

Prescribing Information as of January 2004

CARDIZEM[®] Injectable

(diltiazem HCl injection)

CARDIZEM[®] Lyo-Ject[®] Syringe

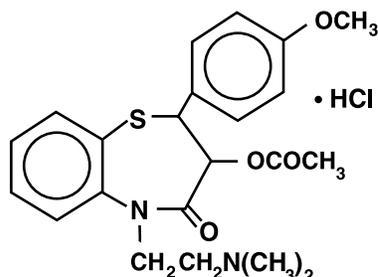
(diltiazem HCl)

CARDIZEM[®] Monovial[®]

(diltiazem HCl for injection)

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 injection) 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.

CARDIZEM Monovial (diltiazem hydrochloride for injection), after reconstitution in an infusion bag, produces a clear, colorless, sterile, nonpyrogenic solution.

CARDIZEM Monovial for continuous intravenous infusion is available in a glass vial with transfer needle set. The vial contains lyophilized powder comprised of diltiazem hydrochloride 100 mg and mannitol USP 75 mg.

CLINICAL PHARMACOLOGY

Mechanisms of Action

CARDIZEM inhibits the influx of calcium (Ca²⁺) 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 injection) 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 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 alpha₁-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, CARDIZEM Lyo-Ject Syringe, or CARDIZEM Monovial (diltiazem hydrochloride for injection) are indicated for the following:

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.

In addition, CARDIZEM Injectable or CARDIZEM Lyo-Ject Syringe are indicated for:

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 CARDIZEM Lyo-Ject Syringe.

The use of CARDIZEM Injectable, CARDIZEM Lyo-Ject Syringe, or CARDIZEM Monovial 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

Injectable forms of diltiazem 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.
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 injectable forms of diltiazem. As such, the initial use of injectable forms of diltiazem 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 injectable forms of diltiazem.
8. In newborns, due to the presence of benzyl alcohol (CARDIZEM Lyo-Ject Syringe 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

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of this enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450 3A4, especially patients with renal and/or

hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels.

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

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

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.

Buspirone. In nine healthy subjects, diltiazem significantly increased the mean buspirone AUC 5.5 fold and C_{max} 4.1 fold compared to placebo. The $T_{1/2}$ and T_{max} of buspirone were not significantly affected by diltiazem. Enhanced effects and increased toxicity of buspirone may be possible during concomitant administration with diltiazem. Subsequent dose adjustments may be necessary during co-administration, and should be based on clinical assessment.

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.

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

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.

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.

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

Quinidine. Diltiazem significantly increases the $AUC_{(0 \rightarrow \infty)}$ of quinidine by 51%, $T_{1/2}$ by 36% and decreases its CL_{oral} by 33%. Monitoring for quinidine adverse effects may be warranted and the dose adjusted accordingly.

Rifampin. Coadministration of rifampin with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with rifampin or any known CYP3A4 inducer should be avoided when possible, and alternative therapy considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic

response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy

Category C. Reproduction studies have been conducted in mice, rats, and rabbits.

Administration of 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.

Geriatric Use

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

Atrial fibrillation or atrial flutter. In clinical studies with CARDIZEM Injectable (diltiazem HCl injection) for AF/Fl, 135 of 257 patients were ≥65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In subgroup analysis of double-blind and open-label trials following first-dose response, 116 patients ≥65 years of age had a response rate of 84%. One hundred two (102) patients <65 had a response rate of 78%. In subgroup analysis following a two-dose procedure in double-blind and open-label studies, 104 patients ≥65 years of age and 95 patients <65 both had a 95% response rate.

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

CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The risk of toxic reactions to this drug may be greater in patients with impaired renal or hepatic function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. As with all drugs, care should be exercised when treating patients with multiple medications. (See Precautions, General and Drug Interactions.)

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, myopathy, 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.

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).

The effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose has been inconsistent. In a few reported cases, overdose with calcium channel blockers associated with hypotension and bradycardia that was initially refractory to atropine became more responsive to atropine after the patients received intravenous calcium. In some cases intravenous calcium has been administered (1 g calcium chloride or 3 g calcium gluconate) over 5 minutes, and repeated every 10-20 minutes as necessary. Calcium gluconate has also been administered as a continuous infusion at a rate of 2 g per hour for 10 hours. Infusions of calcium for 24 hours or more may be required. Patients should be monitored for signs of hypercalcemia.

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 LD₅₀'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 CARDIZEM Lyo-Ject Syringe 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, CARDIZEM Lyo-Ject Syringe, or CARDIZEM Monovial may be administered. (For reconstitution of CARDIZEM Lyo-Ject Syringe or CARDIZEM Monovial, see instructions contained within packaging.) Immediately following bolus administration of 20 mg (0.25 mg/kg) or 25 mg (0.35 mg/kg) CARDIZEM Injectable or CARDIZEM Lyo-Ject Syringe, and reduction of heart rate, begin an intravenous infusion of CARDIZEM Injectable, CARDIZEM Lyo-Ject Syringe, or CARDIZEM Monovial. The recommended initial infusion rate of CARDIZEM Injectable, CARDIZEM Lyo-Ject Syringe, or CARDIZEM Monovial 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, CARDIZEM Lyo-Ject Syringe, or CARDIZEM Monovial for continuous intravenous infusion, aseptically transfer the appropriate quantity (see charts) of CARDIZEM to the desired volume of either Normal Saline, D5W, or D5W/0.45% NaCl. Mix thoroughly. 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). Use within 24 hours.

