CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20792

Trade Name: CARDIZEM MONOVIAL

Generic Name: Diltiazem

Sponsor: HOECHST MARION ROUSSEL

Approval Date: September 5, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20792

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20792

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-792

SEP 5 1997

Hoechst Marion Roussel, Inc.
Attention: J. Michael Nicholas, Ph.D.
P.O. Box 9627
Kansas City, MO 64134-0627

Dear Dr. Nicholas:

Please refer to your December 20, 1996 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardizem Monovial (diltiazem hydrochloride) for Injection, 100 mg.

We acknowledge receipt of your amendments dated July 18 and August 14, 1997.

This new drug application provides for use of a lyophized powder of diltiazem hydrochloride to be reconstituted for continuous intravenous infusion for temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on August 15, 1997. Accordingly, the application is approved effective on the date of this letter.

Please submit one market package of the drug when it is available.

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

If you have any questions, please contact:

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

Sincerely yours,

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

cc:
Original NDA
HF-2/MedWatch (with draft/final labeling)
HFD-2/MLumpkin
HFD-92 (with draft/final labeling)
HFD-101 (with draft/final labeling)
HFD-110
HFD-40 (with draft/final labeling)
HFD-613 (with draft/final labeling)
HFD-735 (with draft/final labeling)
DISTRICT OFFICE
~~HFD-~~810/New Drug Chemistry Division Director
HFD-110/DRoeder
sb/8/21/97;8/26/97;8/28/97
R/D: DCunningham/8/21/97
RWolters/8/22/97
CResnick/8/22/97
KKnudsen/8/25/97
RFenichel/8/26/97
NMorgenstern/8/25/97;8/26/97

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20792

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

D. Meader

NDA 20-792

JUN 19 1997

Hoechst Marion Roussel, Inc.
Attention: Elaine Waller, Pharm.D.
P.O. Box 9627
Kansas City, MO 64134-0627

Dear Dr. Waller:

Please refer to your December 20, 1996 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardizem Monovial (diltiazem hydrochloride) for Injection, 100 mg.

We acknowledge receipt of your amendments and correspondence dated January 7, April 1 and 29, and May 19, 1997.

We have completed the review of this application as submitted with draft labeling and it is approvable. Before the application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug, including the instructions for reconstitution of the monovial product. The labeling should be identical in content to the labeling submitted on December 20, 1996, with the exception of change outlined in the enclosed marked-up draft. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the FPL may be required.

Please submit sixteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

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

Sincerely yours,

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

Enclosure

cc:
Original NDA
HFD-2/MLumpkin
HFD-101
HFD-92
HFD-110
HFD-40 (with draft labeling)
~~DISTRICT~~ OFFICE
HFD-110/DRoeder
sb/5/28/97;6/12/97
R/D: RWolters/5/29/97
CResnick/6/6/97
NMorgenstern/6/11/97

APPROVABLE

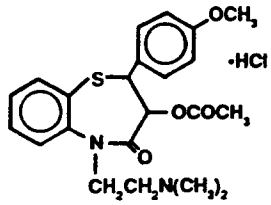
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20792

FINAL PRINTED LABELING

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium channel 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 Injectable (diltiazem hydrochloride) is a clear, colorless, sterile, nonpyrogenic solution. It has a pH range of 3.7 to 4.1.

CARDIZEM Injectable is for direct intravenous bolus injection and continuous intravenous infusion.

25-mg, 5-mL vial—each sterile vial contains 25 mg diltiazem hydrochloride, 3.75 mg citric acid USP, 3.25 mg sodium citrate dihydrate USP, 357 mg sorbitol solution USP, and water for injection USP up to 5 mL. Sodium hydroxide or hydrochloric acid is used for pH adjustment.

50-mg, 10-mL vial—each sterile vial contains 50 mg diltiazem hydrochloride, 7.5 mg citric acid USP, 6.5 mg sodium citrate dihydrate USP, 714 mg sorbitol solution USP, and water for injection USP up to 10 mL. Sodium hydroxide or hydrochloric acid is used for pH adjustment.

CARDIZEM Lyo-Ject Syringe (diltiazem hydrochloride) after reconstitution contains a clear, colorless, sterile, nonpyrogenic solution. It has a pH range of 4.0 to 7.0.

CARDIZEM Lyo-Ject Syringe after reconstitution is for direct intravenous bolus injection and continuous intravenous infusion.

CARDIZEM Lyo-Ject Syringe 25-mg syringe is available in a dual chamber, disposable syringe. Chamber 1 contains lyophilized powder comprised of diltiazem hydrochloride 25 mg and mannitol USP 37.5 mg. Chamber 2 contains sterile diluent composed of 5 mL water for injection with 0.5% benzyl alcohol NF, and 0.6% sodium chloride USP.

CLINICAL PHARMACOLOGY

Mechanisms of Action.

CARDIZEM inhibits the influx of calcium (Ca^{++}) ions during membrane depolarization of cardiac and vascular smooth muscle. The therapeutic benefits of CARDIZEM in supraventricular tachycardias are related to its ability to slow AV nodal conduction time and prolong AV nodal refractoriness. CARDIZEM exhibits frequency (use) dependent effects on AV nodal conduction such that it may selectively reduce the heart rate during tachycardias involving the AV node with little or no effect on normal AV nodal conduction at normal heart rates.

CARDIZEM slows the ventricular rate in patients with a rapid ventricular response during atrial fibrillation or atrial flutter. CARDIZEM converts paroxysmal supraventricular tachycardia (PSVT) to normal sinus rhythm by interrupting the reentry circuit in AV nodal reentrant tachycardias and reciprocating tachycardias, eg, Wolff-Parkinson-White syndrome (WPW).

CARDIZEM prolongs the sinus cycle length. It has no effect on the sinus node recovery time or on the sinoatrial conduction time in patients without SA nodal dysfunction. CARDIZEM has no significant electrophysiologic effects on tissues in the heart that are fast sodium channel dependent, eg, His-Purkinje tissue, atrial and ventricular muscle, and extranodal accessory pathways.

Like other calcium channel antagonists, because of its effect on vascular smooth muscle, CARDIZEM decreases total peripheral resistance resulting in a decrease in both systolic and diastolic blood pressure.

Hemodynamics.

In patients with cardiovascular disease, CARDIZEM Injectable (diltiazem hydrochloride) administered intravenously in single bolus doses, followed in some cases by a continuous infusion, reduced blood pressure, systemic vascular resistance, the rate-pressure product, and coronary vascular resistance and increased coronary blood flow. In a limited number of studies of patients with compromised myocardium (severe congestive heart failure, acute myocardial infarction, hypertrophic cardiomyopathy), administration of intravenous diltiazem produced no significant effect on contractility, left ventricular end diastolic pressure, or pulmonary capillary wedge pressure. The mean ejection fraction and cardiac output/index remained unchanged or increased. Maximal hemodynamic effects usually occurred within 2 to 5 minutes of an injection. However, in rare instances, worsening of congestive heart failure has been reported in patients with preexisting impaired ventricular function.

Pharmacodynamics.

The prolongation of PR interval correlated significantly with plasma diltiazem concentration in normal volunteers using the Sigmoidal E_{max} model. Changes in heart rate, systolic blood pressure, and diastolic blood pressure did not correlate with diltiazem plasma concentrations in normal volunteers. Reduction in mean arterial pressure correlated linearly with diltiazem plasma concentration in a group of hypertensive patients.

In patients with atrial fibrillation and atrial flutter, a significant correlation was observed between the percent reduction in HR and plasma diltiazem concentration using the Sigmoidal E_{max} model. Based on this relationship, the mean plasma diltiazem concentration required to produce a 20% decrease in heart rate was determined to be 80 ng/mL. Mean plasma diltiazem concentrations of 130 ng/mL and 300 ng/mL were determined to produce reductions in heart rate of 30% and 40%.

Pharmacokinetics and Metabolism.

Following a single intravenous injection in healthy male volunteers, CARDIZEM appears to obey linear pharmacokinetics over a dose range of 10.5 to 21.0 mg. The plasma elimination half-life is approximately 3.4 hours. The apparent volume of distribution of CARDIZEM is approximately 305 L. CARDIZEM is extensively metabolized in the liver with a systemic clearance of approximately 65 L/h.

