CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20062/S027

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 2 4 1999

NDA 20-062/S-027

Marion Merrell Dow (Europe) AG
as General Partner of
Carderm Capital L.P.
c/o Westbroke Limited
Attention: Mr. Carlos A. Austin
Richmond House
12 Par-la Ville Road
P.O. Box HM 1022
Hamilton HM DX
Bermuda

Dear Mr. Austin:

Please refer to your supplemental new drug application dated January 7, 1999, received January 11, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardizem CD (diltiazem hydrochloride) 180, 240, 300 and 360 mg Capsules.

We acknowledge receipt of your submissions dated May 11, June 18, and July 27, 1999. Your submission of June 18, 1999 constituted a complete response to our May 7, 1999 action letter.

This supplemental new drug application provides for a new dosage strength, 360 mg Capsules. The formulation of this new capsule strength is slightly modified from the other approved dosage strength capsules. Final printed labeling has been revised to incorporate information regarding this new dosage strength. In addition, the **How Supplied** statement was revised to read as follows:

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

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert and immediate container and carton label submission dated June 18, 1999). Accordingly, the supplemental application is approved effective on the date of this letter.

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

If you have any questions, please contact:

David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

/S/ 8/22/03

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20062/S027

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-062/S-027

MAY - 7 1999

Marion Merrell Dow (Europe) AG
as General Partner of
Cardem Capital L.P.
c/o Westbroke Limited
Attention: Carlos A. Austin
Richmond House
12 Par-la Ville Road
P.O. Box HM 1022
Hamilton HM DX
Bermuda

Dear Mr. Austin:

Please refer to your supplemental new drug application dated January 7, 1999, received January 11, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardizem CD (diltiazem HCl) 120, 180, 240 and 300 mg Capsules.

We acknowledge receipt of your submission dated March 5, 1999.

This supplement provides for a new dosage strength, 360 mg Capsules. The formulation of this new capsule strength is slightly modified from the other approved dosage strength capsules.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) revised as follows:

The Storage Statement should be revised in the package insert and the container labels to read as follows:

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

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please note that stability data at the 12-month time point for the 360 mg strength capsule at 25°C/60% RH and at 30°C/60% RH should be submitted in support of a 24-month expiration date.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

/S/ 5/7/99

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20062/S027

FINAL PRINTED LABELING

Labeling: ORIGINAL

NDA No: 20-162 Rec'd. 6-21-99

Reviewed by: Acceptable

APPROVED AUG 24 1999

50018939

Prescribing Information as of May 1999

CARDIZEM® CD

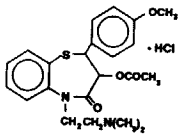
(diltiazem HCl)

Capsules

Prescribing Information as of May 1999
CARDIZEM® CD
(diltiazem HCl)
Capsules

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion 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 chemical structure 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 450.98. CARDIZEM CD is formulated as a once-a-day extended release capsule containing either 120 mg, 180 mg, 240 mg, 300 mg, or 360 mg diltiazem hydrochloride. The 120 mg, 180 mg, 240 mg, and 300 mg capsules also contain: black iron oxide, ethylcellulose, FD&C Blue #1, fumaric acid, gelatin-NF, sucrose, starch, talc, titanium dioxide, white wax, and other ingredients. The 360 mg capsule also contains: black iron oxide, diethyl phthalate, FD&C Blue #1, gelatin-NF, povidone K17, sodium lauryl sulfate, starch, sucrose, talc, titanium dioxide, and other ingredients.
For oral administration.

CLINICAL PHARMACOLOGY

The therapeutic effects of CARDIZEM CD 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. CARDIZEM CD 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. CARDIZEM CD 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 spasm are inhibited by diltiazem.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular 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 nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects

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 have 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.

In hypertensive patients, CARDIZEM CD produces antihypertensive effects both in the supine and standing positions. In a double-blind, parallel, dose-response study–utilizing doses ranging from 90 to 540 mg once daily, CARDIZEM CD lowered supine diastolic blood pressure in an apparent linear manner over the entire dose range studied. The changes in diastolic blood pressure, measured at trough, for placebo, 90 mg, 180 mg, 360 mg, and 540 mg were –2.9, –4.5, –6.1, –9.5, and –10.5 mm Hg, respectively. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects. CARDIZEM CD 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 CARDIZEM CD produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. CARDIZEM CD 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.

In a double-blind, parallel dose-response study of doses from 60 mg to 480 mg once daily, CARDIZEM CD increased time to termination of exercise in a linear manner over the entire dose range studied. The improvement in time to termination of exercise utilizing a Bruce exercise protocol, measured at trough, for placebo, 60 mg, 120 mg, 240 mg, 360 mg, and 480 mg was 29, 40, 56, 51, 69, and 68 seconds, respectively. As doses of CARDIZEM CD were increased, overall angina frequency was decreased. CARDIZEM CD, 180 mg once daily, or placebo was administered in a double-blind study to patients receiving concomitant treatment with long-acting nitrates and/or beta-blockers. A significant increase in time to termination of exercise and a significant decrease in overall angina frequency was observed. In this trial the overall frequency of adverse events in the CARDIZEM CD treatment group was the same as the placebo group.

Intravenous diltiazem 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 CARDIZEM 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

Chronic oral administration of CARDIZEM 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.)

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%. CARDIZEM 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 CARDIZEM is 70% to 80% bound to plasma proteins. Competitive in vitro ligand binding studies have also shown CARDIZEM 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 nine patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

CARDIZEM CD Capsules. When compared to a regimen of CARDIZEM tablets at steady-state, more than 95% of drug is absorbed from the CARDIZEM CD formulation. A single 360-mg dose of the capsule results in detectable plasma levels within 2 hours and peak plasma levels between 10 and 14 hours; absorption occurs throughout the dosing interval. When CARDIZEM CD was coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected. Dose-dumping does not occur. The apparent elimination half-life after single or multiple dosing is 5 to 8 hours. A departure from linearity similar to that seen with CARDIZEM tablets and CARDIZEM SR capsules is observed. As the dose of CARDIZEM CD capsules is increased from a daily dose of 120 mg to 240 mg, there is an increase in the area-under-the-curve of 2.7 times. When the dose is increased from 240 mg to 360 mg there is an increase in the area-under-the-curve of 1.6 times.

INDICATIONS AND USAGE

CARDIZEM CD is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

CARDIZEM CD is indicated for the management of chronic stable angina and angina due to coronary artery spasm.

CONTRAINDICATIONS

CARDIZEM 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.** CARDIZEM 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 CARDIZEM (diltiazem hydrochloride) 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 CARDIZEM 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 CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General

CARDIZEM (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 CARDIZEM. 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 CARDIZEM 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 CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications.

CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

Beta-blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM 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 CARDIZEM (diltiazem hydrochloride) 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, non-significant 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 CARDIZEM 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 CARDIZEM 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.

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.

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 five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater. There are no well-controlled studies in pregnant women; therefore, use CARDIZEM 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 CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

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.

