need to have the SAS data sets, and annotated case report forms should be provided in the NDA. The Sponsor should also provide the program code for the primary efficacy analysis to interpret variables.

Meeting recorder: _____
Denise M. Hinton

Meeting concurrence: _____
Douglas C. Throckmorton, M.D.

Draft: 8May03
Final: 19May03

RD:
Velazquez 12May03
Stockbridge 13 May 03
Throckmorton 15May03

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Denise Hinton
5/19/03 03:14:33 PM
Minutes signed by Dr. Throckmorton and faxed to the sponsor on May 19, 2003.