PRODUCT MONOGRAPH

GEN-DILTIAZEM

(Diltiazem Hydrochloride Tablets, USP)

30 and 60 mg

Anti-Anginal Agent

GEN-DILTIAZEM SR

(Diltiazem Hydrochloride Sustained Release Capsules,

Genpharm Standard)

60, 90 and 120 mg

Antihypertensive Agent, Anti-Anginal Agent

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Date of Preparation:
January 16, 1995

Date of Revision:
October 29, 1997

Control # 051887

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ACTION AND CLINICAL PHARMACOLOGY

GEN-DILTIAZEM (diltiazem HCl) tablets and GEN-DILTIAZEM SR capsules are formulations of diltiazem HCl, which is a calcium ion influx inhibitor (calcium entry blockers or calcium ion antagonists).

Mechanism of Action

The therapeutic effect of this group of drugs is believed to be related to their specific cellular action of selectively inhibiting transmembrane influx of calcium ions into cardiac muscle and vascular smooth muscle. The contractile processes of these tissues are dependent upon the movement

of extracellular calcium into the cells through specific ion channels. Diltiazem blocks transmembrane influx of calcium through the slow channel without affecting to any significant degree the transmembrane influx of sodium through the fast channel. This results in a reduction of free calcium ions available within cells of the above tissues. Diltiazem does not alter total serum calcium.

Angina:

The precise mechanism by which diltiazem relieves angina has not been fully determined but it is believed to be brought about largely by its vasodilator action.

In angina due to coronary spasm, diltiazem increases myocardial oxygen delivery by dilating both large and small coronary arteries and by inhibiting coronary spasm at drug levels which cause little negative inotropic effect. The resultant increases in coronary blood flow are accompanied by dose dependent decreases in systemic blood pressure and decreases in peripheral resistance.

In angina of effort it appears that the action of diltiazem is related to the reduction of myocardial oxygen demand. This is probably caused by a decrease in blood pressure brought about by the reduction of peripheral

resistance and heart rate.

Hypertension:

The antihypertensive effect of diltiazem is believed to be brought about largely by its vasodilator action on peripheral blood vessels with resultant decrease in peripheral vascular resistance.

Hemodynamic and Electrophysiologic Effects

Diltiazem produces antihypertensive effects both in the supine and standing positions. Resting heart rate is usually slightly reduced. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually unaffected. Heart rate at maximum exercise is reduced.

Studies to date, primarily in patients with normal ventricular function, have shown that cardiac output, ejection fraction and left ventricular end-diastolic pressure have not been affected.

Chronic therapy with diltiazem produces no change, or an increase, in circulating plasma catecholamines. However, no increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem inhibits the renal and peripheral effects of angiotensin II.

In man intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. Chronic oral administration of diltiazem in doses up to 540 mg/day has resulted in small increases in PR interval. Second degree and third degree AV block have been observed (see **Warnings**). In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Pharmacokinetics

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect giving absolute bioavailability (compared to intravenous dosing) of about 40%. Therapeutic blood levels appear to be in the 50 to 200 ng/mL range and the plasma elimination half-life (beta-phase) following single or multiple drug administration is approximately 3.5 to 6.0 hours. *In-vitro* human serum binding studies revealed that 70 to 80% of diltiazem is bound to plasma proteins. Following extensive hepatic metabolism, only 2 - 4% of the drug appears unchanged in the urine and 6 - 7% appears as metabolites. The metabolic pathways of diltiazem include N- and O-demethylation (via cytochrome P-450), deacetylation (via plasma and tissue esterases), in addition to conjugation (via sulfation and glucuronidation). *In vitro* studies have demonstrated that CYP 3A4 is the principal CYP isosenzyme involved in

N-demethylation. The major metabolite, desacetyl-diltiazem, is present in the plasma at levels of 10-20% of the parent drug and is 25-50% as potent as diltiazem in terms of coronary vasodilation.

Diltiazem Tablets:

Single oral doses of 30 to 120 mg of diltiazem tablets result in detectable plasma levels within 30 to 60 minutes and peak plasma levels 2 to 4 hours after drug administration. There is a departure from linearity of accumulation of diltiazem when diltiazem tablets are administered to steady-state in normal subjects. A 240 mg daily dose (60 mg q.i.d.) gave plasma levels 2.3 times higher than a 120 mg daily dose (30 mg q.i.d.), and a 360 mg daily dose (90 mg q.i.d.) had levels 1.7 times higher than the 240 mg daily dose.

A summary of the results of a comparative, randomized, steady state, 2-way crossover bioavailability study of GEN-DILTIAZEM (diltiazem HCl) tablets 60 mg and the reference drug CARDIZEM® tablets 60 mg (Nordic, a subsidiary of Hoechst Marion Roussel Canada Inc.) is found in the following table:

Table 1:

Geometric Mean, Arithmetic Mean, (C.V.)			
Parameter	Test DILTIAZEM	Reference CARDIZEM®‡	Ratio of Means (%)
AUC_{0-8} (ng h/mL)	970.10 1068.66 (48.9)	948.23 1016.14 (39.1)	102.3
C_{max}	174.27 188.54 (42.5)	166.83 176.96 (35.3)	104.5
T_{max}*	---- 2.96 [SD = 0.81]	---- 3.13 [SD = 0.65]	----

* For T_{max}, only the arithmetic mean and standard deviation are presented.
‡ Cardizem® (Nordic, Canada) was purchased in Canada.