The following table presents the most common adverse reactions reported receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined

Adverse Reactions	Cardizem CD (n=607)	Placebo (n=301)
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of CARDIZEM CD capsules, CARDIZEM tablets, and CARDIZEM SR capsules involving over 3200 patients, the most common events (ie, 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 were reported infrequently (less than 1%) in angina or hypertension trials:

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, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase

Dermatological: Petechiae, photosensitivity, pruritus, urticaria

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: 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 CARDIZEM 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

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 elimination 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 1.0 mg). If there is no response to vagal blockade, 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 (eg, dopamine or levarterenol bitartrate).

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

Patients controlled on diltiazem alone or in combination with other medications may be switched to CARDIZEM CD capsules at the nearest equivalent total daily dose. Higher doses of CARDIZEM CD 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 doses to 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.

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 usual dosage range studied in clinical trials was 240 to 360 mg once daily. Individual patients may respond to higher doses of up to 480 mg once daily.

Angina. Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 or 180 mg once daily. Individual patients may respond to higher doses of up to 480 mg once daily. When necessary, titration may be carried out over a 7- to 14-day period.

Concomitant Use With Other Cardiovascular Agents.

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

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) Capsules				
Strength	Quantity	NDC Number	Description	Number
120 mg	30 btl	0088-1795-30	Light turquoise blue/light turquoise blue capsule imprinted with cardizem CD and 120 mg on one end.	-1797-30
	90 btl	0088-1795-42		-1797-42
	100 UDI*	0088-1795-49		-1797-49
180 mg	30 btl	0088-1796-30	Light turquoise blue/blue capsule imprinted with cardizem CD and 180 mg on one end.	-1796-30
	90 btl	0088-1796-42		-1796-42
	100 UDI*	0088-1796-49		-1796-49
240 mg	30 btl	0088-1797-30	Blue/blue capsule imprinted with cardizem CD and 240 mg on one end.	-1797-30
	90 btl	0088-1797-42		-1797-42
	100 UDI*	0088-1797-49		-1797-49
300 mg	30 btl	0088-1796-30	Light gray/blue capsule imprinted with cardizem CD and 300 mg on one end.	-1796-30
	90 btl	0088-1796-42		-1796-42
	100 UDI*	0088-1796-49		-1796-49
360 mg	90 btl	0088-1795-42	Light blue/white capsule imprinted with cardizem CD and 360 mg on one end.	-1795-42

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.

Prescribing Information as of May 1999

Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA
www.hmr.com

50018939

Labeling: ORIGINAL

NDA No: 20-160 Rc'd. 6-01-99

Reviewed by: [signature] 8-24-99

ITEM # 50018907	DATE: 5/18/99
	CICERO JOB NO.: 43874
PRODUCT: LABEL, CARDIZEM CD, CAPSULES 360 MG, 90 CT.	
PRINTER: NEW JERSEY PACKAGING	
PMS 293	

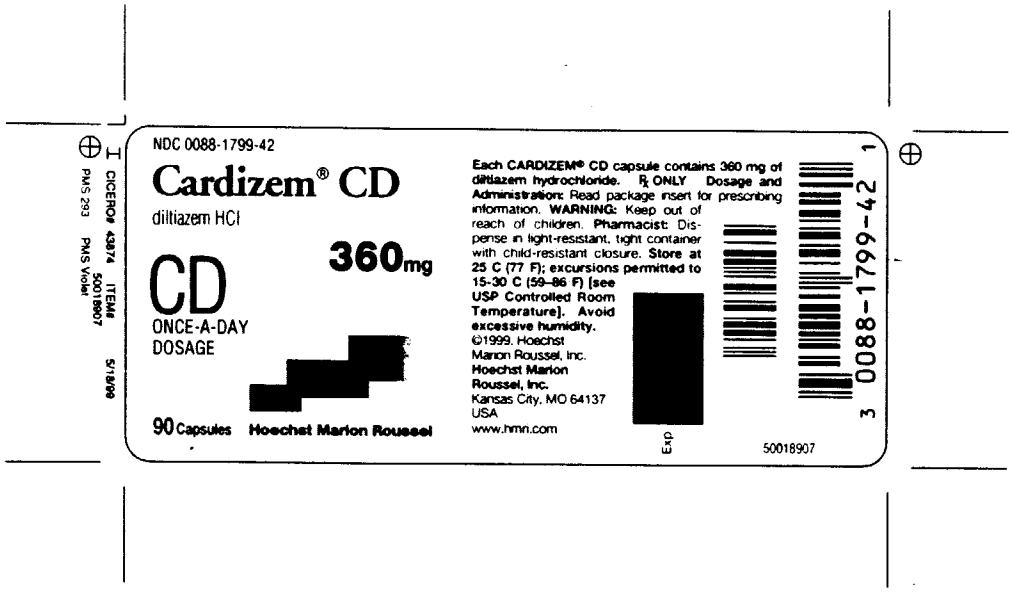
APPROVALS

FUNCTIONAL

PROOFREADING

REGULATORY

APPROVED
AUG 24 1999



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20062/S027

CHEMISTRY REVIEW(S)

JUL 28 1999

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-062
3. Name and Address of Applicant (City & State) Carderm Capital L.P. c/o Westbroke Limited Raymond House 12 Par La Ville Road Hamilton, HM 12 Bermuda		4. Supplement(s) Number(s) Date(s) SCF-027 6/18/99
5. Drug Name CARDIZEM CD	6. Nonproprietary Name Diltiazem hydrochloride	8. Amendments & Other (reports, etc) - Dates Orig - 1/7/99 BC-3/5/99
7. Supplement Provides For: Response to letter of May 7, 1999 for S-027.		
9. Pharmacological Category Ca antagonist (hypertension)	10. How Dispensed [X] Rx [ ] OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Capsules, CD (controlled diffusion, once-a-day)	13. Potency(ies) 120, 180, 240 and 300 mg/capsule	
14. Chemical Name and Structure 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-(dimethyl-phenyl)-, monohydrochloride, (+)-cis-		15. Records/Reports Current [ ] Yes [ ] No Reviewed [ ] Yes [ ] No

16. Comments:

As requested in the letter, final proofs for the bottle labels and final printed labeling for the package insert showing the changes to the storage statement are included.

Updated (12 month) stability report is included. The statistical analysis shows that the projected shelf life of the 360 mg capsules is greater than 24 months is also included.

Labels - storage statement has been corrected. Satisfactory.

17. Conclusions and Recommendations:

For the final printed labeling, Hoechst Marion Roussel needs to use larger font. Unacceptable.