After constant rate intravenous infusion to healthy male volunteers, diltiazem exhibits nonlinear pharmacokinetics over an infusion range of 4.8 to 13.2 mg/h for 24 hours. Over this infusion range, as the dose is increased, systemic clearance decreases from 64 to 48 L/h while the plasma elimination half-life increases from 4.1 to 4.9 hours. The apparent volume of distribution remains unchanged (360 to 391 L). In patients with atrial fibrillation or atrial flutter, diltiazem systemic clearance has been found to be decreased compared to healthy volunteers. In patients administered bolus doses ranging from 2.5 mg to 38.5 mg, systemic clearance averaged 36 L/h. In patients administered continuous infusions at 10 mg/h or 15 mg/h for 24 hours, diltiazem systemic clearance averaged 42 L/h and 31 L/h, respectively.

Based on the results of pharmacokinetic studies in healthy volunteers administered different *oral* CARDIZEM formulations, constant rate intravenous infusions of CARDIZEM at 3, 5, 7, and 11 mg/h are predicted to produce steady-state plasma diltiazem concentrations equivalent to 120-, 180-, 240-, and 360-mg total daily oral doses of CARDIZEM tablets or CARDIZEM SR capsules.

After oral administration, CARDIZEM undergoes extensive metabolism in man by deacetylation, N-demethylation, and O-demethylation via cytochrome P-450 (oxidative metabolism) in addition to conjugation. Metabolites N-monodesmethyldiltiazem, desacetyldiltiazem, desacetyl-N-monodesmethyldiltiazem, desacetyl-O-desmethyldiltiazem, and desacetyl-N, O-desmethyldiltiazem have been identified in human urine. Following oral administration, 2% to 4% of the unchanged CARDIZEM appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Following single intravenous injection of CARDIZEM, however, plasma concentrations of N-monodesmethyldiltiazem and desacetyldiltiazem, two principal metabolites found in plasma after oral administration, are typically not detected. These metabolites are observed, however, following 24 hour constant rate intravenous infusion. Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites which attain higher concentrations than those of digoxin, phenytoin, hydrochlorothiazide, indomethacin, phenylbutazone, propranolol, salicylic acid, tolbutamide, or warfarin.

Renal insufficiency, or even end-stage renal disease, does not appear to influence diltiazem disposition following *oral* administration. Liver cirrhosis was shown to reduce diltiazem's apparent *oral* clearance and prolong its half-life.

INDICATIONS AND USAGE

CARDIZEM Injectable or CARDIZEM Lyo-Ject Syringe (diltiazem hydrochloride) are indicated for the following:

1. **Atrial Fibrillation or Atrial Flutter.** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. **Paroxysmal Supraventricular Tachycardia.** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable or Lyo-Ject Syringe.

The use of CARDIZEM Injectable or Lyo-Ject Syringe for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically as is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable and CARDIZEM Lyo-Ject Syringe are 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 severe hypotension or cardiogenic shock.

Prescribing Information as of September 1995

CARDIZEM® Injectable
(diltiazem HCl)
CARDIZEM® Lyo-Ject Syringe
(diltiazem HCl)

4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable or Lyo-Ject Syringe. As such, the initial use of CARDIZEM Injectable or Lyo-Ject Syringe should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS $\geq$0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.
8. In newborns, due to the presence of benzyl alcohol as a preservative (CARDIZEM Lyo-Ject only).

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** 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 following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.

5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General

CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral 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, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions

Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable or CARDIZEM Lyo-Ject Syringe concomitantly with other agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable or Lyo-Ject Syringe with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis. Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers. Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem 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.

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 ***oral*** diltiazem with carbamazepine has been reported to result in elevated plasma levels of carbamazepine (by 40 to 72%), 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 oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal 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 some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal 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 with oral diltiazem 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

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning) – 3.9%, vasodilation (flushing) – 1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation) – 1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Asystole, atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia

Dermatologic: Pruritus, sweating

Gastrointestinal: Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting

Nervous System: Dizziness, paresthesia

Other: Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia

Although not observed in clinical trials with CARDIZEM Injectable, the following events associated with oral diltiazem may occur:

Cardiovascular: AV block (third degree), bundle branch block, ECG abnormality, palpitations, syncope, tachycardia, ventricular extrasystoles

Dermatologic: Alopecia, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, leukocytoclastic vasculitis, petechiae, photosensitivity, purpura, rash, urticaria

Gastrointestinal: Anorexia, diarrhea, dysgeusia, dyspepsia, mild elevations of SGPT and LDH, thirst, weight increase

Nervous System: Abnormal dreams, amnesia, depression, extrapyramidal symptoms, gait abnormality, hallucinations, insomnia, nervousness, personality change, somnolence, tremor

Other: Allergic reactions, angioedema (including facial or periorbital edema); CPK elevation, epistaxis, eye irritation, gingival hyperplasia, hemolytic anemia, hyperglycemia, impotence, increased bleeding time, leukopenia, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, retinopathy, sexual

OVERDOSAGE

Overdosage experience is limited. In the event of overdosage or an exaggerated response, appropriate supportive measures should be employed. 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.

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.**

The intravenous LD_{50}'s in mice and rats were 60 and 38 mg/kg, respectively. The toxic dose in man is not known.

DOSAGE AND ADMINISTRATION

Direct Intravenous Single Injections (Bolus)

The initial dose of CARDIZEM Injectable or CARDIZEM Lyo-Ject Syringe (see instructions for reconstitution of Lyo-Ject syringe in blister pack) should be 0.25 mg/kg actual body weight as a bolus administered over 2 minutes (20 mg is a reasonable dose for the average patient). If response is inadequate, a second dose may be administered after 15 minutes. The second bolus dose of CARDIZEM Injectable or Lyo-Ject should be 0.35 mg/kg actual body weight administered over 2 minutes (25 mg is a reasonable dose for the average patient). Subsequent intravenous bolus doses should be individualized for each patient. Patients with low body weights should be dosed on a mg/kg basis. Some patients may respond to an initial dose of 0.15 mg/kg, although duration of action may be shorter. Experience with this dose is limited.

Continuous Intravenous Infusion

For continued reduction of the heart rate (up to 24 hours) in patients with atrial fibrillation or atrial flutter, an intravenous infusion of CARDIZEM Injectable or Lyo-Ject may be administered. Immediately following bolus administration of 20 mg (0.25 mg/kg) or 25 mg (0.35 mg/kg) CARDIZEM Injectable or Lyo-Ject and reduction of heart rate, begin an intravenous infusion of CARDIZEM Injectable or Lyo-Ject. The recommended initial infusion rate of CARDIZEM Injectable or Lyo-Ject is 10 mg/h. Some patients may maintain response to an initial rate of 5 mg/h. The infusion rate may be increased in 5 mg/h increments up to 15 mg/h as needed, if further reduction in heart rate is required. The infusion may be maintained for up to 24 hours.

Diltiazem shows dose-dependent, non-linear pharmacokinetics. Duration of infusion longer than 24 hours and infusion rates greater than 15 mg/h have not been studied. Therefore, infusion duration exceeding 24 hours and infusion rates exceeding 15 mg/h are not recommended.

Dilution: To prepare CARDIZEM Injectable or Lyo-Ject for continuous intravenous infusion aseptically transfer the appropriate quantity (see chart) of CARDIZEM Injectable or Lyo-Ject to the desired volume of either Normal Saline, D5W, or D5W/0.45% NaCl. Mix thoroughly. Use within 24 hours. Keep refrigerated until use.

Diluent Volume	Quantity of CARDIZEM Injectable or Lyo-Ject to Add	Final Concentration	Administration	
			Dose*	Infusion Rate
100 mL	125 mg (25 mL) Final Volume 125 mL	1.0 mg/mL	10 mg/h 15 mg/h	10 mL/h 15 mL/h
250 mL	250 mg (50 mL) Final Volume 300 mL	0.83 mg/mL	10 mg/h 15 mg/h	12 mL/h 18 mL/h
500 mL	250 mg (50 mL) Final Volume 550 mL	0.45 mg/mL	10 mg/h 15 mg/h	22 mL/h 33 mL/h

* 5 mg/h may be appropriate for some patients

CARDIZEM Injectable and CARDIZEM Lyo-Ject Syringe were tested for compatibility with three commonly used intravenous fluids at a maximal concentration of 1 mg diltiazem hydrochloride per milliliter. CARDIZEM Injectable and Lyo-Ject were found to be physically compatible and chemically stable in the following parenteral solutions for at least 24 hours when stored in glass or polyvinylchloride (PVC) bags at controlled room temperature 15-30°C (59-86°F) or under refrigeration 2-8°C (36-46°F).

- dextrose (5%) injection USP
- sodium chloride (0.9%) injection USP
- dextrose (5%) and sodium chloride (0.45%) injection USP.