Diltiazem SR Capsules (Twice-A-day):

Diltiazem is absorbed from the sustained release (SR) capsule formulation to about 93% of the tablet form at steady-state. A single 120 mg dose of the capsule resulted in detectable plasma levels within 2 to 3 hours and peak plasma levels at 7 to 11 hours. The apparent elimination half-life after single or multiple dosing is 5 to 7 hours. A departure from linearity similar to that observed with the diltiazem tablet is observed. As the dose of diltiazem SR capsules is increased from a daily dose of 120 mg (60 mg b.i.d.) to 240 mg (120 mg b.i.d.) daily, there is an increase in bioavailability of 2.6 times. When the dose is increased from 240 mg to 360 mg daily there is an increase in bioavailability of 1.8 times. The average plasma levels of the capsule dosed twice daily at steady-state are equivalent to the tablet dosed four times daily when the same daily dose is administered.

Results of a comparative bioavailability study performed on GEN-DILTIAZEM SR Capsules 60 mg (Genpharm) and CARDIZEM® SR Capsules (Nordic) are summarized in Table 2.

Results of 3 comparative bioavailability studies of GEN-DILTIAZEM SR Capsules 120 mg (Genpharm), and CARDIZEM(R) SR Capsules (Nordic, Canada) are summarized in Tables 3 - 5.

Table 2: Comparative, randomized, single-dose, 2-way crossover bioavailability study of Genpharm and Nordic (CARDIZEM SR) 60 mg Diltiazem HCl sustained-release capsules in healty adult males under FASTED conditions:

Geometric Mean, Arithmetic Mean, (C.V.)			
Parameter	**Test DILTIAZEM**	**Reference CARDIZEM SR‡**	**Ratio of Means (%)**
AUC_{0-t} (ng.h/mL)	1160.85 1225.0 (32.9)	1077.98 1133.9 (34.4)	107.5
AUC_{0-12} (ng.h/mL)	704.71 758.3 (39.5)	673.73 713.1 (36.1)	104.2
AUC_{0-inf} (ng.h/mL)	1202.56 1266.3 (32.3)	1111.22 1167.7 (34.1)	108.1
C_{max}	131.09 141.05 (37.9)	117.69 128.30 (45.2)	111.0
T_{max}*	--- 6.66 (26.5)	--- 6.72 (15.3)	
$T_{½}$*	--- 5.75 (22.7)	--- 5.67 (16.1)	

* The T_{max} and $T_{½}$ parameters are expressed as the arithmetic means.
‡ Carizem SR (Nordic, Canada) was purchased in Canada.

Table 3: Comparative, randomized, single-dose, 2-way crossover bioavailability study of Genpharm and Nordic (CARDIZEM® SR) 120 mg diltiazem HCl sustained-release capsules in healthy adult males under **FASTED** conditions:

Geometric Mean, Arithmetic Mean, (C.V.)			
Parameter	Test DILTIAZEM	Reference CARDIZEM® SR‡	Ratio of Means (%)
AUC_{0-t} (ng.h/mL)	915.98 955.5 (29.5)	906.87 942.5 (30.6)	101.0%
AUC_{0-12} (ng.h/mL)	528.48 551.7 (29.0)	533.79 551.3 (26.4)	99.0%
AUC_{0-inf} (ng.h/mL)	953.37 995.3 (29.9)	934.49 975.0 (30.9)	102.0%
C_{max}	91.13 96.427 (33.7)	90.24 93.079 (25.0)	101.0%
T_{max}*	---- 7.067 (15.3)	---- 7.100 (16.3)	
$T_{½}$*	---- 6.399 (20.9)	---- 6.002 (16.7)	

* The T_{max} and $T_{½}$ parameters are expressed as the arithmetic means.
‡ Cardizem® SR (Nordic, Canada) was purchased in Canada.

Table 4: Comparative, randomized, **STEADY STATE**, 2-way crossover bioavailability study of Genpharm and Nordic (CARDIZEM® SR) 120 mg diltiazem HCl sustained-release capsules in healthy adult males:

Geometric Mean, Arithmetic Mean, (C.V.)			
Parameter	Test DILTIAZEM	Reference CARDIZEM® SR ‡	Ratio of Means (%)
AUC_{0-T} (ng.h/mL)	1442.31 1523.3 (34.7)	1373.34 1449.3 (32.9)	105.02%
C_{max} (ng/mL)	173.43 182.77 (32.9)	167.80 177.34 (33.2)	103.35%
C_{min} (ng/mL)	---- 82.86 (37.6)	---- 76.76 (39.8)	
T_{max} *	---- 6.643 (14.9)	---- 6.643 (17.5)	

* The C_{min} and T_{max} parameters are expressed as the arithmetic means.
‡ Cardizem® SR (Nordic, Canada) was purchased in Canada.