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	/S/	June 29, 1999

Distribution: [X] Original Jacket [ ] Reviewer [ ] Division File [ ] CSO

20062S27.AM1

/S/ 7-28-99

MAY 6 1999

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-062
3. Name and Address of Applicant (City & State) Carderm Capital L.P. c/o Westbroke Limited Raymond House 12 Par La Ville Road Hamilton, HM 12 Bermuda		4. Supplement(s) Number(s) Date(s) SCF-027 1/7/99
5. Drug Name CARDIZEM CD	6. Nonproprietary Name Diltiazem hydrochloride	8. Amendments & Other (reports, etc) - Dates Bc 3/5/99 ltr
7. Supplement Provides For: addition of 360 mg capsule strength (slightly modified) to the Cardizem CD capsules.		
9. Pharmacological Category Ca antagonist (hypertension)	10. How Dispensed ☒ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Capsules, CD (controlled diffusion, once-a-day)	13. Potency(ies) 120, 180, 240 and 300 mg/capsule	
14. Chemical Name and Structure 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-(dimethyl-phenyl)-, monohydrochloride, (+)-cis-		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. **Comments:**

The formulation change is found in the Active Bead. All other aspects, including the sustained release coating, of the manufacturing process of the capsule remain unchanged from that which is currently approved.

This new capsule will be manufactured and controlled by Hoechst Marion Roussel, Inc. in Kansas City, MO. No change in formulation to the other approved strengths is proposed in this supplement.

17. **Conclusions and Recommendations:**

EES requested on 1/19/99. Acceptable on 5/5/99
Biopharmaceutics review requested on 1/19/99. Approvable - 4/23/99.

Approvable - due to labeling issues. Storage statement has to be modified: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Container label - storage statement should be changed.

18. REVIEWER		
Name Danute G. Cunningham	**Signature** /S/	**Date Completed** May 5, 1999

Distribution: ☒ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

20062S27.SUP

5/5/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20062/S027

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APR 23 1999

Clinical Pharmacology/Biopharmaceutics Review

NDA 20-062
Serial #: SCF-027
Compound #: Cardizem CD 360mg Capsules
Hoechst Marion Roussel
Submission Date: January 7, 1999

Reviewer: Thomas A. Parmelee, Pharm.D.

Type of Submission: Supplement for New Formulation Study Report-Cardizem CD 360mg Capsules- A Bioequivalence Study and a Food Effect Study

BACKGROUND

NDA-062 has been approved for Cardizem CD (diltiazem HCl) Capsules in the strengths of 120mg, 180mg, 240mg, and 300mg. The maximum daily dose for diltiazem extended release capsules is established at 360mg. A new 360mg capsule formulation has been developed, and is the topic of this supplemental submission. The new 360mg capsule contains a formulation that is slightly modified from the currently approved lower strength capsules. The formulation change is found in the active bead of the drug product.

Two studies were submitted to the Office of Clinical Pharmacology and Biopharmaceutics for review. These studies were designed to show that the new Cardizem CD 360mg capsule formulation is bioequivalent to two Cardizem CD 180mg marketed capsules. One study is a bioequivalence study comparing single-dose and multiple-dose administration of the new 360mg capsules to the marketed 180mg strength capsules. The second study examines the effect of food on the single-dose pharmacokinetics of the new 360mg diltiazem capsule formulation. These studies are summarized in Appendix 1 and Appendix 2, respectively.

RESULTS

It appears that both lots of the new 360mg capsule formulation are bioequivalent to the marketed 180mg capsule formulation in the single-dose comparisons in terms of both AUC (0-inf) and Cmax for both parent diltiazem and N-desmethyl metabolite.

In the steady-state comparisons, bioequivalency is met in terms of AUC, ss and Cmax, ss between treatments, and only fails the 80-125% rule for Treatment B (lot # RH9738) in terms of Cmin, ss for parent diltiazem.

The 90% confidence intervals between the high-fat breakfast treatment and the fasted treatment were within the 80-125% rule for both AUC (0-inf) and Cmax when looking at parent diltiazem and the N-desmethyl metabolite. Food does not appear to significantly affect the PK parameters of either lot of 360mg diltiazem capsules.

COMMENTS

1) Gender should not have been considered inclusion/exclusion criteria for these two clinical studies unless there was a specific reason for doing so. This point was mentioned to the sponsor via a teleconference before the start of the study.
2) The dissolution specifications are appropriate for the new strength capsule.
3) The draft prescription labeling submitted from the sponsor shows that the 360mg capsules contain black iron oxide, FD&C Blue #1, and starch. These ingredients were not listed in the composition of the capsules for review.

RECOMMENDATIONS

The new dosage strength for Cardizem CD 360mg capsules is approvable from the standpoint of the Office of Clinical Pharmacology and Biopharmaceutics. The comment above regarding the draft prescription labeling was conveyed to the review chemist. The dissolution methodology and specifications for the new strength are:

Apparatus:	USP Type 2 (paddle)
Speed:	100 rpm
Media:	900mL degassed 0.1N HCl
Temperature:	37 C +/- 0.5 C

Time (hrs.)	Specifications (%)
6 hours	%
12 hours	%
18 hours	%
24 hours	NLT %
30 hours	NLT %

The draft prescription labeling (updated October 1998) and label included with the submission are attached to this review. The labeling for all diltiazem products is currently being updated and reviewed by this division (updated November 1998). The labeling for this new Cardizem CD 360mg capsule formulation should reflect the final printed labeling decided upon by the sponsor and the Agency for all Cardizem CD products.

/S/

Thomas A. Parmelee, Pharm.D. 4/23/99

APPENDIX 1

"BIOEQUIVALENCE OF 360MG DILTIAZEM HCL FORMULATIONS AND CARDIZEM CD AFTER SINGLE AND MULTIPLE DOSE ADMINISTRATIONS IN HEALTHY MALE SUBJECTS"

STUDY: Protocol # DZPR0207
Report K-98-0235-D

SPONSOR: Licensed to:
Hoechst Marion Roussel Inc.
P.O. Box 9627, H3-M2112
Kansas City, MO 64134-0627

Authorized by:
Carderm Capital L.P.
Raymond House
12 Par La Ville Road
Hamilton, HM 12 Bermuda

INVESTIGATOR AND STUDY SITE:

OBJECTIVES:

To determine whether 360mg Diltiazem HCL capsule formulations are bioequivalent to marketed 180mg Cardizem CD capsules.

FORMULATIONS:

1) Diltiazem 360mg capsules (lot# RH9736); Batch size
2) Diltiazem 360mg capsules (lot# RH9738); Batch size
3) Cardizem CD 180mg marketed capsules (lot# P31048)

The following table shows the composition of the new formulation of Cardizem CD 360mg Capsules:

STUDY DESIGN:

The study design was a randomized, open-label, single- and multiple-dose, 3-period, crossover study with a washout period of 12 days between treatments. The study population was 26 healthy, non-smoking males between the ages of 18 to 45 years. Subjects received each of the three treatment regimens in a randomized fashion:

Treatment A: One diltiazem 360mg capsule (RH9736) given as a SD on day 1, and then q.d. on days 3-9.
Treatment B: One diltiazem 360mg capsule (RH9738) given as a SD on day 1, and then q.d. on days 3-9.
Treatment C: Two Cardizem CD 180mg capsules (P31048) given as a SD on day 1, and then q.d. on days 3-9.