Because of potential physical incompatibilities, it is recommended that CARDIZEM Injectable and Lyo-Ject not be mixed with any other drugs in the same container. If possible, it is recommended that CARDIZEM Injectable or Lyo-Ject Syringe not be co-infused in the same intravenous line.

Physical incompatibilities (precipitate formation or cloudiness) were observed when CARDIZEM Injectable or Lyo-Ject was infused in the same intravenous line with the following drugs: acetazolamide, acyclovir, aminophylline, ampicillin, ampicillin sodium/sulbactam sodium, cefamandole, cefoperazone, diazepam, furosemide, hydrocortisone sodium succinate, insulin, (regular: 100 units/mL), methylprednisolone sodium succinate, mezlocillin, nafcillin, phenytoin, rifampin, and sodium bicarbonate.

NOTE: CARDIZEM Lyo-Ject was found to be compatible with insulin (regular, 100 units/mL).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Transition to Further Antiarrhythmic Therapy.

Transition to other antiarrhythmic agents following administration of CARDIZEM Injectable is generally safe. However, reference should be made to the respective agent manufacturer's package insert for information relative to dosage and administration.

In controlled clinical trials, therapy with antiarrhythmic agents to maintain reduced heart rate in atrial fibrillation or atrial flutter or for prophylaxis of PSVT was generally started within 3 hours after bolus administration of CARDIZEM Injectable. These antiarrhythmic agents were intravenous or oral digoxin, Class 1 antiarrhythmics (eg, quinidine, procainamide), calcium channel blockers, and oral beta-blockers.

Experience in the use of antiarrhythmic agents following maintenance infusion of CARDIZEM Injectable is limited. Patients should be dosed on an individual basis and reference should be made to the respective manufacturer's package insert for information relative to dosage and administration.

HOW SUPPLIED

CARDIZEM® Injectable (diltiazem hydrochloride injection) is supplied in boxes of six 5-mL vials with each vial containing 25 mg of diltiazem hydrochloride (5 mg/mL) (NDC 0088-1790-32) and boxes of six 10-mL vials with each vial containing 50 mg diltiazem hydrochloride (5 mg/mL) (NDC 0088-1790-33).

SINGLE-USE CONTAINERS. DISCARD UNUSED PORTION.

STORE PRODUCT UNDER REFRIGERATION 2-8°C (36-46°F). DO NOT FREEZE. MAY BE STORED AT ROOM TEMPERATURE FOR UP TO 1 MONTH. DESTROY AFTER 1 MONTH AT ROOM TEMPERATURE.

CARDIZEM Lyo-Ject 25-mg syringe is supplied in a single molded nonsterile tray in cartons of 6 syringes (NDC 0088-1790-17). PRODUCT IS TO BE STORED AT ROOM TEMPERATURE 15-30°C (59-86°F). DO NOT FREEZE. RECONSTITUTED MATERIAL IS STABLE FOR 24 HOURS AT CONTROLLED ROOM TEMPERATURE. SINGLE-USE CONTAINERS. DISCARD UNUSED PORTION.

Prescribing Information as of September 1995

Mfd for:
Hoechst Marion Roussel, Inc.
Kansas City, MO 64114 USA

in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral 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, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions

Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable or CARDIZEM Lyo-Ject Syringe concomitantly with other agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable or Lyo-Ject Syringe with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis. Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers. Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). *Oral* administration of diltiazem 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.

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 *oral* diltiazem with carbamazepine has been reported to result in elevated plasma levels of carbamazepine (by 40 to 72%), 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 oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal 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 some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal 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 with oral diltiazem 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

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning) – 3.9%, vasodilation (flushing) – 1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation) – 1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Asystole, atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia

Dermatologic: Pruritus, sweating

Gastrointestinal: Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting

Nervous System: Dizziness, paresthesia

Other: Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia

Although not observed in clinical trials with CARDIZEM Injectable, the following events associated with oral diltiazem may occur:

Cardiovascular: AV block (third degree), bundle branch block, ECG abnormality, palpitations, syncope, tachycardia, ventricular extrasystoles

Dermatologic: Alopecia, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, leukocytoclastic vasculitis, petechiae, photosensitivity, purpura, rash, urticaria

Gastrointestinal: Anorexia, diarrhea, dysgeusia, dyspepsia, mild elevations of SGPT and LDH, thirst, weight increase

Nervous System: Abnormal dreams, amnesia, depression, extrapyramidal symptoms, gait abnormality, hallucinations, insomnia, nervousness, personality change, somnolence, tremor

Other: Allergic reactions, angioedema (including facial or periorbital edema); CPK elevation, epistaxis, eye irritation, gingival hyperplasia, hemolytic anemia, hyperglycemia, impotence, increased bleeding time, leukopenia, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, retinopathy, sexual difficulties, thrombocytopenia, tinnitus

Events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease for the patient.

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.

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.

The intravenous LD_{50}'s in mice and rats were 60 and 38 mg/kg, respectively. The toxic dose in man is not known.

DOSAGE AND ADMINISTRATION

Direct Intravenous Single Injections (Bolus)

The initial dose of CARDIZEM Injectable or CARDIZEM Lyo-Ject Syringe (see instructions for reconstitution of Lyo-Ject syringe in blister pack) should be 0.25 mg/kg actual body weight as a bolus administered over 2 minutes (20 mg is a reasonable dose for the average patient). If response is inadequate, a second dose may be administered after 15 minutes. The second bolus dose of CARDIZEM Injectable or Lyo-Ject should be 0.35 mg/kg actual body weight administered over 2 minutes (25 mg is a reasonable dose for the average patient). Subsequent intravenous bolus doses should be individualized for each patient. Patients with low body weights should be dosed on a mg/kg basis. Some patients may respond to an initial dose of 0.15 mg/kg, although duration of action may be shorter. Experience with this dose is limited.

Continuous Intravenous Infusion

For continued reduction of the heart rate (up to 24 hours) in patients with atrial fibrillation or atrial flutter, an intravenous infusion of CARDIZEM Injectable or Lyo-Ject may be administered. Immediately following bolus administration of 20 mg (0.25 mg/kg) or 25 mg (0.35 mg/kg) CARDIZEM Injectable or Lyo-Ject and reduction of heart rate, begin an intravenous infusion of CARDIZEM Injectable or Lyo-Ject. The recommended initial infusion rate of CARDIZEM Injectable or Lyo-Ject is 10 mg/h. Some patients may maintain response to an initial rate of 5 mg/h. The infusion rate may be increased in 5 mg/h increments up to 15 mg/h as needed, if further reduction in heart rate is required. The infusion may be maintained for up to 24 hours.

Diltiazem shows dose-dependent, non-linear pharmacokinetics. Duration of infusion longer than 24 hours and infusion rates greater than 15 mg/h have not been studied. Therefore, infusion duration exceeding 24 hours and infusion rates exceeding 15 mg/h are not recommended.

Dilution: To prepare CARDIZEM Injectable or Lyo-Ject for continuous intravenous infusion aseptically transfer the appropriate quantity (see chart) of CARDIZEM Injectable or Lyo-Ject to the desired volume of either Normal Saline, D5W, or D5W/0.45% NaCl. Mix thoroughly. Use within 24 hours. Keep refrigerated until use.

Diluent Volume	Quantity of CARDIZEM Injectable or Lyo-Ject to Add	Final Concentration	Administration	
			Dose*	Infusion Rate
100 mL	125 mg (25 mL) Final Volume 125 mL	1.0 mg/mL	10 mg/h 15 mg/h	10 mL/h 15 mL/h
250 mL	250 mg (50 mL) Final Volume 300 mL	0.83 mg/mL	10 mg/h 15 mg/h	12 mL/h 18 mL/h
500 mL	250 mg (50 mL) Final Volume 550 mL	0.45 mg/mL	10 mg/h 15 mg/h	22 mL/h 33 mL/h

* 5 mg/h may be appropriate for some patients

CARDIZEM Injectable and CARDIZEM Lyo-Ject Syringe were tested for compatibility with three commonly used intravenous fluids at a maximal concentration of 1 mg diltiazem hydrochloride per milliliter. CARDIZEM Injectable and Lyo-Ject were found to be physically compatible and chemically stable in the following parenteral solutions for at least 24 hours when stored in glass or polyvinylchloride (PVC) bags at controlled room temperature 15-30°C (59-86°F) or under refrigeration 2-8°C (36-46°F).

- dextrose (5%) injection USP
- sodium chloride (0.9%) injection USP
- dextrose (5%) and sodium chloride (0.45%) injection USP.

Because of potential physical incompatibilities, it is recommended that CARDIZEM Injectable and Lyo-Ject not be mixed with any other drugs in the same container. If possible, it is recommended that CARDIZEM Injectable or Lyo-Ject Syringe not be co-infused in the same intravenous line.

