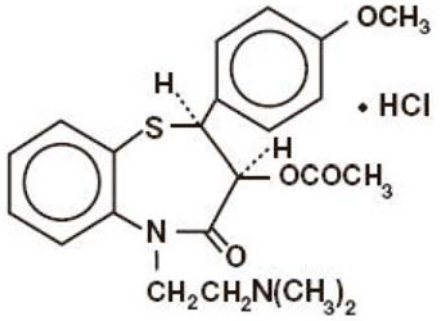
Tiazac®
(diltiazem hydrochloride)
Extended-Release Capsules

USP Drug Release Test 6
LB0001-13 Rev. 04/10
Rx Only

DESCRIPTION

Tiazac® (diltiazem hydrochloride) is a calcium ion cellular influx inhibitor (slow channel blocker). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5*H*)-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 and has a molecular weight of 450.98. Tiazac capsules contain diltiazem hydrochloride in extended-release beads at doses of 120, 180, 240, 300, 360 and 420 mg.

Tiazac also contains: black iron oxide, D&C Red No. 28, ethyl acrylate and methyl methacrylate copolymer dispersion, FD&C Blue No. 1, FD&C Green No. 3, FD&C Red No. 40, gelatin, hypromellose, magnesium stearate, microcrystalline cellulose, polysorbate, povidone, simethicone, sucrose stearate, talc, and titanium Dioxide.

For oral administration.

CLINICAL PHARMACOLOGY

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

Mechanisms of Action

Hypertension: Diltiazem produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension: thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Angina: Diltiazem HCl has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal work loads.

Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasms are inhibited by diltiazem.

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

Hemodynamic and Electrophysiologic Effects

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

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

Tiazac produces antihypertensive effects both in the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects.

Diltiazem hydrochloride decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually reduced. Chronic therapy with diltiazem hydrochloride produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem hydrochloride reduces the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio. In man, transient natriuresis and kaliuresis have been reported, but only in high intravenous doses of 0.5 mg/kg of body weight.

Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases). Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%.

In two short term, double-blind, placebo-controlled studies in 256 hypertensive patients with doses up to 540 mg/day, Tiazac showed a clinically unimportant but statistically significant, dose-related increase in PR interval (0.008 seconds). There were no instances of greater than first-degree AV block in any of the clinical trials (see **WARNINGS**).

Pharmacodynamics

Hypertension: In short term, double blind, placebo-controlled clinical trials, Tiazac demonstrated a dose-related antihypertensive response among patients with mild to moderate hypertension. In one parallel-group study of 198 patients Tiazac was given for four weeks. The changes in diastolic blood pressure measured at trough (24 hours after the dose) for placebo, 90 mg, 180 mg, 360 mg and 540 mg were -5.4, -6.3, -6.2, -8.2, and -11.8 mm Hg, respectively. Supine diastolic blood pressure as well as standing diastolic and systolic blood pressures also showed statistically significant linear dose response effects.

In another clinical trial that followed a dose-escalation design, Tiazac also reduced blood pressure in a linear dose-related manner. Supine diastolic blood pressure measured following two-week intervals of treatment was reduced by -3.7 mm Hg with 120 mg/day versus -2.0 mm Hg with placebo, by -7.6 mm Hg after escalation to 240 mg/day versus -2.3 mm Hg with placebo, by -8.1 mm Hg after escalation to 360 mg/day versus -0.9 mm Hg with placebo, and by -10.8 mm Hg after escalation to 480/540 mg/day versus -2.2 mm Hg with placebo.

Angina: In a double-blind parallel group placebo-controlled trial (approximately 50 patients/group, in patients with chronic stable angina), Tiazac at doses of 120 to 540 mg/day increased exercise tolerance time. At trough, 24 hours after dosing, exercise tolerance times using a Bruce exercise protocol, increased by 14, 26, 41, 33 and 32 seconds over baseline for placebo and the 120 mg, 240 mg, 360 mg, and 540 mg treated patient groups, respectively. At peak, 8 hours after dosing, exercise tolerance times relative to baseline were statistically significantly increased by 13, 38, 64, 55 and 42 seconds for placebo and 120 mg, 240 mg, 360 mg, and 540 mg Tiazac treated patients, respectively. Compared to baseline, Tiazac treated patients experienced statistically significant reductions in anginal attacks and decreased nitroglycerin requirements when compared to placebo treated patients.