Subjects were continuously monitored for general health and any adverse reactions. Heart rate, blood pressure, and 12-lead ECG recordings, clinical chemistry, and hematological exams were done before the study and upon completion. Plasma samples were collected before the SD on day 1 and 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 21, 24, 36, and 48 hours following the dose. The subjects received seven days of multiple dosing during days 3-9. Trough plasma samples were obtained before the dose on days 8 and 9, and 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 21, and 24 hours following the day 9 dose.

ASSAY:

Table B: Dissolution Data for Cardizem CD 360mg Capsules

Time	Specifications (%)	RH9738 (%)	Percent Dissolved RH9736 (%)	P31048 180mg (%)
3 hours				
6 hours	%			
9 hours				
12 hours	%			
15 hours				
18 hours	%			
24 hours	NLT %			
30 hours	NLT %			

DATA ANALYSIS:

Pharmacokinetic analysis of diltiazem and MA metabolite concentrations in plasma was conducted by non-compartmental methods. The metabolite DAD concentrations were presented by descriptive statistics only (mean, standard deviation, CV%). The primary PK comparisons include Cmax and AUC (0-inf) following single dose administration; and Cmax,ss, Cmin,ss, trough plasma concentrations (days 8, 9, and 10), and AUCss for multiple dose steady-state findings.

Comparisons between treatments were made for diltiazem and MA metabolite pharmacokinetic parameters and trough plasma levels. An analysis of variance (ANOVA) was performed for each parameter using PROC MIXED SAS with terms for sequence, subject within sequence, period, and treatment. Least square means, treatment differences, and 90% confidence intervals for treatment differences were determined. These log-transformed results were back-transformed by exponentiation to obtain adjusted means, treatment ratios, and 90% confidence intervals for these treatment ratios. Each lot of the diltiazem 360mg (Treatments A and B) was compared to the marketed reference Cardizem CD 180mg (Treatment C). Bioequivalence was to

be concluded if the limits of the 90% confidence interval on the ratio of treatment means falls entirely within the 80-125% range.

Trough plasma concentrations for each treatment were also compared using an ANOVA with terms for subject and day. From this ANOVA, least square means for each day, estimated differences between days, and 90% confidence intervals for the differences between days were calculated. These log-transformed results were back-transformed by exponentiation to obtain adjusted means, day ratios, and 90% confidence intervals for these ratios.

RESULTS:

Both lots of the 360mg capsules appear to be bioequivalent to the reference Cardizem CD 180mg capsules in the single-dose comparisons. Treatment A (lot # RH9736) appears to be bioequivalent to the reference capsules in the multiple-dose steady state comparison, however, treatment B (lot # 9738) is outside the 80-125% BE limits for Cmin, ss. Please refer to the following tables and figures:

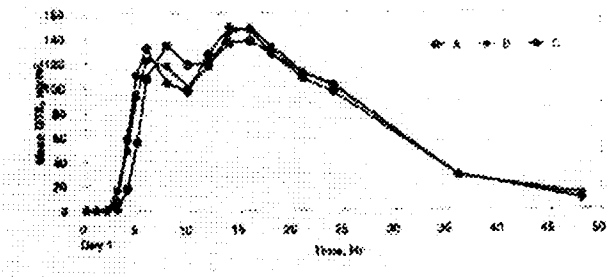


Figure 3. Mean diltiazem plasma concentrations following 360 mg single dose of once-daily capsules on day 1, protocol DZP9207

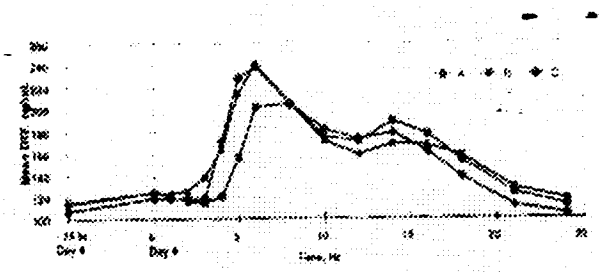


Figure 4. Mean diltiazem plasma concentrations following 360 mg dose (time 0) of once-daily capsules on day 8, -24 hours = trough sample on day 8, Protocol DZP9207

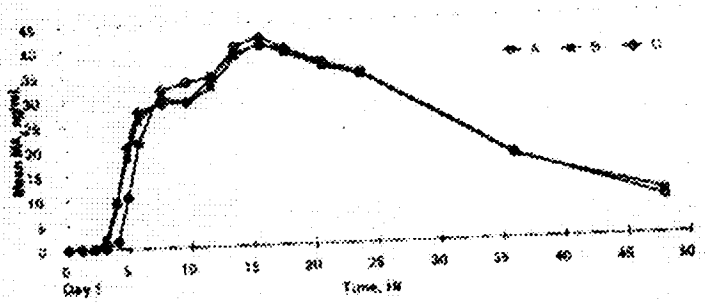


Figure 5. Mean N-desmethyldiltiazem plasma concentrations following 360 mg single dose on day 1 of once-daily capsules, Protocol DZPR0207

A= lot P9697J6 fasted (n=24), B= lot P9697J8 fasted (n=23), C= lot P31048 fasted (n=23)
(Cardizem CD)

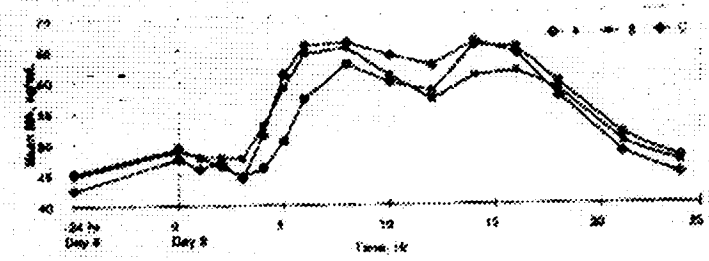


Figure 6. Mean N-desmethyldiltiazem plasma concentrations following 360 mg dose (time 0) on day 9 of once-daily capsules. -24 hours = trough sample on day 8, Protocol DZPR0207

A= lot P9697J6 fasted (n=24), B= lot P9697J8 fasted (n=23), C= lot P31048 fasted (n=23)
(Cardizem CD)

Table 9. Mean diltiazem (DTZ) pharmacokinetic parameters following 360 mg single dose on day 1, Protocol DZPR0207

	TRT	Number	Raw mean	Adjusted mean	CV%	Pair	Ratio (%)	90% CI[a] on ratio	P value
AUC(0-∞) (ng/mLxh)	A	24	3437.58	3254.72	30.91	A/C	100.83	(88.5, 114.8)	0.916
	B	23	3676.08	3436.67	36.23	B/A	105.59	(92.7, 120.3)	0.487
	C	23	3478.85	3228.07	39.54	B/C	106.46	(93.4, 121.3)	0.425
C_{max} (ng/mL)	A	24	170.69	160.18	38.54	A/C	102.47	(90.6, 115.8)	0.740
	B	23	169.69	158.35	35.20	B/A	98.86	(87.4, 111.8)	0.876
	C	23	166.58	156.32	36.49	B/C	101.30	(89.6, 114.5)	0.861
$t_{1/2}$ (h)	A	24	6.98	6.86	16.61	A/C	95.33	(86.7, 104.8)	0.403
	B	23	7.48	7.10	45.65	B/A	103.51	(94.1, 113.9)	0.546
	C	23	7.30	7.20	19.48	B/C	98.68	(89.7, 108.6)	0.816
t_{max} (h)	A	24	13.08	12.17	35.13	A/C	106.27	(88.0, 128.3)	0.589
	B	23	13.22	12.45	30.52	B/A	102.34	(84.8, 123.6)	0.837
	C	23	12.39	11.45	34.30	B/C	108.77	(90.0, 131.5)	0.460