Physical incompatibilities (precipitate formation or cloudiness) were observed when CARDIZEM Injectable or Lyo-Ject was infused in the same intravenous line with the following drugs: acetazolamide, acyclovir, aminophylline, ampicillin, ampicillin sodium/sulbactam sodium, cefamandole, cefoperazone, diazepam, furosemide, hydrocortisone sodium succinate, insulin, (regular: 100 units/mL), methylprednisolone sodium succinate, meziocillin, nafcillin, phenytoin, rifampin, and sodium bicarbonate.

NOTE: CARDIZEM Lyo-Ject was found to be compatible with insulin (regular, 100 units/mL).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Transition to Further Antiarrhythmic Therapy.

Transition to other antiarrhythmic agents following administration of CARDIZEM Injectable is generally safe. However, reference should be made to the respective agent manufacturer's package insert for information relative to dosage and administration.

In controlled clinical trials, therapy with antiarrhythmic agents to maintain reduced heart rate in atrial fibrillation or atrial flutter or for prophylaxis of PSVT was generally started within 3 hours after bolus administration of CARDIZEM Injectable. These antiarrhythmic agents were intravenous or oral digoxin, Class 1 antiarrhythmics (eg, quinidine, procainamide), calcium channel blockers, and oral beta-blockers.

Experience in the use of antiarrhythmic agents following maintenance infusion of CARDIZEM Injectable is limited. Patients should be dosed on an individual basis and reference should be made to the respective manufacturer's package insert for information relative to dosage and administration.

HOW SUPPLIED

CARDIZEM® Injectable (diltiazem hydrochloride injection) is supplied in boxes of six 5-mL vials with each vial containing 25 mg of diltiazem hydrochloride (5 mg/mL) (NDC 0088-1790-32) and boxes of six 10-mL vials with each vial containing 50 mg diltiazem hydrochloride (5 mg/mL) (NDC 0088-1790-33).

SINGLE-USE CONTAINERS. DISCARD UNUSED PORTION.

STORE PRODUCT UNDER REFRIGERATION 2-8°C (36-46°F). DO NOT FREEZE. MAY BE STORED AT ROOM TEMPERATURE FOR UP TO 1 MONTH. DESTROY AFTER 1 MONTH AT ROOM TEMPERATURE.

CARDIZEM Lyo-Ject 25-mg syringe is supplied in a single molded nonsterile tray in cartons of 6 syringes (NDC 0088-1790-17). PRODUCT IS TO BE STORED AT ROOM TEMPERATURE 15-30°C (59-86°F). DO NOT FREEZE. RECONSTITUTED MATERIAL IS STABLE FOR 24 HOURS AT CONTROLLED ROOM TEMPERATURE. SINGLE-USE CONTAINERS. DISCARD UNUSED PORTION.

Prescribing Information as of September 1995

Mfd for:
Hoechst Marion Roussel, Inc.
Kansas City, MO 64114 USA

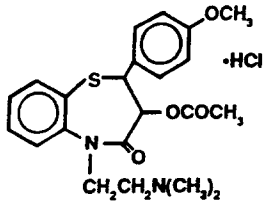
Prescribing Information as of September 1995

CARDIZEM® Injectable
(diltiazem HCl)

CARDIZEM® Lyo-Ject Syringe
(diltiazem HCl)

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium channel 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 Injectable (diltiazem hydrochloride) is a clear, colorless, sterile, nonpyrogenic solution. It has a pH range of 3.7 to 4.1.

CARDIZEM Injectable is for direct intravenous bolus injection and continuous intravenous infusion.

25-mg, 5-mL vial–each sterile vial contains 25 mg diltiazem hydrochloride, 3.75 mg citric acid USP, 3.25 mg sodium citrate dihydrate USP, 357 mg sorbitol solution USP, and water for injection USP up to 5 mL. Sodium hydroxide or hydrochloric acid is used for pH adjustment.

50-mg, 10-mL vial–each sterile vial contains 50 mg diltiazem hydrochloride, 7.5 mg citric acid USP, 6.5 mg sodium citrate dihydrate USP, 714 mg sorbitol solution USP, and water for injection USP up to 10 mL. Sodium hydroxide or hydrochloric acid is used for pH adjustment.

CARDIZEM Lyo-Ject Syringe (diltiazem hydrochloride) after reconstitution contains a clear, colorless, sterile, nonpyrogenic solution. It has a pH range of 4.0 to 7.0.

CARDIZEM Lyo-Ject Syringe after reconstitution is for direct intravenous bolus injection and continuous intravenous infusion.

CARDIZEM Lyo-Ject Syringe 25-mg syringe is available in a dual chamber, disposable syringe. Chamber 1 contains lyophilized powder comprised of diltiazem hydrochloride 25 mg and mannitol USP 37.5 mg. Chamber 2 contains sterile diluent composed of 5 mL water for injection with 0.5% benzyl alcohol NF, and 0.6% sodium chloride USP.

CLINICAL PHARMACOLOGY

Mechanisms of Action.

CARDIZEM inhibits the influx of calcium (Ca^{++}) ions during membrane depolarization of cardiac and vascular smooth muscle. The therapeutic benefits of CARDIZEM in supraventricular tachycardias are related to its ability to slow AV nodal conduction time and prolong AV nodal refractoriness. CARDIZEM exhibits frequency (use) dependent effects on AV nodal conduction such that it may selectively reduce the heart rate during tachycardias involving the AV node with little or no effect on normal AV nodal conduction at normal heart rates.

CARDIZEM slows the ventricular rate in patients with a rapid ventricular response during atrial fibrillation or atrial flutter. CARDIZEM converts paroxysmal supraventricular tachycardia (PSVT) to normal sinus rhythm by interrupting the reentry circuit in AV nodal reentrant tachycardias and reciprocating tachycardias, eg, Wolff-Parkinson-White syndrome (WPW).

CARDIZEM prolongs the sinus cycle length. It has no effect on the sinus node recovery time or on the sinoatrial conduction time in patients without SA nodal dysfunction. CARDIZEM has no significant electrophysiologic effects on tissues in the heart that are fast sodium channel dependent, eg, His-Purkinje tissue, atrial and ventricular muscle, and extranodal accessory pathways.

Like other calcium channel antagonists, because of its effect on vascular smooth muscle, CARDIZEM decreases total peripheral resistance resulting in a decrease in both systolic and diastolic blood pressure.

Hemodynamics.

In patients with cardiovascular disease, CARDIZEM Injectable (diltiazem hydrochloride) administered intravenously in single bolus doses, followed in some cases by a continuous infusion, reduced blood pressure, systemic vascular resistance, the rate-pressure product, and coronary vascular resistance and increased coronary blood flow. In a limited number of studies of patients with compromised myocardium (severe congestive heart failure, acute myocardial infarction, hypertrophic cardiomyopathy), administration of intravenous diltiazem produced no significant effect on contractility, left ventricular end diastolic pressure, or pulmonary capillary wedge pressure. The mean ejection fraction and cardiac output/index remained unchanged or increased. Maximal hemodynamic effects usually occurred within 2 to 5 minutes of an injection. However, in rare instances, worsening of congestive heart failure has been reported in patients with preexisting impaired ventricular function.

Pharmacodynamics.

The prolongation of PR interval correlated significantly with plasma diltiazem concentration in normal volunteers using the Sigmoidal E_{max} model. Changes in heart rate, systolic blood pressure, and diastolic blood pressure did not correlate with diltiazem plasma concentrations in normal volunteers. Reduction in mean arterial pressure correlated linearly with diltiazem plasma concentration in a group of hypertensive patients.

In patients with atrial fibrillation and atrial flutter, a significant correlation was observed between the percent reduction in HR and plasma diltiazem concentration using the Sigmoidal E_{max} model. Based on this relationship, the mean plasma diltiazem concentration required to produce a 20% decrease in heart rate was determined to be 80 ng/mL. Mean plasma diltiazem concentrations of 130 ng/mL and 300 ng/mL were determined to produce reductions in heart rate of 30% and 40%.

Pharmacokinetics and Metabolism.

Following a single intravenous injection in healthy male volunteers, CARDIZEM appears to obey linear pharmacokinetics over a dose range of 10.5 to 21.0 mg. The plasma elimination half-life is approximately 3.4 hours. The apparent volume of distribution of CARDIZEM is approximately 305 L. CARDIZEM is extensively metabolized in the liver with a systemic clearance of approximately 65 L/h.