Pharmacokinetics and Metabolism

Diltiazem is well absorbed from the gastrointestinal tract but undergoes substantial hepatic first-pass effect. The absolute bioavailability of an oral dose of an immediate- release formulation (compared to intravenous administration) is approximately 40%. Only 2% to 4% of unchanged diltiazem appears in the urine. The plasma elimination half-life of diltiazem is approximately 3.0 to 4.5 h. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition. Therapeutic blood levels of diltiazem appear to be in the range of 40 to 200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose.

The two primary metabolites of diltiazem are desacetyldiltiazem and desmethyldiltiazem. The desacetyl metabolite is approximately 25% to 50% as potent a coronary vasodilator as diltiazem and is present in plasma at concentrations of 10% to 20% of parent diltiazem. However, recent studies employing sensitive and specific analytical methods have confirmed the existence of several sequential metabolic pathways of diltiazem. As many as nine diltiazem metabolites have been identified in the urine of humans. Total radioactivity measurements following single intravenous dose administration in healthy volunteers suggest the presence of other unidentified metabolites. These metabolites are more slowly excreted (with a half-life of total radioactivity of approximately 20 hours), and attain concentrations in excess of diltiazem.

In vitro binding studies show diltiazem HCl is 70% to 80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown diltiazem HCl binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. A study that compared patients with normal hepatic function to patients with cirrhosis who received immediate-release diltiazem found an increase in diltiazem elimination half-life and a 69% increase in bioavailability in the hepatically impaired patients. Patients with severely impaired renal function (creatinine clearance <50 mL/min) who received immediate-release diltiazem had modestly increased diltiazem concentrations compared to patients with normal renal function.

Tiazac Capsules. When compared to a regimen of immediate-release tablets at steady-state, approximately 93% of drug is absorbed from the Tiazac formulation. When Tiazac was coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected; T_{max}, however, occurred slightly earlier. The apparent elimination half-life after single or multiple dosing is 4 to 9.5 hours (mean 6.5 hours).

Tiazac demonstrates non-linear pharmacokinetics. As the daily dose of Tiazac capsules is increased from 120 to 540 mg, there was a more than proportional increase in diltiazem plasma concentrations as evidenced by an increase of AUC, C_{max} and C_{min} of 6.8, 6 and 8.6 times, respectively, for a 4.5 times increase in dose.

INDICATIONS AND USAGE

Hypertension:

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

Chronic Stable Angina:

Tiazac is indicated for the treatment of chronic stable angina.

CONTRAINDICATIONS

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

WARNINGS

1. Cardiac Conduction. Diltiazem hydrochloride prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral

diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem hydrochloride in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

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

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

PRECAUTIONS

General

Diltiazem hydrochloride is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

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

Drug Interactions

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem hydrochloride concomitantly with other agents known to affect cardiac contractility and/or conduction (see **WARNINGS**). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with Tiazac (see **WARNINGS**). As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of the 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 channel blockers should be titrated carefully.

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

Beta-blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem hydrochloride and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro*, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see **WARNINGS**).

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 $T_{½}$ 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 coadministration, and should be based on clinical assessment.

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 AUC (53%) after a 1-week course of cimetidine 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.

Clonidine. Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concurrently with diltiazem. Monitor heart rate in patients receiving concomitant diltiazem and clonidine.

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

Quinidine. Diltiazem significantly increases the $AUC_{(0\rightarrow\infty)}$ of quinidine by 51%, $T_{½}$ 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.

Statins. Diltiazem is an inhibitor of CYP3A4 and has been shown to increase significantly the AUC of some statins. The risk of myopathy and rhabdomyolysis with statins metabolized by CYP3A4 may be increased with concomitant use of diltiazem. When possible, use a non-CYP3A4-metabolized statin together with diltiazem; otherwise, dose adjustments for both diltiazem and the statin should be considered along with close monitoring for signs and symptoms of any statin related adverse events.

In a healthy volunteer cross-over study (N=10), co-administration of a single 20 mg dose of simvastatin at the end of a 14 day regimen with 120 mg BID diltiazem SR resulted in a 5-fold increase in mean simvastatin AUC versus simvastatin alone. Subjects with increased average steady-state exposures of diltiazem showed a greater fold increase in simvastatin exposure. Computer-based simulations showed that at a daily dose of 480 mg of diltiazem, an 8- to 9-fold mean increase in simvastatin AUC can be expected. If co-administration of simvastatin with diltiazem is required, limit the daily doses of simvastatin to 10 mg and diltiazem to 240 mg.