[a] percent ratio and 90% confidence interval (CI) were calculated from ANOVA using log transformed data

TRT A = one 360 mg CD capsule (lot RH9736) given fasted
TRT B = one 360 mg CD capsule (lot RH9738) given fasted
TRT C = two 180 mg Cardizem CD Capsule (lot P31048) given fasted
Supporting Data:
Appendix B.3.3 Details of treatment comparisons, diltiazem single dose pharmacokinetic parameters, page 214 and Appendix C.2.2 Pharmacokinetic listings, page 639

Table 10. Mean diltiazem (DTZ) steady-state pharmacokinetic parameters following 360 mg dose on day 9, protocol DZPR0207

	TRT	Number	Raw mean	Adjusted mean	CV%	Pair	Ratio (%)	90% CI[b] on ratio	P value
AUC_{ss} (ng/mLxh)	A	24	3754.53	3551.98	28.57	A/C	100.69	(94.0, 107.9)	0.868
	B	23	3896.27	3558.25	36.19	B/A	100.18	(93.5, 107.3)	0.966
	C	23	3811.93	3527.75	33.13	B/C	100.86	(94.2, 108.1)	0.834
$C_{max,ss}$ (ng/mL)	A	24	224.18	212.39	29.46	A/C	89.55	(83.5, 96.1)	0.011
	B	23	245.21	225.41	34.48	B/A	106.13	(98.9, 113.9)	0.163
	C	23	256.14	237.17	33.81	B/C	95.04	(88.6, 101.9)	0.230
$C_{min,ss}$ (ng/mL)	A	24	97.29	87.97	38.53	A/C	104.02	(92.8, 116.6)	0.564
	B	23	109.15	97.94	41.76	B/A	111.33	(99.3, 124.8)	0.122
	C	23	94.05	84.57	41.10	B/C	115.80	(103.3, 129.8)	0.036
RATIO ($C_{max,ss}$/ $C_{min,ss}$)	A	24	2.55	2.41	49.16	A/C	85.77	(77.1, 95.4)	0.020
	B	23	2.36	2.31	25.23	B/A	95.78	(86.1, 106.6)	0.501
	C	23	2.89	2.81	29.11	B/C	82.14	(73.8, 91.4)	0.004
t_{max} (h)	A	24	9.75	9.38	43.75	A/C	149.54	(127.7, 175.1)	<0.001
	B	23	6.65	6.30	35.86	B/A	67.15	(57.3, 78.7)	<0.001
	C	23	6.65	6.27	36.15	B/C	100.42	(85.8, 117.5)	0.965
Trough Plasma Conc[a] (ng/mL)	A	24	116.96	110.78	31.37	A/C	108.12	(100.8, 116.0)	0.069
	B	23	119.28	110.00	36.39	B/A	99.29	(92.5, 106.5)	0.866
	C	23	110.28	102.46	34.20	B/C	107.36	(100.1, 115.2)	0.097

[a] mean of trough plasma concentrations on days 8, 9, and 10

[b] percent ratio and 90% confidence interval (CI) were calculated from ANOVA using log transformed data

TRT A = one 360 mg CD capsule (lot RH9736) given on days 3 through 9
TRT B = one 360 mg CD capsule (lot RH9738) given on days 3 through 9
TRT C = two 180 mg Cardizem CD Capsule (lot P31048) given on days 3 through 9
Supporting Data:
Appendix B.3.7 Details of treatment comparisons, diltiazem steady state pharmacokinetic parameters, page 223
Appendix C.2.2 Pharmacokinetic listings, page 639

Table 11. Mean N-desmethyldiltiazem (MA) pharmacokinetic parameters following 360 mg dose on day 1, Protocol DZPR0207

	TRT	Number	Raw mean	Adjusted mean	CV%	Pair	Ratio (%)	90% CI[a] on ratio	P value
AUC(0-∞) (ng/mLxh)	A	24	1246.89	1176.76	32.17	A/C	99.12	(87.2, 112.6)	0.907
	B	23	1402.22	1272.85	56.64	B/A	108.17	(95.2, 122.9)	0.309
	C	23	1263.94	1187.27	36.93	B/C	107.21	(94.3, 121.9)	0.366
C_{max} (ng/mL)	A	24	43.05	40.43	35.32	A/C	97.49	(87.5, 108.6)	0.695
	B	23	43.37	41.12	28.05	B/A	101.72	(91.3, 113.4)	0.792
	C	23	43.86	41.47	29.52	B/C	99.17	(89.0, 110.5)	0.898
$T_{1/2}$ (h)	A	24	11.16	10.96	18.53	A/C	99.14	(86.2, 114.0)	0.917
	B	23	13.79	12.09	86.90	B/A	110.31	(95.9, 126.9)	0.245
	C	23	11.22	11.06	23.65	B/C	109.36	(95.0, 125.9)	0.291
T_{max} (h)	A	24	16.63	16.12	22.49	A/C	100.83	(88.2, 115.2	0.918
	B	23	16.52	15.38	47.86	B/A	95.42	(83.5, 109.1)	0.559
	C	23	16.09	15.99	19.20	B/C	96.21	(84.1, 110.0)	0.631

[A] percent ratio and 90% confidence interval (CI) were calculated from ANOVA using log transformed data

TRT A = one 360 mg CD capsule (lot RH9736) given fasted
TRT B = one 360 mg CD capsule (lot RH9738) given fasted
TRT C = two 180 mg Cardizem CD Capsule (lot P31048) given fasted

Supporting Data:
Appendix B.3.14 Details of treatment comparisons, MA single dose pharmacokinetic parameters, page 237
Appendix C.2.2 Pharmacokinetic listings, page 639

Table 12. Mean N-desmethyldiltiazem (MA) steady-state pharmacokinetic parameters following 360 mg dose on day 9, Protocol DZPR0207