After constant rate intravenous infusion to healthy male volunteers, diltiazem exhibits nonlinear pharmacokinetics over an infusion range of 4.8 to 13.2 mg/h for 24 hours. Over this infusion range, as the dose is increased, systemic clearance decreases from 64 to 48 L/h while the plasma elimination half-life increases from 4.1 to 4.9 hours. The apparent volume of distribution remains unchanged (360 to 391 L). In patients with atrial fibrillation or atrial flutter, diltiazem systemic clearance has been found to be decreased compared to healthy volunteers. In patients administered bolus doses ranging from 2.5 mg to 38.5 mg, systemic clearance averaged 36 L/h. In patients administered continuous infusions at 10 mg/h or 15 mg/h for 24 hours, diltiazem systemic clearance averaged 42 L/h and 31 L/h, respectively.

Based on the results of pharmacokinetic studies in healthy volunteers administered different *oral* CARDIZEM formulations, constant rate intravenous infusions of CARDIZEM at 3, 5, 7, and 11 mg/h are predicted to produce steady-state plasma diltiazem concentrations equivalent to 120-, 180-, 240-, and 360-mg total daily oral doses of CARDIZEM tablets or CARDIZEM SR capsules.

After oral administration, CARDIZEM undergoes extensive metabolism in man by deacetylation, N-demethylation, and O-demethylation via cytochrome P-450 (oxidative metabolism) in addition to conjugation. Metabolites N-monodesmethyldiltiazem, desacetyldiltiazem, desacetyl-N-monodesmethyldiltiazem, desacetyl-O-desmethyldiltiazem, and desacetyl-N, O-desmethyldiltiazem have been identified in human urine. Following oral administration, 2% to 4% of the unchanged CARDIZEM appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Following single intravenous injection of CARDIZEM, however, plasma concentrations of N-monodesmethyldiltiazem and desacetyldiltiazem, two principal metabolites found in plasma after oral administration, are typically not detected. These metabolites are observed, however, following 24 hour constant rate intravenous infusion. Total radioactivity ... diltiazem and are more slowly eliminated, half-life of total radioactivity is about 20 hours compared to 2 to 5 hours for diltiazem.

CARDIZEM is 70% to 80% bound to plasma proteins. In vitro studies suggest alpha$_1$-acid glycoprotein binds approximately 40% of the drug at clinically significant concentrations. Albumin appears to bind approximately 30% of the drug, while other constituents bind the remaining bound fraction. Competitive in vitro ligand binding studies have shown that CARDIZEM binding is not altered by therapeutic concentrations of digoxin, phenytoin, hydrochlorothiazide, indomethacin, phenylbutazone, propranolol, salicylic acid, tolbutamide, or warfarin.

Renal insufficiency, or even end-stage renal disease, does not appear to influence diltiazem disposition following *oral* administration. Liver cirrhosis was shown to reduce diltiazem's apparent *oral* clearance and prolong its half-life.

INDICATIONS AND USAGE

CARDIZEM Injectable or CARDIZEM Lyo-Ject Syringe (diltiazem hydrochloride) are indicated for the following:

1. **Atrial Fibrillation or Atrial Flutter.** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. **Paroxysmal Supraventricular Tachycardia.** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable or Lyo-Ject Syringe.

The use of CARDIZEM Injectable or Lyo-Ject Syringe for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable and CARDIZEM Lyo-Ject Syringe are 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 severe hypotension or cardiogenic shock.

Prescribing Information as of September 1995

CARDIZEM® Injectable
(diltiazem HCl)

CARDIZEM® Lyo-Ject Syringe
(diltiazem HCl)

4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable or Lyo-Ject Syringe. As such, the initial use of CARDIZEM Injectable or Lyo-Ject Syringe should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS $\geq$0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.
8. In newborns, due to the presence of benzyl alcohol as a preservative (CARDIZEM Lyo-Ject only).

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase ...

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20792

CHEMISTRY REVIEW(S)

JUL 30 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-792 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 30-Jul-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	20-Dec-96	23-Dec-96	30-Dec-96
AMENDMENT [BL] Methods validation	18-Jul-97	21-Jul-97	22-Jul-97

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel Inc.
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

DRUG PRODUCT NAME

Proprietary:	Cardizem, Monovial for Injection
Nonproprietary/USAN:	Diltiazem hydrochloride
Code Name/#:	CAS - 33286-22-5 CAS - 42399-41-7 (diltiazem)
Chem.Type/Ther.Class:	1 Z

ANDA Suitability Petition/DESI/Patent Status: None.

PHARMACOL.CATEGORY/INDICATION: Calcium ion influx inhibitor (slow-channel blocker or calcium channel antagonist).

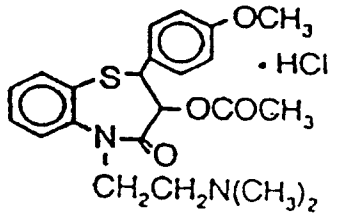
DOSAGE FORM: Injection after reconstitution in infusion bag

STRENGTHS: 100 mg vial

ROUTE OF ADMINISTRATION: Continuous infusion

DISPENSED: __X__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical Name(s):

1,5-Benzothiazepin-4(5H)one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrate,(+)-cis

Molecular Formula: $C_{22}H_{26}N_2O_4S.HCl$ Molecular Weight: 450.98

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None.

CONSULTS: Microbiological consult was requested.

REMARKS/COMMENTS:

This application for lyophilized powder for injection is being submitted to support marketing approval for one indication: "atrial fibrillation or atrial flutter".

The manufacturer and packager of the drug product is Gruppo Lepetit S.p.A., a subsidiary of Hoechst Marion Roussel, Inc. In Anagni, Italy.

EER was requested on 1/14/97. Acceptable on 3/4/97.

Microbiology consult was requested on December 20, 1996. Acceptable 5/8/97.

Methods validation was done by Philadelphia District Laboratory. No problems were encountered.

On July 18, 1997 labeling amendment was submitted. It is satisfactory for DESCRIPTION and HOW SUPPLIED sections.

CONCLUSIONS & RECOMMENDATIONS:

Response to deficiencies was satisfactory.

cc:
Orig. NDA 20-792
HFD-110/Division File
HFD-110/CunninghamD/7/30/97
HFD-100/CSO
HFD-810/Hoiberg
District

R/D Init by: TEAM LEADER

Danute G. Cunningham, Review Chemist
filename: 20792R03.NDA

Jrsolt 7/30/97

MAY 6 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-792 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 05-May-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	20-Dec-96	23-Dec-96	30-Dec-96
AMENDMENT [BC]	29-Apr-97	30-Apr-97	05-May-97

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel Inc.
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

DRUG PRODUCT NAME

Proprietary:	Cardizem, Monovial for Injection
Nonproprietary/USAN:	Diltiazem hydrochloride
Code Name/#:	CAS - 33286-22-5 CAS - 42399-41-7 (diltiazem)
Chem.Type/Ther.Class:	1 Z

ANDA Suitability Petition/DESI/Patent Status: None.

PHARMACOL.CATEGORY/INDICATION: Calcium ion influx inhibitor (slow-channel blocker or calcium channel antagonist).

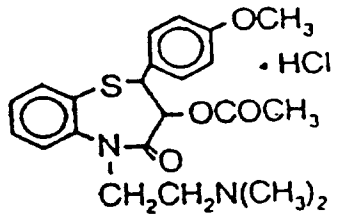
DOSAGE FORM: Injection after reconstitution in infusion bag

STRENGTHS: 100 mg vial

ROUTE OF ADMINISTRATION: Continuous infusion

DISPENSED: __X__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical Name(s):

1,5-Benzothiazepin-4(5H)one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrate,(+)-cis

Molecular Formula: $C_{22}H_{26}N_2O_4S.HCl$ Molecular Weight: 450.98

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None.

CONSULTS: Microbiological consult was requested.

REMARKS/COMMENTS:

This application for lyophilized powder for injection is being submitted to support marketing approval for one indication: "atrial fibrillation or atrial flutter".

The manufacturer and packager of the drug product is Gruppo Lepetit S.p.A., a subsidiary of Hoechst Marion Roussel, Inc. In Anagni, Italy.

EER was requested on 1/14/97. Acceptable on 3/4/97.

Microbiology consult was requested on December 20, 1996.

Methods validation will be done by DDA, St. Louis laboratory.