Table 5: Comparative, randomized, single-dose, 2-way crossover bioavailability study of Genpharm and Nordic (CARDIZEM® SR) 120 mg diltiazem HCl sustained-release capsules in healthy adult males under **FED** conditions:

Geometric Mean, Arithmetic Mean, (C.V.)			
Parameter	Test DILTIAZEM	Reference CARDIZEM SR‡	Ratio of Means (%)
AUC_{0-t} (ng.h/mL)	982.52 1024.3 (30.5)	963.40 994.1 (26.5)	102.0%
AUC_{0-12} (ng.h/mL)	569.08 601.8 (33.9)	551.97 570.0 (25.7)	103.1%
AUC_{0-inf} (ng.h/mL)	1008.55 1051.2 (30.5)	989.57 1020.8 (26.3)	101.9%
C_{max}	112.55 120.1 (36.8)	102.94 107.9 (31.5)	109.3%
T_{max}*	---- 8.111 (12.6)	---- 8.056 (13.1)	
$T_{½}$*	---- 5.320 (17.4)	---- 5.319 (16.6)	

* The T_{max} and $T_{½}$ parameters are expressed as the arithmetic means.
‡ Cardizem® SR (Nordic, Canada) was purchased in Canada.

A study which compared patients with normal hepatic function to liver cirrhosis patients noted an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single dose study in patients with severely impaired renal function showed no difference in the half-life of diltiazem as compared to patients with normal renal function (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

INDICATIONS AND CLINICAL USE

GEN-DILTIAZEM Tablets

Angina:

1. GEN-DILTIAZEM tablets (diltiazem HCl) may be used in the management of angina resulting from coronary artery spasm.

2. GEN-DILTIAZEM tablets are indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents.

3. GEN-DILTIAZEM tablets may be useful in unstable angina when spasm of the coronary vessels is definitely a contributing factor (e.g. ST segment elevation). In the absence of objective evidence of a spastic component, nitrates or nitrates plus a beta-blocker are at present the treatment of choice. If, in the view of a cardiologist, the addition of diltiazem to this regimen is considered necessary and safe, then the use of GEN-DILTIAZEM tablets might be considered. Generally, the patient should be hospitalized and treatment initiated under the supervision of a cardiologist.

GEN-DILTIAZEM tablets may be tried in combination with beta-blockers

in chronic stable angina in patients with normal ventricular function. When such concomitant therapy is introduced, patients must be monitored closely (see **WARNINGS**).

GEN-DILTIAZEM SR Capsules

Angina:

1. GEN-DILTIAZEM SR capsules (diltiazem HCl) are indicated for maintenance therapy in the management of chronic stable angina. **Treatment should be initiated and individual titration of dosage carried out using the regular tablets.** The sustained release formulation may be substituted as maintenance, provided the dosage requirement is suitable (see also **ACTION AND CLINICAL PHARMACOLOGY**). When patients who have been stabilized on tablets are switched to SR capsules for maintenance, close medical supervision is recommended since in some patients the dosage of the SR formulation may require adjustment.

2. Since the safety and efficacy of SR capsules in the management of unstable or vasospastic angina has not been substantiated, use of this formulation for these indications is not recommended.

Hypertension:

GEN-DILTIAZEM SR capsules are indicated in the treatment of mild to

moderate essential hypertension. GEN-DILTIAZEM SR capsules should be normally used in those patients in whom treatment with diuretics or beta-blockers has been associated with unacceptable adverse effects.

GEN-DILTIAZEM SR capsules can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated, or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

Combination of GEN-DILTIAZEM SR capsules with a diuretic has been found to be compatible and showed additive antihypertensive effect. In a single clinical study, the concomitant use of diltiazem with captopril was also found to be compatible.

Safety of concurrent use of GEN-DILTIAZEM SR capsules with other antihypertensive agents has not been established.

CONTRAINDICATIONS

Diltiazem hydrochloride is contraindicated:

1. In patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker;
2. In patients with second or third degree AV block;

3. In patients with known hypersensitivity to diltiazem;

4. In patients with severe hypotension (less than 90 mm Hg systolic);

5. In myocardial infarction patients, who have left ventricular failure manifested by pulmonary congestion;

6. In pregnancy and in women of child-bearing potential. Fetal malformations and adverse effects on pregnancy have been reported in animals. In repeated dose studies a high incidence of vertebral column malformations were present in the offspring of mice receiving more than 50 mg/kg of diltiazem HCl orally.

In the offspring of mice receiving a single oral dose of 50 or 100 mg/kg on day 12 of gestation, the incidence of cleft palate and malformed extremities was significantly higher. Vertebral malformations were most prevalent when they received the drug on day 9. In rats, a significantly higher fetal death rate was present when 200 and 400 mg/kg were given orally on days 9 to 14 of gestation. Single oral dose studies in rats resulted in a significant incidence of skeletal malformations in the offspring of the group receiving 400 mg/kg on day 11. In rabbits, all pregnant dams receiving 70 mg/kg orally from day 6 to 18 of gestation aborted; at 35 mg/kg, a significant increase in skeletal malformations was recorded in the offspring (see **REPRODUCTION STUDIES**).

WARNINGS

Cardiac Conduction

Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (6 of 1208 patients or 0.5%).

Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction.

Congestive Heart Failure

Because diltiazem has a negative inotropic effect *in vitro* and it affects cardiac conduction, the drug should only be used with caution and under careful medical supervision in patients with congestive cardiac failure (see also **CONTRAINDICATIONS**).