CARDIZEM Injectable or CARDIZEM Lyo-Ject Syringe

Diluent Volume	Quantity of CARDIZEM Injectable or CARDIZEM Lyo-Ject to Add	Final Concentration	Administration	
			Dose*	Infusion Rate
100 mL	125 mg (25 mL) Final Volume 125 mL	1 mg/mL	10 mg/h	10 mL/h
			15 mg/h	15 mL/h
250 mL	250 mg (50 mL) Final Volume 300 mL	0.83 mg/mL	10 mg/h	12 mL/h
			15 mg/h	18 mL/h
500 mL	250 mg (50 mL) Final Volume 550 mL	0.45 mg/mL	10 mg/h	22 mL/h
			15 mg/h	33 mL/h

* 5 mg/h may be appropriate for some patients

CARDIZEM Monovial

Diluent Volume	Quantity of CARDIZEM Monovial to Add	Final Concentration	Administration	
			Dose*	Infusion Rate
100 mL	100 mg (1 monovial)	1 mg/mL	10 mg/h	10 mL/h
			15 mg/h	15 mg/h
250 mL	200 mg (2 monovials)	0.80 mg/mL	10 mg/h	10 mg/h
			15 mg/h	18.8 mL/h
500 mL	200 mg (2 monovials)	0.40 mg/mL	10 mg/h	25 mL/h
			15 mg/h	37.5 mL/h

*5 mg/h may be appropriate for some patients

Compatibility: CARDIZEM Injectable, CARDIZEM Lyo-Ject Syringe, and CARDIZEM Monovial were tested for compatibility with three commonly used intravenous fluids at a maximal concentration of 1 mg diltiazem hydrochloride per milliliter. CARDIZEM Injectable, CARDIZEM Lyo-Ject Syringe, and CARDIZEM Monovial were found to be physically compatible and chemically stable in the following parenteral solutions for at least 24 hours when stored in glass (CARDIZEM Injectable/CARDIZEM Lyo-Ject Syringe only) 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.

Physical Incompatibilities:

Because of potential physical incompatibilities, it is recommended that CARDIZEM Injectable, CARDIZEM Lyo-Ject Syringe, or CARDIZEM Monovial not be mixed with any other drugs in the same container. If possible, it is recommended that CARDIZEM Injectable, CARDIZEM Lyo-Ject Syringe, or CARDIZEM Monovial not be co-infused in the same intravenous line. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

CARDIZEM Injectable/CARDIZEM Lyo-Ject Syringe. Physical incompatibilities (precipitate formation or cloudiness) were observed when CARDIZEM Injectable or CARDIZEM Lyo-Ject Syringe 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 Syringe was found to be compatible with insulin (regular, 100 units/mL).

CARDIZEM Monovial. Physical incompatibilities (precipitate formation or cloudiness) were observed when CARDIZEM Monovial at a concentration of 1 mg/mL diluted in normal saline was infused in the same intravenous line with the following drugs: acetazolamide, acyclovir, cefoperazone sodium, diazepam, furosemide, phenytoin and rifampin.

NOTE: CARDIZEM Monovial at a concentration of 1 mg/mL diluted in normal saline was infused in the same intravenous line and was found to be compatible with the following drugs: aminophylline, ampicillin sodium, ampicillin sodium/sulbactam sodium, cefamandole, hydrocortisone sodium succinate, regular insulin (100 units/mL), methylprednisolone sodium succinate, mezlocillin sodium, nafcillin sodium and sodium bicarbonate.

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)(Insert NDC # - formerlyNDC 0088-1790-32) and boxes of six 10-mL vials with each vial containing 50 mg diltiazem hydrochloride (5 mg/mL) (Insert NDC # - formerlyNDC 0088-1790-33). 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. SINGLE-USE CONTAINERS. DISCARD UNUSED PORTION.

CARDIZEM Lyo-Ject 25-mg syringe is supplied in a single molded nonsterile tray in cartons of 6 syringes (Insert NDC # - formerly NDC 0088-1789-17 /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.

CARDIZEM Monovial for continuous infusion (100 mg) is supplied in a glass vial with transfer needle set (Insert NDC # - formerly NDC 0088-1788-16). 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 VIAL.

Monovial[®] is a registered trademark of Becton Dickinson S.A.

Cardizem[®] is a registered trademark of Biovail Pharmaceuticals

Lyo-Ject[®] is a registered trademark of Arzneimittel GmbH Apotheker Vetter & Company.

Prescribing Information as of January 2004

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