CONCLUSIONS & RECOMMENDATIONS:

Response to deficiencies was satisfactory.

cc:
Orig. NDA 20-792
HFD-110/Division File
HFD-110/CunninghamD/5/5/97
HFD-100/CSO
HFD-810/Hoiberg
District

R/D Init by: TEAM LEADER

Danute G. Cunningham, Review Chemist
filename: 20792R02.NDA

5/16/97

D. Kreder

MAR 5 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-792 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 28-Feb-97
05-Mar-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL AMENDMENT [AC]	20-Dec-96	23-Dec-96	30-Dec-96

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel Inc.
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

DRUG PRODUCT NAME

Proprietary:	Cardizem, Monovial for Injection
Nonproprietary/USAN:	Diltiazem hydrochloride
Code Name/#:	CAS - 33286-22-5 CAS - 42399-41-7 (diltiazem)
Chem.Type/Ther.Class:	1 Z

ANDA Suitability Petition/DESI/Patent Status: None.

PHARMACOL.CATEGORY/INDICATION: Calcium ion influx inhibitor (slow-channel blocker or calcium channel antagonist).

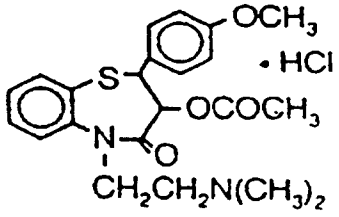
DOSAGE FORM: Injection after reconstitution in infusion bag

STRENGTHS: 100 mg vial

ROUTE OF ADMINISTRATION: Continuous infusion

DISPENSED: __X__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical Name(s):

1,5-Benzothiazepin-4(5H)one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrate,(+)-cis

Molecular Formula: $C_{22}H_{26}N_2O_4S.HCl$ Molecular Weight: 450.98

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None.

CONSULTS: Microbiological consult was requested.

REMARKS/COMMENTS:

This application for lyophilized powder for injection is being submitted to support marketing approval for one indication: "atrial fibrillation or atrial flutter".

The manufacturer and packager of the drug product is Gruppo Lepetit S.p.A., a subsidiary of Hoechst Marion Roussel, Inc. In Anagni, Italy.

EER was requestec on 1/14/97.

Microbiology consult was requested on December 20, 1996.

CONCLUSIONS & RECOMMENDATIONS:

Some minor requests are made in deficiency lotter.

cc:
Orig. NDA 20-792
HFD-110/Division File
HFD-110/CunninghamD/2/28/97
HFD-100/CSO
HFD-810/Hoiberg
District

R/D Init by: TEAM LEADER

Danute G. Cunningham, Review Chemist
filename: 20792R01.NDA

3/5/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20792

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

CARDIZEM MONOVIAL

diltiazem hydrochloride
(100 mg)

NDA 20-792

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-792

CARDIZEM MONOVIAL

Diltiazem hydrochloride
(100 mg)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Cardizem Monovial, Hoechst Marion Roussel Inc. referred to their approved NDA 20-027 for Cardizem Injection and prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31a (a), (Tier 0) which evaluates the potential environmental impacts of the manufacture, use and disposal of the drug product. NDA 20-027 is very similar to NDA 20-792; the only significant difference is the dosage form of diltiazem. Cardizem Injection is an aqueous solution of diltiazem, Cardizem Monovial is the lyophilized dosage form of diltiazem. Cardizem Monovial is an alternative for Cardizem Injection that is not expected to increase the overall use of diltiazem.

Diltiazem hydrochloride is a drug substance manufactured by Tanabe Seiyaku Co., Ltd., in Onoda, Japan. This manufacturing site is specifically listed in NDA 20-027 that was approved on October 24, 1991. Diltiazem hydrochloride is obtained by chemical syntheses.

The drug product is formulated and packaged by Gruppo Lepetit S.p.A., Anagni, Italy. This manufacturing site is specifically listed in NDA 20-027 S-002 that was approved on May 24, 1994. Diltiazem hydrochloride is combined with other components in a lyophilized dosage form for reconstitution in an infusion bag.

The drug product is a calcium ion influx inhibitor. The drug product will be used in hospitals and clinics. The drug substance and its metabolites will be excreted into the sewer system. The Expected Introduction Concentration (EIC) into the aquatic environment is well below 1 part per billion.

Disposal includes out of specification lots, unused or expired materials and packaging. Waste associated with drug substance manufacturing will be disposed by Tanabe Seiyaku Co., Ltd., in Onoda, Japan. Waste associated with drug product manufacturing will be disposed by Gruppo Lepetit S.p.A. Empty or partially empty packages generated in American hospitals and clinics will be disposed according to their regulations.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

5/23/97
Date

Florian Zielinski
Prepared by: Florian Zielinski, Ph.D., Review Chemist
Division of New Drug Chemistry I

5/29/97
Date

Division Concurrence: Robert J Wolters, Ph.D.
Division of New Drug Chemistry I

10/1/97
Date

Nancy B Sager
Approved by: Nancy B. Sager, Team Leader
Environmental Assessment Team,
Center for Drug Evaluation and Research

Attachments: FOI Environmental Assessment
Material Safety Data Sheet (Diltiazem hydrochloride)

Original: NDA 20-792
HFD-357 FONSI File [NDA # 20-792]
HFD-004 Docket File
HFD-205 FOI COPY
HFD-110 Division File
HFD-110 CSO, David Roeder
HFD-110 Review Chemist, Florian Zielinski

Attachment 2

FOI Copy

NDA# 20-792
Cardizem Monovial
(diltiazem hydrochloride for injection)
Amendment to Environmental Assessment

The following information provides additional information to the environmental assessment for Cardizem Monovial New Drug Application. The EA for Cardizem Injectable (NDA # 20-027) is included as Exhibit 1 as a reference

Diltiazem drug substance is manufactured by Tanabe in Onoda, Japan. Cardizem Monovial drug product is manufactured by Gruppo Lepetit S.p.A., Anagni, Italy, an affiliate of Hoechst Marion Roussel, Inc.

Diltiazem undergoes extensive metabolism in which only 2% to 4% of the unchanged drug appears in the urine. The FONSI for Tiazac (diltiazem hydrochloride) Capsules NDA (20-401) EA is included as Exhibit 2 and states "Chemical and physical data indicate the drug and its metabolites are restricted to the aquatic environment and are degraded by hydrolysis." Therefore degradation processes should decrease the environmental concentration of diltiazem and its metabolites even further. The amount of diltiazem hydrochloride manufactured for all dosage forms and strengths for the next 5 years is included in Exhibit 3 (Confidential; not included)

Due to extensive metabolism of diltiazem, hydrolysis of drug and its metabolites, and projected production volume, the Expected Introduction Concentration (EIC) of diltiazem is well below 1 ppb. Therefore, the use of diltiazem hydrochloride meets Tier 0 requirement and it is unlikely to have a significant impact on the environment.

C. Environmental Assessment (EA)

1. Date:

   September 30, 1992.

2. Name of Applicant/Petitioner:

   Marion Merrell Dow Inc.

3. Address:

   Marion Park Drive
   Kansas City, Missouri 64137

4. Description of the Proposed Action:

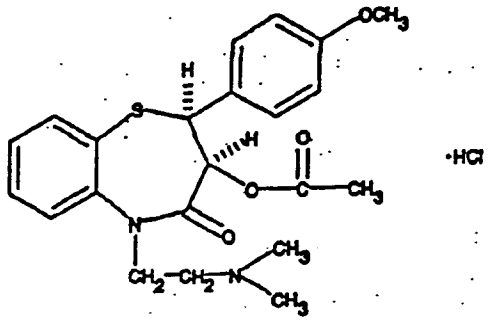
   The Applicant requests approval for an additional production site for Cardizem Injectable, which is currently formulated at Sanofi Winthrop Pharmaceuticals (formerly Sterling Drug, Inc.) production facilities located in McPherson, Kansas. The additional production site requested is Gruppo Lepetit S.p.A., a Marion Merrell Dow affiliate located in Anagni, Italy.