Use with Beta-Blockers

The combination of diltiazem and beta-blockers warrants caution since in some patients additive effects on heart rate, AV conduction, blood pressure or left ventricular functions have been observed. Close medical supervision is recommended.

Generally, diltiazem should not be given to patients with impaired left ventricular function while they receive beta-blockers. However, in exceptional cases when, in the opinion of the physician, concomitant use is considered essential, such use should be instituted gradually in a hospital setting.

Diltiazem gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by gradual reduction of the dose of beta-blocker.

Hypotension

Since diltiazem lowers peripheral vascular resistance, decreases in blood pressure may occasionally result in symptomatic hypotension. In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of diltiazem should be taken into consideration.

Patients with Myocardial Infarction

Use of immediate-release diltiazem at 240 mg per day started 3 to 15 days after a myocardial infarction was associated with an increase in cardiac events in patients with pulmonary congestion, and no overall effect on mortality.

Although there has not been a study of extended-release diltiazem in

acute myocardial infarction reported, the use of extended-release diltiazem may have effects similar to those of immediate-release diltiazem in acute myocardial infarction.

Acute Hepatic Injury

In rare instances, significant elevations in alkaline phosphatase, CPK, LDH, SGOT, SGPT and symptoms consistent with acute hepatic injury have been observed. These reactions have been reversible upon discontinuation of drug therapy. Although a causal relationship to diltiazem has not been established in all cases, a drug-induced hypersensitivity reaction is suspected (see **ADVERSE REACTIONS**). As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals.

PRECAUTIONS

Impaired Hepatic or Renal Function

Because diltiazem is extensively metabolized by the liver and excreted by the kidney and in bile, monitoring of laboratory parameters and cautious dosage titration are recommended in patients with impaired hepatic or renal function (see **ADVERSE REACTIONS**).

Use in Children

The safety of diltiazem in children has not yet been established.

Nursing Mothers

Diltiazem has been reported to be excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. Since diltiazem safety in newborns has not been established, it should not be given to nursing mothers.

Use in the Elderly

Administration of diltiazem to elderly patients (over or equal to 65 years of age) requires caution. The incidence of adverse reactions is approximately 13% higher in this group. Those adverse reactions which occur more frequently include: peripheral edema, bradycardia, palpitation, dizziness, rash and polyuria. Therefore, particular care in titration is advisable (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions

As with all drugs, care should be exercised when treating patients with multiple medications. Calcium channel blockers undergo biotransformation by the cytochrome P450 system. Coadministration of diltiazem with other drugs which follow the same route of

biotransformation may result in altered bioavailability. Dosages of similarly metabolised drugs, particularly those of low therapeutic ratio, especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, warfarin.

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.

Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, terfenadine, theophylline.

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 channel blockers should be titrated carefully.

Benzodiazepines: Diltiazem significantly increases peak plasma levels and elimination half-life of triazolam and midazolam.

Beta-Blockers: The concomitant administration of diltiazem with beta-adrenergic blocking drugs warrants caution and careful monitoring. Such an association may have an additive effect on heart rate, on AV conduction or on blood pressure (see **WARNINGS**). Appropriate dosage adjustments may be necessary. A study in 5 normal subjects showed that diltiazem increased propranolol bioavailability by approximately 50%.

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

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/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: Diltiazem and digitalis glycosides may have an additive effect in prolonging AV conduction. In clinical trials concurrent administration of diltiazem and digoxin have resulted in increase in serum digoxin levels with prolongation of AV conduction. This increase may result from a decrease in renal clearance of digoxin. Patients on concomitant therapy, especially those with renal impairment, should be carefully monitored. The dose of digoxin may need downward adjustment.

Rifampin: Administration of diltiazem with rifampin markedly reduced plasma diltiazem concentrations and the therapeutic effect of diltiazem.

Short and Long-Acting Nitrates: Diltiazem may be safely coadministered with nitrates, but there have been few controlled studies to evaluate the anti-anginal effectiveness of this combination.

Other Calcium Antagonists: Limited clinical experience suggests that in certain severe conditions not responding adequately to verapamil or to nifedipine, using diltiazem in conjunction with either of these drugs may be beneficial.

ADVERSE REACTIONS

(see also **Overall Diltiazem Safety Profile**)

DILTIAZEM Tablets

A safety evaluation was carried out in controlled clinical trials with 1208 North American angina patients, some of whom were severely ill and were receiving multiple concomitant therapy. Adverse effects were reported in 19.6% of patients and required discontinuation of treatment in 7.2%.

The most common occurrences and their frequency are: nausea (2.7%),

swelling/edema (2.4%), arrhythmia (2.0%) (AV block, bradycardia, tachycardia and sinus arrest), headache (2.0%), rash (1.8%) and asthenia (1.1%).

In addition, the following events were reported in less than 1% of cases:

Cardiovascular:

Angina, bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope. A patient with Prinzmetal's angina, experiencing episodes of vasospastic angina, developed periods of transient asymptomatic asystole approximately 5 hours after receiving a single 60 mg dose of diltiazem.

Nervous System:

Amnesia, confusion, depression, dizziness, drowsiness, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, tremor, weakness.

Gastrointestinal:

Anorexia, constipation, diarrhea, dyspepsia, vomiting.

Dermatologic:

Petechiae, pruritus, urticaria.