	TRT	Number	Raw mean	Adjusted mean	CV%	Pair	Ratio (%)	90% CI[b] on ratio	P value
AUC_{ss} (ng/mLxh)	A	24	1333.87	1254.56	31.56	A/C	98.30	(94.1, 102.7)	0.512
	B	23	1344.84	1254.89	33.11	B/A	100.03	(95.7, 104.5)	0.992
	C	23	1365.51	1276.27	33.37	B/C	98.33	(94.1, 102.7)	0.517
$C_{max,ss}$ (ng/mL)	A	24	70.41	66.52	31.41	A/C	97.52	(93.0, 102.2)	0.376
	B	23	68.45	64.15	30.65	B/A	96.45	(92.0, 101.1)	0.205
	C	23	72.68	68.21	32.45	B/C	94.05	(89.7, 98.6)	0.034
$C_{min,ss}$ (ng/mL)	A	24	41.31	37.48	39.71	A/C	102.20	(95.1, 109.8)	0.614
	B	23	43.80	40.62	35.07	B/A	108.36	(100.8, 116.5)	0.068
	C	23	40.07	36.68	38.79	B/C	110.73	(103.1, 119.0)	0.022
RATIO ($C_{max,ss}$/ $C_{min,ss}$)	A	24	1.82	1.78	33.29	A/C	95.41	(89.5, 101.8)	0.227
	B	23	1.59	1.58	12.60	B/A	89.04	(83.5, 95.0)	0.004
	C	23	1.88	1.86	20.76	B/C	84.95	(79.6, 90.6)	<0.001
t_{max} (h)	A	24	13.54	11.90	31.40	A/C	115.57	(92.6, 144.2)	0.278
	B	23	10.00	9.11	43.06	B/A	76.55	(61.3, 95.6)	0.049
	C	23	11.26	10.30	36.73	B/C	88.47	(70.8, 110.6)	0.361
Trough Plasma Conc[a] (ng/mL)	A	24	47.21	44.67	32.31	A/C	105.95	(101.4, 110.7)	0.032
	B	23	46.66	43.85	33.66	B/A	98.18	(94.0, 102.6)	0.486
	C	23	44.84	42.16	33.08	B/C	104.02	(99.6, 108.7)	0.137

[a] mean of trough plasma concentrations on days 8, 9, and 10

[b] percent ratio and 90% confidence interval (CI) were calculated from ANOVA using log transformed data

TRT A = one 360 mg CD capsule (lot RH9736) given on days 3 through 9
TRT B = one 360 mg CD capsule (lot RH9738) given on days 3 through 9
TRT C = two 180 mg Cardizem CD Capsule (lot P31048) given on days 3 through 9
Supporting Data:
Appendix B.3.18 Details of treatment comparisons, MA steady state pharmacokinetic parameters, page 246 and Appendix C.2.2 Pharmacokinetic listings, page 639

APPENDIX 2

"EFFECT OF FOOD ON THE SINGLE-DOSE PHARMACOKINETICS OF DILTIAZEM HCl 360MG FORMULATIONS IN HEALTHY MALE SUBJECTS"

STUDY: Protocol # DZPR0208
Report K-98-0236-D

SPONSOR: Licensed to:
Hoechst Marion Roussel Inc.
P.O. Box 9627, H3-M2112
Kansas City, MO 64134-0627

Authorized by:
Carderm Capital L.P.
Raymond House
12 Par La Ville Road
Hamilton, HM 12 Bermuda

INVESTIGATOR AND STUDY SITE:

OBJECTIVES:

To determine the effects of a high-fat breakfast on the rate and extent of absorption of a single oral dose of 360mg diltiazem HCl capsule formulation.

FORMULATIONS:

1) Diltiazem HCl 360mg capsules (lot# RH9736)
2) Diltiazem HCl 360mg capsules (lot# RH9738)

STUDY DESIGN:

The study design was a randomized, open-label, single-dose 4-period, crossover study with a washout period of 7 days between treatments. The study population was 22 healthy, non-smoking males between the ages of 18 to 45 years. Subjects received each of the four treatment regimens in a randomized fashion:

Treatment A: One diltiazem 360mg capsule (RH9736) dosed under fasting conditions.

Treatment B: One diltiazem 360mg capsule (RH9736) dosed with a high-fat breakfast.
Treatment C: One diltiazem 360mg capsule (RH9738) dosed under fasting conditions.
Treatment D: One diltiazem 360mg capsule (RH9738) dosed with a high-fat breakfast.

Subjects were continuously monitored for general health and adverse events. Heart rate, blood pressure, and 12-lead ECG recordings, clinical chemistry, and hematological exams were done before the study and upon completion. Heart rate, blood pressure (5 minutes supine), and lead II ECG measurements were taken 4 hours following each single dose. Plasma samples were collected before each dose on day 1 and 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 21, 24, 36, and 48 hours following the dose.

ASSAY:

DATA ANALYSIS:

Pharmacokinetic analysis of diltiazem and MA metabolite concentrations in plasma was conducted by non-compartmental methods. The metabolite DAD concentrations were presented by descriptive statistics only (mean, standard deviation, CV%). The primary PK comparisons include Cmax and AUC (0-inf) for plasma concentrations.

Comparisons between treatments were made for diltiazem and MA metabolite pharmacokinetic parameters. An analysis of variance (ANOVA) was performed for each parameter using PROC MIXED SAS with terms for sequence, subject within sequence, period, and treatment. Least square means, treatment differences, and 90% confidence intervals for treatment differences were determined. These log-transformed results were back-transformed by exponentiation to obtain adjusted means, treatment ratios, and 90% confidence intervals for these treatment ratios. Treatment B was compared to Treatment A with Treatment A serving as the reference, and Treatment D was compared to Treatment C with Treatment C as the reference treatment. Equivalence was defined as the limits of the 90% confidence interval on the ratio of treatment means falling entirely within 80% to 125%.

RESULTS:

Twenty subjects completed all four treatments. The differences in AUC (0-inf) and Cmax between the high-fat and fasting treatments were small. The 90% confidence intervals for the differences between treatments were within the limits of 80% to 125% using the fasted treatments as the references. Please refer to the following tables and figures:

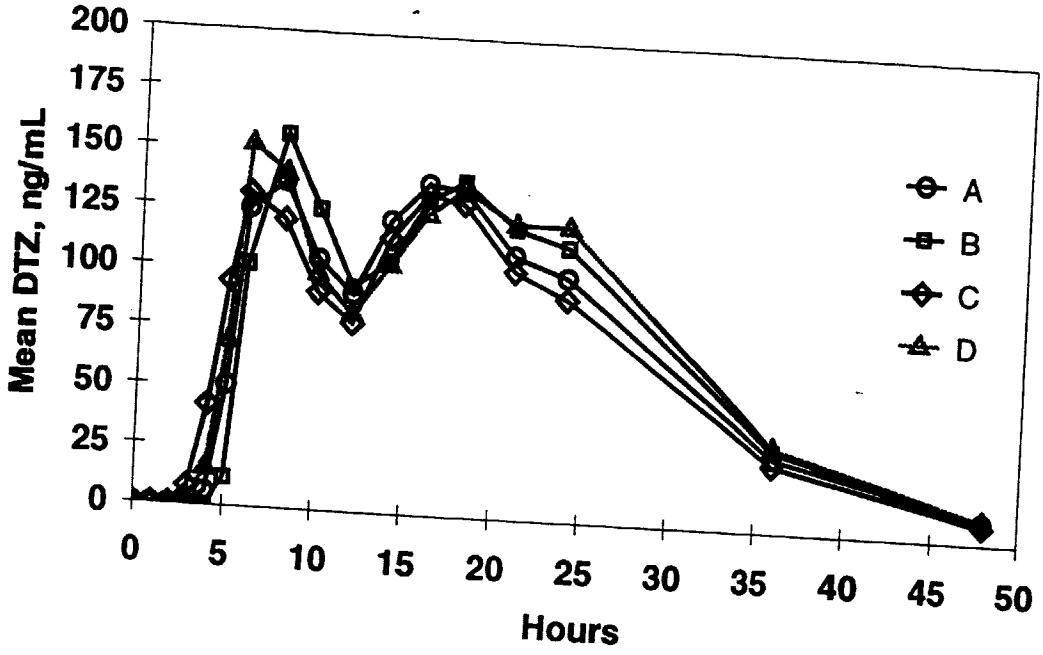


Figure 3. Mean diltiazem plasma concentrations following 360 mg single dose of once-daily capsules, Protocol DZPR0208