   Drug substance will continue to be manufactured by Tanabe in Onoda, Japan. The Environmental Assessment for manufacture of diltiazem hydrochloride in Japan is addressed in Tanabe's Drug Master File

5. Identification of Chemical Substances that are the Subject of the Proposed Action:

Product Name:	Cardizem Injectable
Generic Name:	Diltiazem hydrochloride
Chemical Name:	1,5-Benzothiazepin-4(5H) one, 3-(acetyloxy)-5-[2-(dimethylamino) ethyl]-2,3-dihydro-2-(4-methoxyphenyl) - monohydrochloride,(+)-cis
CAS Reg. No.:	33286-22-5
Empirical Formula:	$C_{22}H_{26}N_2O_4S \cdot HCl$
Molecular Weight:	450.98

Structural Formula:



Physical Description: Clear, colorless solution

Additives	CAS Number
Citric Acid USP, Monohydrate	5949-29-1
Sodium Citrate USP, Dihydrate	68-04-2
Sorbitol Solution USP	50-70-4
Sodium Hydroxide NF	1310-73-2
Hydrochloric Acid NF	7647-01-0
Water for Injection USP	7732-18-5

6. Introduction of Substances into the Environment:

The formulation and packaging of drug product at the Gruppo Lepetit S.p.A. facility in Anagni are conducted in compliance with applicable local, regional, and national environmental regulations. Applicable laws include the following:

D.P.R. 203/88 relating to air emissions
National Law 319/76 relating to waste water discharge

Certifications of Lepetit's compliance with these laws are included in Appendices A, B, C, D, and E. Disposal of hazardous waste has been contracted to Company I.P.I. S.r.L. whose headquarters are in Rome; authorization of this company by the Regional Authority is in Appendix F.

Information supplied in Section 6 of the original Environmental Assessment still applies for other sites.

7, 8, 9, 10, and 11 of the original Environmental Assessment have not changed as a result of this amendment.

12. List of Preparers:

Carole L. Smith, Ph.D., Environmental Assessment Advisor, Regulatory Services, Marion Merrell Dow Inc.; Ph.D. in Pharmacology from the Medical University of South Carolina; B.S. in Chemistry from University of Texas at Arlington; Diplomate of the American Board of Toxicology; 10 years experience in toxicology in the pharmaceutical industry.

3. Chemistry, Manufacturing and Controls
C. Environmental Assessment (EA)

13. **Certification:**

The undersigned official of Marion Merrell Dow certifies that the information presented is true, accurate and complete to the best knowledge of Marion Merrell Dow Inc.

Date 11/12/92

Name Dhiren N. Shah, Ph.D.

Signature Dhiren N. Shah

Title Manager, Regulatory/CMC Operations

Appendix A Application submitted by Gruppo Lepetit S.p.A. to Giunta Regionale Lazio for Air Emission Permit, on the basis of the relevant law (D.P.R. 203/88), with attachments on the site activities and on the sampling and testing, carried out by a special contractor (Bioconsult), which demonstrated site compliance with the current regulations. English translation, followed by copy of the original Italian document.

Appendix B Certification from the Environmental Bureau of Frosinone district that Lepetit S.p.A. is in compliance with air emissions based on the relevant law (D.P.R. 203/88). English translation, followed by copy of the original Italian document.

Appendix C Authorization for waste water disposal granted by the Anagni Public Health Authority to Gruppo Lepetit S.p.A., relevant to Law No. 319/76.

Appendix D Favorable opinion of Unita Sanitaria Locale FR/1 - Anagni (Local Health Agency), concerning application for registration of authorization for final waste disposal by Gruppo Lepetit S.p.A. English translation, followed by copy of the original Italian document.

Appendix E Certification from the Unita Sanitaria Locale FR/1 - Anagni, stating that Gruppo Lepetit S.p.A. is in compliance with National Law 319/76 regarding waste water disposal, with specific reference to Cardizem I.V. English translation, followed by copy of the original Italian document.

Appendix F Authorization for solid waste disposal granted by the Lazio Regional Board to the Company I.P.I. S.r.L., to whom Gruppo Lepetit S.p.A. contracts solid waste disposal. English translation, followed by copy of the original Italian document.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20792

MICROBIOLOGY REVIEW(S)

D. Breder

MAY 12 1997

REVIEW FOR HFD-110

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review #1 of NDA 20-792
May 8, 1997

A. 1. **APPLICATION NUMBER:** 20-792

APPLICANT: Hoechst Marion Roussel, Inc.
P.O. Box 9627
Kansas City, MO 64134-0627
(816) 966-5000

2. **PRODUCT NAME:** CARDIZEM® Monovial®

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Diltiazem hydrochloride (lyophilized powder,100 mg/vial) for use in conjunction with most standard plastic infusion bags for intravenous injection.

4. **METHODS OF STERILIZATION:**
   -
   -
   -
   -

5. **PHARMALOGICAL CATAGORY and/or PRINCIPLE INDICATION:** A calcium ion influx inhibitor indicated for atrial fibrillation or atrial flutter..

6. **DRUG PRIORITY CLASSIFICATION:** 3S

B. 1. **DATE OF INITIAL SUBMISSION:** December 20, 1996

2. RELATED DOCUMENTS:

3. **DATE OF CONSULT:** December 24, 1996

4. **ASSIGNED FOR REVIEW:** January 6, 1997

C. **REMARKS:** The NDA provides for the manufacturing of the drug product by Gruppo Lepetit S.P.A., a subsidiary of Hoechst Marion Roussel, Inc. (Anagni, Italy).

D. CONCLUSIONS:

The submission is recommended for approval for microbiology issues concerning, sterility assurance.

Neal Sweeney 5/8/97
Neal Sweeney, Ph.D.

PHC 5/12/97

cc: NDA 20-792
HFD-110/Division File
HFD-110/CSO/D. Roeder
HFD-805/Consult File/N. Sweeney

Drafted by: N. Sweeney, May 8, 1997
R/D initialed by P. Cooney, May 8, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20792

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-792 **SUPPL #** -

Trade Name Cardizem (diltiazem HCl) Monovial **Generic Name** _____

Applicant Name Hoechst Marion Roussel **HFD-** 110

Approval Date _____

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 /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

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

   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 /___/ 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 /✓/

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

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

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 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /___/ NO /✓/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 /___/ 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 8:**

_____

_____

(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 /___/

(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 /___/

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 /___/

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 # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/
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 /___/
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 #__, Study # _____

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 # _____ YES /___/ 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 /___/

If yes, explain: _____

_____

_____

_____

David Rada
Signature
Title: Project Manager

6-12-97
Date

Ray Lipicky
Signature of Division Director

6/17/97
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

8/8/95

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-792 Trade (generic) names Cardizem (diltiazem HCl) Monovial

Check any of the following that apply and explain, as necessary, on the next page:

__X__ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__X__ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Ray Lipicky

Signature of Preparer

6/17/97

Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

SEP 5 1997

Approval Overview

Application: NDA 20-792
Cardizem Monovial (diltiazem HCl) for Injection

Sponsor: Hoechst Marion Roussel

Date of AE Letter: June 19, 1997

An approvable letter was issued on June 19, 1997, requesting final printed labeling. Since then, the sponsor submitted an amendment with a labeling change. The chemist reviewed that amendment and found it to be acceptable (July 30, 1997). The sponsor submitted final printed labeling on August 15, 1997 (letter date, August 14, 1997).

Note: This application shares a package insert with NDA 20-027. The final printed labeling for NDA 20-792 contains a labeling change from pending NDA 20-027/016, but the pending supplemental NDA 20-027/S-016 does not contain the information from NDA 20-792. Therefore, supplemental NDA 20-027/S-016 should be approved prior to NDA 20-792.

David Roeder
Regulatory Health Project Manager

dr/8-21-97

cc: NDA 20-792
HFD-110
HFD-110/DRoeder

RHPM Package Overview

Application: NDA 20-792
Cardizem Monovial (diltiazem HCl)

Sponsor: Hoechst Marion Roussel, Inc.

Date of Submission: December 20, 1996

Receipt Date: December 20, 1996

User Fee Goal: December 20, 1997

Cardizem Injection and Cardizem Lyoject are currently approved for the temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter and for rapid conversion of PSVT to normal sinus rhythm under NDA 20-027. NDA 20-792 provides for a new lyophilized formulation of diltiazem, Cardizem Monovial. Since this product is for use only as a continuous infusion, the sponsor has proposed that it be indicated only for the temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. The same package insert will be used for all three products.

This application contained no preclinical or clinical data.

Chemistry

Reviewer: Danute Cunningham

Date of Reviews: 3-5-97 5-6-97

All Chemistry Issues are resolved.

EER

Acceptable: 3-6-97

Environmental Assessment

Reviewer: Florian Zielinski, Ph.D.

Signed off by Nancy Sager on June 1, 1997

Microbiology

Reviewer: Neal Sweeney, Ph.D.

Date of Review: May 12, 1997

The microbiology reviewers has recommended approval.

Pharmacology

No Review necessary.

Clinical

No Review necessary.

Statistical

No Review necessary.

Secondary Review

Dr. Lipicky will write the secondary review.