Other:

Amblyopia, decreased sexual performance, dysgeusia, dyspnea, epistaxis, eye irritation, hyperglycemia, nocturia, osteo-articular pain, paresthesia, photo-sensitivity, polyuria, thirst, tinnitus, weight increase.

Rarely, reports of extremely elevated liver enzymes, cholestasis, hyperbilirubinemia, jaundice, epigastric pain, anorexia, nausea, vomiting, stool discoloration, dark urine and weight loss have been reported. The symptoms and laboratory test abnormalities have been reversible on drug discontinuation (see **WARNINGS**).

Two incidents of marked hyperglycemia, hyperkalemia, bradycardia, asthenia, hypotension and gastrointestinal disturbances have been reported in diabetic patients receiving diltiazem, glyburide and a beta-blocker along with several other medications. Drugs were discontinued and supportive measures were administered which resulted in the patients fully recovering within a few days.

Laboratory Tests:

In rare instances, mild to moderate transient elevations of alkaline

phosphatase, SGOT, SGPT, LDH and CPK, have been noted during diltiazem therapy.

DILTIAZEM SR Capsules (Twice-A-day)

A safety evaluation was carried out in controlled and open label studies in 611 hypertensive patients treated with diltiazem SR either alone or in combination with other antihypertensive agents. Adverse effects were reported in 34.2% of patients and required discontinuation of therapy in 7.2%.

The most common adverse effects were: peripheral edema (8.3%), headache (4.9%), dizziness (4.7%), asthenia (3.9%), vasodilation (flushing) (2.3%) and bradycardia (2.1%).

The following percentage of adverse effects, divided by system, were reported:

Cardiovascular:

Edema Peripheral	8.3%
Vasodilation (flushing)	2.3%
Bradycardia	2.1%
AV Block (first degree)	1.6%
Palpitations	1.3%
Arrhythmia	1.0%
Heart Failure Right	0.5%

Central Nervous System:

Headache	4.9%

Dizziness	4.7%
Asthenia	3.9%
Somnolence	1.0%
Nervousness (anxiety)	0.8%
Paresthesia	0.7%
Insomnia	0.5%
Depression	0.5%
Dream Abnormality	0.5%
Tinnitus	0.5%
Gastrointestinal:	
Dyspepsia	1.1%
Nausea	1.1%
Constipation	0.7%
Dermatologic:	
Rash	1.6%
Laboratory Tests:	
Increased Alkaline Phosphatase	0.7%
Other:	
Impotence	1.6%
Musculoskeletal Pain	1.5%
Nocturia	1.1%
Polyuria	1.0%
Rhinitis	0.5%

The following additional adverse effects have occurred with an incidence of less than 0.5% in clinical trials: syncope, AV block, postural hypotension, chest pain, dyspnea, tremor, gait abnormality, vertigo, taste alteration, anorexia, increased appetite, dry mouth, vomiting, diarrhea, increased saliva, acute hepatic injury, pruritus, urticaria, conjunctivitis, amblyopia, ejaculation abnormality, malaise, fever.

The following abnormal laboratory findings have been rarely reported: increased SGOT/SGPT, bilirubinemia, hyperproteinemia, hypercholesteremia, hyperlipidemia, hyperglycemia, hypokalemia, urine abnormality (see **PRECAUTIONS**).

Overall Diltiazem Safety Profile

In clinical trials diltiazem tablets, diltiazem SR capsules and diltiazem controlled delivery capsules involving over 3300 patients, the most common adverse reactions were headache (4.6%), edema (4.6%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.5%), nausea (1.4%), and dyspepsia (1.0%).

In addition, the following events were reported with a frequency of less than 1.0%:

Cardiovascular:

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

Nervous System:

Amnesia, depression, gait abnormality, nervousness, somnolence, hallucinations, paresthesia, personality change, tinnitus, tremor, abnormal

dreams, insomnia.

Gastrointestinal:

Anorexia, diarrhea, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see **WARNINGS**), vomiting, weight increase, thirst, constipation.

Dermatological:

Petechiae, pruritus, photosensitivity, urticaria.

Other:

Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturia, osteoarticular pain, impotence, dry mouth, polyuria, hyperuricemia.

The following postmarketing events have been reported infrequently in patients receiving Diltiazem: allergic reactions, alopecia, asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, detached retina, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. In addition, events such as

myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well documented cases of generalized rash, some characterized as leukocyctoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem therapy is yet to be established.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been reports of diltiazem overdose in amounts ranging from <1 g to 18 g. In cases with a fatal outcome, the majority involved multiple drug ingestion.

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

The effectiveness of intravenous calcium channel 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 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.

In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. Limited data suggests that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination. The following measures may be considered:

Bradycardia:

Administer atropine. If there in 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:

Vasopressor (e.g., dopamine or norepinephrine).

Actual treatment and dosage should depend on the severity of the clinical situation.

DOSAGE AND ADMINISTRATION

GEN-DILTIAZEM Tablets

Angina:

Chronic Stable Angina or Vasospastic Angina

Dosage must be adjusted to each patient's needs. Starting with 30 mg 4 times daily, before meals and at bedtime, dosage may be increased gradually to 240 mg a day (given in 3 to 4 equally divided doses) at 1 to 2 day intervals, until optimum response is obtained. Limited clinical experience in rare resistant cases suggests that dosage of up to 360 mg a day in 3 to 4 equally divided doses may be tried under careful supervision.