A= lot RH9736 fasted (n=20), B= lot RH9736 fed (n=20), C= lot RH9738 fasted (n=20), D= lot RH9738 fed (n=21).

Supporting Data:
Appendix C.2.2 Pharmacokinetic listings,

page 473

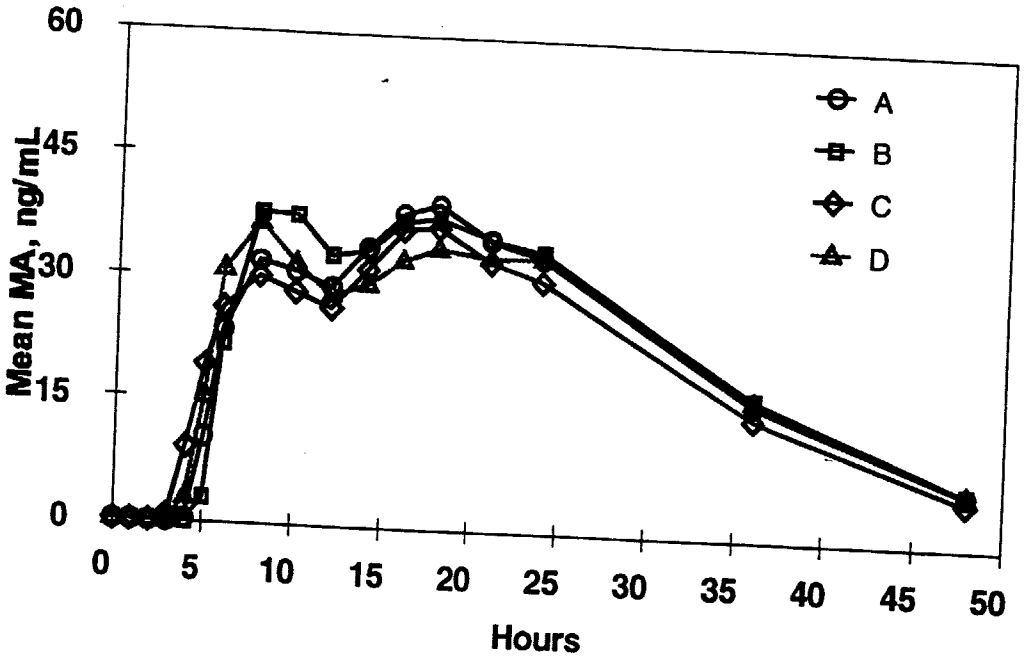


Figure 4. Mean N-desmethyldiltiazem plasma concentrations following 360 mg single dose of once-daily capsules, Protocol DZPR0208

A= lot RH9736 fasted (n=20), B= lot RH9736 fed (n=20), C= lot RH9738 fasted (n=20), D= lot RH9738 fed (n=21).

Supporting Data:
Appendix C.2.2 Pharmacokinetic listings,

page 473

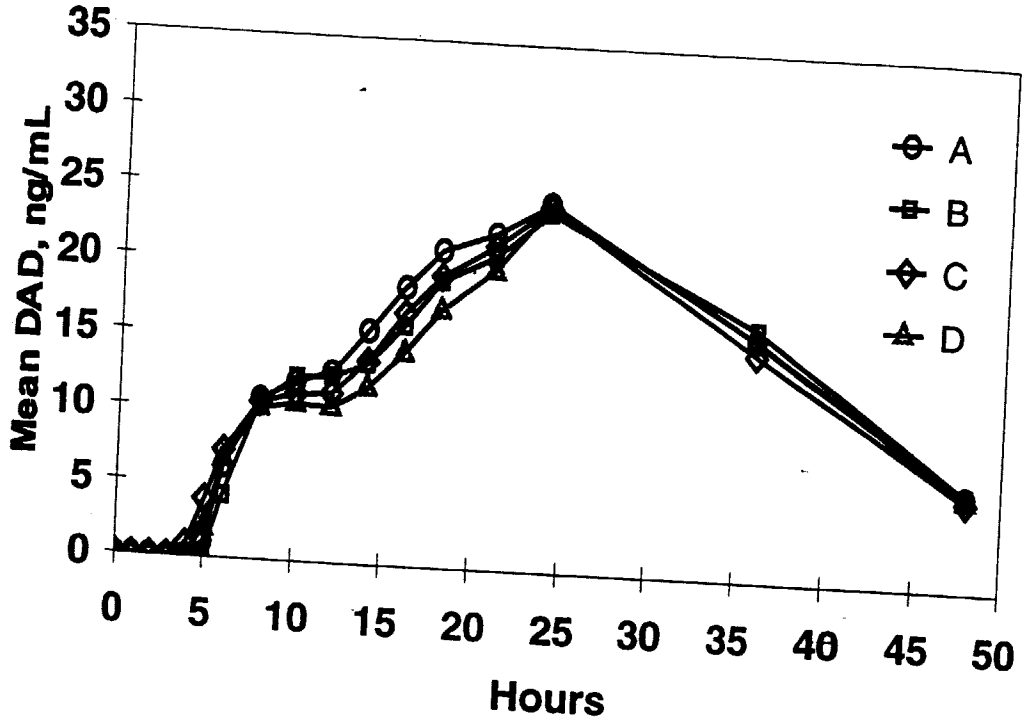


Figure 5. Mean DAD plasma concentrations, Protocol DZPR0208

A= lot RH9736 fasted, B= lot RH9736 fed, C= lot RH9738 fasted, D= lot RH9738 fed.