David Roeder
Regulatory Health Project Manager

dr/5-22-97/6-4-97

cc: NDA 20-792
HFD-110
HFD-110/DRoeder/SBenton

JUN 19 1997

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION **Public Health Service**
Division of Cardio-Renal Drug Products

Memorandum

DATE :

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110 Lipicky

SUBJECT: NDA 20-792, Cardizem Monovial, Parenteral diltiazem. Hoechst Marion Roussel

TO : NDA 20-792 File

This NDA is nothing more than a reformulation of already approved parenteral diltiazem. This is a lyophilized formulation packaged (in glass and also in a plastic bag) so that when reconstituted, it is easily used for an intravenous infusion. The other 2 formulations of parenteral diltiazem (Cardizem Injectable and Cardizem Lyo-Ject Syringe) are mainly intended for single IV bolus injections (although they could be used in a similar fashion if they were injected into an IV bottle or bag). It is sort of strange that there should be need for another NDA number, but that is indeed the case.

It is stranger that the formulation (appropriately) needs a change in the indications section, although it is really just a chemistry supplement. Since Cardizem Monovial is packaged for purposes of being convenient for use as an IV infusion (over hours) and would be very inconvenient for single dose bolus injection, the sponsor suggests that its (Cardizem Monovial) be Indicated for those supraventricular arrhythmias where not only a bolus but also a longer term infusion are needed (Atrial Fibrillation/Flutter). The Paroxysmal Supraventricular Tachycardia Indication (that is an approved indication for parenteral diltiazem) requires only a single bolus injection (and therefore would not be suitable for Cardizem Monovial).

Although this convenience business and different Trade Names for each convenience as well as different Indications for the Trade Names is confusing and not very desirable, the sponsors case is a reasonable one. With the Indication change, there is less likely to be confusion. So, it is approvable.

cc: NDA 20-792
HFD-110
HFD-110/DRoeder

RHPM Review of Draft Labeling

Application: NDA 20-792
Cardizem Monovial (diltiazem HCl)

Sponsor: Hoechst Marion Roussel, Inc.

Date of Submission: December 20, 1996

Receipt Date: December 20, 1996

Cardizem Injection and Cardizem Lyoject are currently approved for the temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter and for rapid conversion of PSVT to normal sinus rhythm under NDA 20-027. NDA 20-792 provides for a new lyophilized formulation of diltiazem, Cardizem Monovial. Since this product is for use only as a continuous infusion, the sponsor has proposed that it be indicated only for the temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. The same package insert will be used for all three products.

The labeling of the currently approved diltiazem injection products has to be revised to incorporate information about Cardizem Monovial. The following revisions have been made:

Under **DESCRIPTION** and **HOW SUPPLIED**, a description of the Monovial product has been added.

Under **INDICATIONS AND USAGE**, the format was revised to show that Cardizem Injection and Cardizem Lyoject are approved for both indications and that Cardizem Monovial is approved only for the atrial fibrillation/atrial flutter indication.

The **DOSAGE AND ADMINISTRATION** section has been revised as follows:

A dilution table and compatibility/incompatibility information for Cardizem Monovial were added.

Under **Continuous Intravenous Infusion**, a reference is made to the reconstitution instructions for Cardizem Lyoject and Cardizem Monivial that can be found in the packaging.

Under **Dilution** the sponsor deleted the statement, "Keep refrigerated until use."

The headings "Compatibility" and "Physical Incompatibilities" were added to the appropriate sections.

Recommendations

1) The sponsor should add the statement "Keep refrigerated until use" to the end of the first paragraph of the **DOSAGE AND ADMINISTRATION: Dilution** subsection.

2) The sponsor did not include a copy of the instructions for reconstitution for the Monovial product (referred to in the **DOSAGE AND ADMINISTRATION** section). They should be asked to do so with their submission of final printed labeling.

David Roeder
Regulatory Health Project Manager
dr/5-22-97

cc: NDA 20-792
HFD-110
HFD-110/DRoeder/SBenton

Debarment Certification

Hoechst Marion Roussel, Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) in connection with this application.

Elaine Waller, PharmD
Vice President, North American Drug
Regulatory Affairs

7 Jan 97
Date

13/14. Patent Information/Certification

None

Submitted by:

Elaine Waller
Vice President,
North America Drug Regulatory Affairs

D. Roeder

SEP 5 1997

RHPM Review of Final Printed Labeling

Application: NDA 20-792
Cardizem Monovial (diltiazem HCl) for Injection

Sponsor: Hoechst Marion Roussel

Letter Date: August 14, 1997

Receipt Date: August 15, 1997

Review

An approvable letter was issued for NDA 20-792 on June 19, 1997. The sponsor amended the application on July 18, 1997 to change the dilution instruction under **HOW SUPPLIED** to read as follows:

> Keep diluted Cardizem Injectable refrigerated until use. Diluted Cardizem Lyo-Ject Syringe and Cardizem Monovial may be stored at room temperature 15°-30°C (59-86°F).

The change regarding Cardizem (diltiazem HCl) Injectable was supported in a separate supplemental application to NDA 20-027. The Chemist reviewed this amendment and found it to be acceptable.

The sponsor submitted final printed labeling to NDA 20-792 in a submission dated August 14, 1997. I reviewed the labeling and found it to be identical to the draft labeling in the approvable letter except for the changes mentioned above.

Recommendation

I recommend that the application be approved.

David Roeder
Regulatory Health Project Manager

dr/8-20-97

cc: NDA 20-792
HFD-110
HFD-110/DRoeder/SBenton

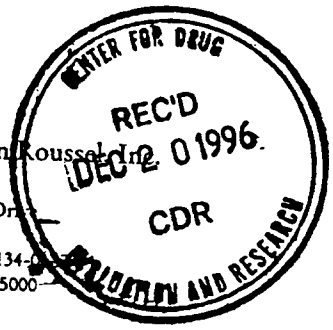
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20792

CORRESPONDENCE

Hoechst Marion Roussel

Hoechst Marion Roussel Inc.
10236 Marion Park Dr.
Mail: P.O. Box 9627
Kansas City, MO 64134-9627
Telephone (816) 966-5000



December 20, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
Document Control Room 16B-30
5600 Fishers Lane
Rockville, MD 20857

Attn: Central Document Room
12229 Wilkens Avenue
Rockville, MD 20852

RE: NDA 20-792
CARDIZEM® Monovial®
(diltiazem HCl for injection)

NEW DRUG APPLICATION

Dear Sir/Madam

In accordance with 21 CFR 314.1, Hoechst Marion Roussel, Inc. is submitting an eight-volume new drug application for CARDIZEM Monovial. Per user fee bundling guidance, this application for a lyophilized powder for injection is being submitted to support marketing approval for one indication: "atrial fibrillation or atrial flutter."

This New Drug Application provides for the manufacture and packaging of the drug product by Gruppo Lepetit S.P.A, a subsidiary of Hoechst Marion Roussel, Inc. in Anagni, Italy. Safety and efficacy for this NDA were previously established in NDA 20-027, Cardizem Injectable. Cross reference to NDA 20-027 can be found on the Form FDA 356h, in the Index to this application and as appropriate in the text.

Pursuant to 21 CFR 314.50(h)(3) and in accordance with the FDA Final Rule dated September 8, 1993, we are providing a field copy of this NDA to the FDA District Office in Lenexa, KS.

If you have any questions, please contact:

J. Michael Nicholas (816-966-5720) or
Dhiren Shah (816-966-7104)
Hoechst Marion Roussel, Inc.
P.O. Box 9627
Kansas City, MO 64134-0627

Sincerely,

Elaine Waller

Elaine Waller, PharmD
Vice President, North America Drug Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

D'Arcy

Food and Drug Administration
Rockville MD 20857

NDA 20-792

MAR 19 1997

Hoechst Marion Roussel, Inc.
Attention: Elaine Waller, Pharm.D.
P.O. Box 9627
Kansas City, MO 64134-0627

Dear Dr. Waller:

Please refer to your pending December 20, 1996 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Cardizem Monovial (diltiazem hydrochloride) for Injection.

We have completed our review of the chemistry, manufacturing and controls section of your submission and have identified the following deficiencies:

1. If you plan to Cardizem Monovial, please provide the appropriate information.

2. Please correct the typographical error in volume 1.2 page 3-45 - you specify testing the first three commercial batches additionally at time points of 4 and 9 months; it should be at 3 and 9 months.

3. What is the actual batch size for Cardizem Monovial batch 001? Page 41 of volume 1.2 lists it as vials and in the same volume on page 44 it is listed as vials.

4.

Please submit the required information.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

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

Sincerely yours,

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

cc:
Original NDA
HFD-110
HFD-110/DRoeder
sb/3/13/97;3/18/97
R/D: DCunningham/3/14/97
RWolters/3/17/97
NMorgenstern/3/17/97

INFORMATION REQUEST