In patients with vasospastic angina, the last dose of the day may be given at bedtime to help minimize angina pain which in such patients frequently occurs in early morning.

Unstable Angina Pectoris

Dosage of GEN-DILTIAZEM (diltiazem HCl) tablets should be carefully titrated in the Intensive Care Unit, up to 360 mg/day given in 3 to 4 equally divided doses. The titration should be done as rapidly as possible with consideration of concomitant therapy (see **DRUG INTERACTIONS**).

Use in the Elderly:

Pharmacokinetics of diltiazem in elderly patients has not been fully elucidated. Preliminary results in elderly patients (over 65 years old) suggest that a lower dosage might be required in this age group (see **PRECAUTIONS**).

There are few available data concerning dosage requirements in patients with impaired renal or hepatic function. If diltiazem must be used in these patients, the dosage should be carefully and gradually adjusted depending on patient tolerance and response (see **PRECAUTIONS**).

GEN-DILTIAZEM SR Capsules (Twice-A-day)

Angina:

GEN-DILTIAZEM SR (diltiazem HCl) is intended for maintenance therapy in chronic stable angina patients requiring doses within the range of 120 to 360 mg/day. **Initiation of treatment and individual titration of dosage should be carried out using conventional diltiazem tablets.** GEN-DILTIAZEM SR may be preferred for maintenance because of the convenience of twice daily dosage. Patients stabilized on a maintenance regimen between 120 and 360 mg of regular tablets may be changed to the same daily dosage of GEN-DILTIAZEM SR capsules divided into two equal doses and taken every 12 hours. **When patients are switched to SR capsules, close medical supervision is recommended since in some**

patients the dosage of the SR formulation may require adjustment.

Hypertension:

Dosage should be individualized depending on patient's tolerance and responsiveness to GEN-DILTIAZEM SR capsules and to concurrent antihypertensive medications (see **INDICATIONS and PRECAUTIONS**).

The adult dose range is 120 to 360 mg per day administered in two equally divided doses. Although individual patients may respond to any dosage level, the average optimum dosage range in clinical trials is between 240 and 360 mg/day. Maximum antihypertensive effect is usually observed by the second to fourth week of chronic therapy, therefore, dosage adjustments should be scheduled accordingly.

A maximum daily dose of 360 mg should not be exceeded.

There is evidence that the effective dose in the elderly (over 65 years of age) is somewhat lower than in younger patients (average dose: 255 mg *vs* 288 mg respectively), therefore, GEN-DILTIAZEM SR should be administered cautiously to elderly patients and the dosage should be carefully and gradually adjusted depending on patient tolerance and response (see **PRECAUTIONS**).

GEN-DILTIAZEM SR has an additive antihypertensive effect when used concomitantly with other antihypertensive agents. Therefore, it may be necessary to decrease the dose of GEN-DILTIAZEM SR and/or the dose of the concomitant antihypertensive drug when adding one to the other (see **INDICATIONS AND WARNINGS**).

GEN-DILTIAZEM SR should not be used in severe hepatic or renal dysfunction.

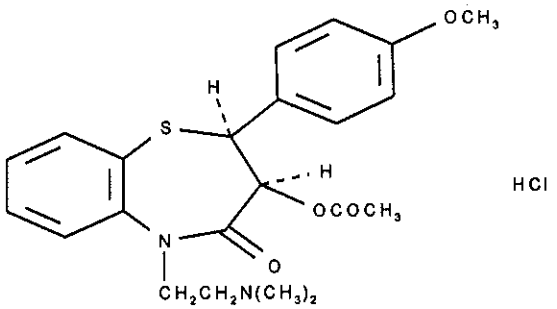
PHARMACEUTICAL INFORMATION

Drug Substance

Proper 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-.

Structural Formula:



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

Molecular Weight: 450.98

Description:

Diltiazem hydrochloride is a white to off-white crystalline substance or powder having a bitter taste or odour. It has a melting point of 207.5 to 212°C. It is considered freely soluble in water, methanol or chloroform, slightly soluble in absolute ethanol and barely soluble in benzene.

Composition:

GEN-DILTIAZEM (diltiazem HCl) 30 and 60 mg Tablets

These tablets are formulated as modified-release preparations. These dosage forms contain lactose, povidone, methylcellulose, D&C Yellow No. 10 quinoline lake , FD&C Blue No. 1 brilliant lake or Yellow sunset

lake, ethylcellulose, ethanol, water, polyethylene glycol, cottonseed oil, magnesium stearate, and talc.

GEN-DILTIAZEM SR 60, 90 and 120 mg Capsules (Twice-A-day)

These capsules are formulated as sustained or extended-release preparations. These dosage forms contain sucrose, starch, povidone, methacrylic acid copolymer, ethylcellulose, diethyl phthalate, talc, isopropyl alcohol, acetone, alcohol, and gelatin.

Stability and Storage Recommendations

Store between 15 and 30° C. Protect from light.

AVAILABILITY OF DOSAGE FORM

GEN-DILTIAZEM Tablets (diltiazem HCl tablets)

30 mg Tablets:

Green, round, biconvex tablets, with "DT 30" on one side and "G" on the other side, and approximately 9 mm in diameter and available in bottles of 100 & 500 tablets.