Supporting Data:
Appendix C.2.2 Pharmacokinetic listings,

page 473

Table 9. Mean diltiazem (DTZ) pharmacokinetic parameters, 360 mg single dose, protocol DZPR0208

	TRT	Number	Raw mean	Adjusted mean	CV%	Pair	Ratio (%)	90% CI[a] on ratio	P value
AUC(0-∞)	A	20	3384.33	3106.43	29.03	--	--	--	--
(ng/mLxh)	B	20	3517.52	3240.02	31.23	B/A	104.30	(95.1, 114.4)	0.451
	C	20	3214.98	2961.00	27.04	--	--	--	--
	D	21	3633.28	3272.02	47.82	D/C	110.50	(100.7, 121.2)	0.077
C_{max}	A	20	160.48	149.61	30.10	--	--	--	--
(ng/mL)	B	20	179.60	166.93	34.52	B/A	111.58	(101.8, 122.3)	0.051
	C	20	153.51	144.68	24.63	--	--	--	--
	D	21	174.18	159.05	43.74	D/C	109.93	(100.3, 120.5)	0.089
$t_{1/2}$	A	20	6.87	6.68	16.06	--	--	--	--
(h)	B	20	6.65	6.49	13.47	B/A	97.16	(92.7, 101.8)	0.306
	C	20	6.77	6.60	13.55	--	--	--	--
	D	21	6.49	6.41	16.21	D/C	97.03	(92.6, 101.7)	0.283
t_{max}	A	20	11.40	10.15	45.93	--	--	--	--
(h)	B	20	10.10	9.33	40.37	B/A	91.93	(73.3, 115.3)	0.536
	C	20	13.00	11.85	38.18	--	--	--	--
	D	21	10.48	9.21	57.24	D/C	77.73	(62.2, 97.2)	0.065

[a] percent ratio and 90% confidence interval (CI) were calculated from ANOVA using log transformed data

TRT A = one 360 mg CD capsule (lot RH9736) given fasted
TRT B = one 360 mg CD capsule (lot RH9736) given with high-fat breakfast
TRT C = one 360 mg CD capsule (lot RH9738) given fasted
TRT D = one 360 mg CD capsule (lot RH9738) given with high-fat breakfast

Supporting Data:
Appendix B.3.3 Details of treatment comparisons, page 201 and Appendix C.2.2 Pharmacokinetic listings, page 473

Table 10. Mean N-desmethyldiltiazem (MA) pharmacokinetic parameters, 360 mg single dose, protocol DZPR0208

	TRT	Number	Raw mean	Adjusted mean	CV%	Pair	Ratio (%)	90% CI[a] on ratio	P value
AUC (0-∞)	A	20	1161.61	1083.07	27.09	–	–	–	–
(ng/mLxh)	B	20	1196.27	1133.09	23.05	B/A	104.62	(97.7, 112.0)	0.272
	C	20	1081.72	1011.27	24.71	–	–	–	–
	D	21	1166.22	1116.67	29.43	D/C	110.42	(103.2, 118.2)	0.018
C_{max}	A	20	41.29	39.18	27.14	–	–	–	–
(ng/mL)	B	20	43.22	41.68	25.04	B/A	106.38	(99.8, 113.4)	0.109
	C	20	38.12	36.43	21.19	–	–	–	–
	D	21	40.04	38.85	24.78	D/C	106.64	(100.1, 113.6)	0.095
$t_{1/2}$	A	20	10.22	9.89	17.45	–	–	–	–
(h)	B	20	10.32	10.01	17.03	B/A	101.20	(96.3, 106.4)	0.689
	C	20	9.97	9.64	17.05	–	–	–	–
	D	21	10.40	10.15	22.52	D/C	105.24	(100.1, 110.6)	0.091
t_{max}	A	20	16.85	16.29	18.99	–	–	–	–
(h)	B	20	12.45	11.55	35.97	B/A	70.88	(58.6, 85.7)	0.004
	C	20	16.10	15.77	18.68	–	–	–	–
	D	21	12.14	10.83	50.92	D/C	68.68	(56.9, 82.9)	0.001

[a] percent ratio and 90% confidence interval (CI) were calculated from ANOVA using log transformed data

TRT A = one 360 mg CD capsule (lot RH9736) given fasted
TRT B = one 360 mg CD capsule (lot RH9736) given with high-fat breakfast
TRT C = one 360 mg CD capsule (lot RH9738) given fasted
TRT D = one 360 mg CD capsule (lot RH9738) given with high-fat breakfast

Supporting Data:
Appendix B.3.7 Details of treatment comparisons, page 209 and Appendix C.2.2 Pharmacokinetic listings, page 473

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20062/S027

ADMINISTRATIVE DOCUMENTS

RHPM Review of Final Printed Labeling

AUG 2 4 1999

Application:	NDA 20-062 Cardizem CD (diltiazem HCl) Capsules
Applicant:	Carderm Capital L.P.
Supplement Date:	January 7, 1999
FPL Letter Date:	June 18, 1999
FPL Receipt Date:	June 21, 1999

Background

NDA 20-062/S-027 provides for a new dosage strength, 360 mg Capsules. The formulation of this new capsule strength is slightly modified from the other approved dosage strength capsules. An approvable letter was issued on May 7, 1999. In addition to the labeling changes under **DESCRIPTION** and **HOW SUPPLIED** relating to the new dosage strength, the approvable letter requested a revision of the **Storage Statement**.

Review

The applicant submitted final printed labeling in a submission dated June 18, 1999. The labeling was revised to include information on the 360 mg capsule under **DESCRIPTION** and **HOW SUPPLIED**. In addition, the **Storage Statement** was revised to read as follows:

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

These changes were made in accordance with the requests in the approvable letter. An approval letter will be drafted for Dr. Lipicky's signature.

/S/

David Roeder
Regulatory Health Project Manager

cc: NDA 20-062
HFD-110
HFD-110/DRoeder/ABlount

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20062/S027`

CORRESPONDENCE

NDA 20-062/S-027

JUL 19 1999

Hoechst Marion Roussel, Inc.
Attention: Janet K. DeLeon
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

Dear Ms. DeLeon:

Please refer to your January 7, 1999 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for CARDIZEM CD (dilitazem hydrochloride) Capsules, 180 mg, 240 mg, 300 mg and 360 mg.

The supplemental application provides for a new dosage strength, 360 mg Capsules. The formulation of this new capsule strength is slightly modified from the other approved dosage strength capsules.

We have completed our validation of the analytical methods for the 360 mg capsules and request the following additional information regarding the dissolution test:

The method refers to dissolution software used to correct for UV absorbance interference from diethyl phthalate, an excipient in the product. Attempts on April 8, 1999 by the analyst to get detailed information and explicit calculation formulas from your firm for dissolution calculations for the excipient contribution were not entirely successful. Please include a detailed description of the software and the calculations used to obtain the final results in the method.

The method does not specify whether aliquots taken out are replaced or not. If not replaced, please state whether final results are corrected for the volume taken during sampling. The validating analyst did not replace aliquots and corrected the volume withdrawn. It may be that sample aliquots are circulated back into the dissolution bath after samples are read. If this is the case, it should be stated in the method.

We would appreciate your prompt written response.

If you have any questions, please contact Danute G. Cunningham at (301) 594-5351 or Kasturi Srinivasachar, Ph.D. at (301) 594-5376.

Sincerely yours,

/S/ 7-19-99

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I, for the
Division of Cardio-Renal Drug Products, (HFD-110)
Office of New Drug Chemistry
Center for Drug Evaluation and Research