60 mg Tablets:

Yellow, round, biconvex tablets, with "DT" breakline "60" on one side and "G" on the other side, and approximately 10 mm in diameter and

available in bottles of 100 & 500 tablets.

GEN-DILTIAZEM SR Capsules (diltiazem HCl extended release capsules)

60 mg Capsules:

Ivory/brown, extended release capsules, imprinted with "G" on one end and "DSR60" on the opposite end, and available in bottles of 100 capsules and in blister packs of 100 capsules.

90 mg Capsules:

Gold/brown, extended release capsules, imprinted with "G" on one end and "DSR90" on the opposite end, and available in bottles of 100 & 300 capsules and in blister packs of 100 capsules.

120 mg Capsules:

Caramel/brown, extended release capsules, imprinted with "G" on one end and "DSR120" on the opposite end, and available in bottles of 100 & 300 capsules and in blister packs of 100 capsules.

PHARMACOLOGY

In Vitro Observations

Initial experimental work revealed that diltiazem was a coronary and peripheral vasodilator. Subsequent work substantiated that diltiazem's smooth muscle relaxant effect, as well as negative inotropic effect, resulted from the drug's ability to block excitation-contraction coupling by inhibiting slow calcium channel conductance. In a muscle bath study with isolated human coronary artery segments obtained at the time of cardiac transplantation, diltiazem produced nearly complete relaxation of potassium-contracted segments.

Studies in various experimental models have confirmed the negative inotropic effect of diltiazem. At low doses (1.1×10^{-7} M) diltiazem caused a reduction in contractile force of guinea pig papillary muscle with no demonstrable effect on the action potential. However, at higher concentrations (1.1×10^{-5} M) both a decrease in contractile tension and a lowering of maximum dp/dt were seen.

Studies done in isolated perfused rat hearts showed that diltiazem (10^{-6} M) decreases contractility without affecting action potential duration or resting membrane potential. In several experimental models it has been shown that the concentration of diltiazem required to produce smooth

muscle relaxation and vasodilation is significantly less than the concentration required to produce a negative inotropic effect.

***In Vivo* Observations**

Experiments in both open and closed chest dog models showed that diltiazem increases coronary blood flow and reduces coronary vascular resistance. Intravenous diltiazem (100 μg/kg) increased coronary blood flow by 90%, with a predominant effect on large coronary arteries and collaterals. Increase in coronary blood flow was observed following diltiazem administration in both the epicardial and subendocardial regions in ischemic and non-ischemic models. There was also a dose-related decrease in mean aortic pressure and systemic vascular resistance with an increase in stroke volume and cardiac output. No significant change was noted in determinants of LV function such as LVEDP or LV dP/dT. The reduction in blood pressure that is seen with diltiazem is due to a direct vasodilator effect on the blood vessels and is not mediated by sympathetic alpha receptor blockade, beta receptor stimulation, or ganglionic blockade. Diltiazem was shown to inhibit the pressor responses induced by norepinephrine and angiotensin II.

In animal studies, the negative inotropic effect of diltiazem appears to be offset by its ability to decrease afterload and induce a mild reflex

adrenergic response.

TOXICOLOGY

Acute Toxicity

The acute toxicity of diltiazem in mice and rats are summarized below:

Animal	Sex	Route	LD_{50} (mg/kg)	LD_{50} 95% Confidence Limits (mg/kg)
Mice	M & F	Oral	415-700	(343-736)
Rats	M & F	Oral	560-810	(505-1004)
Mice	M & F	S.C.	260-550	(220-672)
Mice	M & F	I.P.	187	(165-211)
Rats	M & F	I.P.	211	(155-287)
Mice	M & F	I.V.	58-61	(52-69)
Rats	M & F	I.V.	38-39	(34-44)

Toxic effects appeared rapidly and included reduction of spontaneous activity, ptosis, piloerection, ataxia, loss of muscle tone and loss of righting reflex. Gross autopsy of animals who died as well as the survivors revealed no abnormalities.

Tolerance was evaluated in rabbits and dogs. Dogs received oral doses of 12.5, 25, 50 or 100 mg/kg. Ataxia, disorientation, decreased activity diuresis and mydriasis were observed at 25 mg/kg. In addition, heavy

sedation and emesis were seen at 50 mg/kg. At 100 mg/kg, convulsions occurred and one of the two animals died. Rabbits received 100, 200, 300 or 400 mg/kg. The major symptoms were decreased activity, increased respiration, salivation and opisthotonos. One of the two rabbits died at 300 mg/kg and the two rabbits at 400 mg/kg group died.

Subacute Toxicity

In rats, oral doses of 10, 20, 50, 100, 250 or 500 mg/kg/day of diltiazem were administered for 28 or 30 days. The relative liver weights of animals receiving 250 and 500 mg/kg/day were increased. Microscopic examination revealed drug-related degeneration of hepatic and renal cells in the highest dose group.

When the drug was given to rats intraperitoneal at 25 mg/kg/day for 30 days, hepatic and renal cell degeneration was seen. Macular hyaloid degeneration of the heart also was seen in 50% of the rats in this study.

Thirty day subacute studies in dogs revealed hepatic and renal cell degeneration when diltiazem was given at doses of 25 mg/kg/day orally and 5 mg/kg/day intravenously. Two dogs out of 5 receiving 50 mg/kg/day orally, died.

Chronic Toxicity/Carcinogenicity

In mice, diltiazem was administered at doses of 5, 15 or 30 mg/kg/day for a period of 21 months in females. Because of a lower survival, males were terminated at 20 months. Gross and histopathological examination failed to reveal any treatment-related increase in the incidence of either neoplastic or other toxic lesions.

Rats received 6.25, 25 or 100 mg/kg/day of diltiazem for 24 months. An additional group received 200 mg/kg for 12 months. Treatment was terminated at 23 months in females receiving 100 mg/kg because of the low survival. Females had increased weight gain at 100 and 200 mg/kg, food consumption was increased among both sexes at these dose levels. Organ weight data revealed a significant increase in liver weight for rats of both sexes given 200 mg/kg. Microscopic evaluation revealed some evidence of dose dependent hepatic cytoplasmic vacuolization in the rats treated with doses of 100 and 200 mg/kg/day and killed at 12 months. At 24 months, there were similar findings in control and treated animals. There was no increase in the incidence of neoplastic or other toxic lesions in rats treated with diltiazem.

Diltiazem was administered orally to dogs for 12 months at doses of 5, 10 or 20 mg/kg/day. A dose related suppression of body weight gain

became noticeable after 6 months.

Mutagenicity

No mutagenic changes were observed in the recombination test and two Ames mutagenicity assays.

Reproductive Studies

Results in Mice

Route	Doses (mg/kg)	Time of Administration During Gestation	Results and Findings in the Offspring
Oral	10, 25, 50, 100, 200, 400.	Days 7 to 12.	High incidence of vertebral column malformations when more than 50 mg/kg was administered.
Oral	Single doses of 12.5, 25, 50, 100, 200.	One of days 7 to 14.	Cleft palate and malformations of extremities or trunk were significantly higher at 50 or 100 mg/kg administered on day 12. Vertebral malformations were most prevalent when 50 or 100 mg/kg was given on day 9.
Intra-peritoneal	0.2, 3.1, 6.3, 12.5, 25.	Days 7 to 12.	Fetal mortality greatly increased when 12.5 mg/kg or more was administered. No teratogenic effect was demonstrated.
Intra-peritoneal	Single dose of 3.1, 6.3, 12.5, 25, 50.	One of days 5 to 16.	Brachydactyly and hematoma in the extremities when 50 mg/kg was administered on day 13. Vertebral column malformations from the thoracic to coccygeal level and malformations of the ribs were observed when a dose of 25 mg/kg or greater was administered on day 9.

Results in Rats

Route	Doses (mg/kg)	Time of Administration During Gestation	Results and Findings in the Offspring
Oral	10, 50, 100, 200, 400.	Days 9 to 14.	No teratogenic effect. High fetal death rate at 200 and 400 mg/kg was administered.
Oral	10, 30, 100.	Days 6 to 15.	No teratogenic effect.
Oral	Single doses of 300, 400, 600.	One of days 9 to 14.	Significant incidence of skeletal malformations involving vertebrae and sternebrae when 400 mg/kg was administered on day 11. General edema, short or absent tail was observed when 600 mg/kg was administered on day 12.
Intra-peritoneal	0.2, 2, 20, 40, 80.	Days 9 to 14.	Brachydactyly and hematoma in the front paw and tail and a high fetal mortality rate were observed when 80 mg/kg was administered.
Intra-peritoneal	80.	Days 9 to 11.	Vertebral anomalies
Intra-peritoneal	80.	Days 12 to 14.	Brachydactyly, hematoma of the front paw and tail deformities and high fetal mortality rate.
Intra-peritoneal	Single dose of 80.	One of days 9 to 14.	Fetal mortality increased on day 11, reached 100% on day 12 and decreased thereafter. Limb and tail deformities were induced when 80 mg/kg was administered on day 13 and 14. Vertebral column deformities were induced when 80 mg/kg was administered on day 11.
	Single dose of 40.	One of days 11 to 14.	No teratogenic effect.

Results in Rabbits

Route	Doses (mg/kg)	Time of Administration During Gestation	Results and Findings in the Offspring
Oral	17.5, 35, 70.	Days 6 to 18.	Significant increase in skeletal malformations occurred when 35 mg/kg was administered. All pregnant dams aborted between days 21 and 25 of gestation when 70 mg/kg was administered.
Intra-peritoneal	6.3, 12.5, 25.	Days 7 to 16.	Fetal mortality greatly increased at 12.5, reached 100% at 25 mg/kg. Skeletal defects & external malformations were induced when 12.5 mg/kg was administered. Their incidence was not statistically significant due to the low number of surviving fetuses.

In fertility studies female rats received doses of 12.5, 25, 50 and 100 mg/kg p.o.. In the 100 mg/kg group there was a reduction in the number showing a positive mating. However, the overall pregnancy rates and the average pre-coital time were comparable.

In peri- and post-natal studies, rats recieved diltiazem in doses of 10, 30 or 100 mg/kg/day from day 14 of gestation through day 21 post-partum. Diltiazem was associated with a reduction in early individual weights and survival rates of the pups. At 100 mg/kg/day dystocia was evident. Retinal and tongue malformations were more frequent in the offspring of the 30 and 100 mg/kg/day group.

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