In a ten-subject randomized, open label, 4-way cross-over study, co-administration of diltiazem (120 mg BID diltiazem SR for 2 weeks) with a single 20 mg dose of lovastatin resulted in 3- to 4-fold increase in mean lovastatin AUC and C_{max} versus lovastatin alone. In the same study, there was no significant change in 20 mg single dose pravastatin AUC and C_{max} during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy

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

pregnant women; therefore, use diltiazem hydrochloride in pregnant women only if the potential benefit justifies the potential risk to the fetus.

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

Pediatric Use
Safety and effectiveness in children have not been established.

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

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies with Tiazac, as well as with other diltiazem formulations. It should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies. A total of 256 hypertensives were treated for between 4 and 8 weeks; a total of 207 patients with chronic stable angina were treated for 3 weeks with doses of Tiazac ranging from 120 to 540 mg once daily. Two patients experienced first-degree AV block at the 540 mg dose. The following table presents the most common adverse reactions, whether or not drug-related, reported in placebo-controlled trials in patients receiving Tiazac up to 360 mg and up to 540 mg with rates in placebo patients shown for comparison.

MOST COMMON ADVERSE EVENTS IN DOUBLE-BLIND PLACEBO-CONTROLLED HYPERTENSION TRIALS*

	Placebo	Tiazac	
Adverse Events (COSTART Term)	n=57 # pts (%)	Up to 360 mg n=149 # pts (%)	480 - 540mg n=48 # pts (%)
edema, peripheral	1 (2)	8 (5)	7 (15)
dizziness	4 (7)	6 (4)	2 (4)
vasodilation	1 (2)	5 (3)	1 (2)
dyspepsia	0 (0)	7 (5)	0 (0)
pharyngitis	2 (4)	3 (2)	3 (6)
rash	0 (0)	3 (2)	0 (0)
infection	2 (4)	2 (1)	3 (6)
diarrhea	0 (0)	2 (1)	1 (2)
palpitations	0 (0)	2 (1)	1 (2)
nervousness	0 (0)	3 (2)	0 (0)

MOST COMMON ADVERSE EVENTS IN DOUBLE-BLIND PLACEBO-CONTROLLED ANGINA TRIALS*

	Placebo	Tiazac	
Adverse Events (COSTART Term)	n=50 # pts (%)	Up to 360 mg n=158 # pts (%)	540 mg n=49 # pts (%)
headache	1 (2)	13 (8)	4 (8)
edema, peripheral	1 (2)	3 (2)	5 (10)
pain	1 (2)	10 (6)	3 (6)
dizziness	0 (0)	5 (3)	5 (10)
asthenia	0 (0)	1 (1)	2 (4)
dyspepsia	0 (0)	2 (1)	3 (6)
dyspnea	0 (0)	1 (1)	3 (6)
bronchitis	0 (0)	1 (1)	2 (4)
AV block	0 (0)	0 (0)	2 (4)
infection	0 (0)	2 (1)	1 (2)
flu syndrome	0 (0)	0 (0)	1 (2)
cough increase	0 (0)	2 (1)	1 (2)
extrasystoles	0 (0)	0 (0)	1 (2)
gout	0 (0)	2 (1)	1 (2)
myalgia	0 (0)	0 (0)	1 (2)
impotence	0 (0)	0 (0)	1 (2)
conjunctivitis	0 (0)	0 (0)	1 (2)
rash	0 (0)	2 (1)	1 (2)
abdominal enlargement	0 (0)	0 (0)	1 (2)

* Adverse events occurring in treated patients at 2% or more than placebo-treated patients.

In addition, the following events have been reported infrequently (less than 2%) in clinical trials with other diltiazem products:

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

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

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see **WARNINGS, Acute Hepatic Injury**), nausea, thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus.

Other: Albuminuria, allergic reaction, amblyopia, asthenia, CPK increase, crystalluria, dyspnea, edema, epistaxis, eye irritation, headache, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal

congestion, neck rigidity, nocturia, osteoarticular pain, pain, polyuria, rhinitis, sexual difficulties, gynecomastia.

In addition, the following postmarketing events have been reported infrequently in patients receiving diltiazem hydrochloride: acute generalized exanthematous pustulosis, alopecia, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, photosensitivity (including lichenoid keratosis and hyperpigmentation at sun-exposed skin areas), leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem hydrochloride therapy is yet to be established.

OVERDOSAGE

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

The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases. There have been 29 reports of diltiazem overdose in doses ranging from less than 1 gm to 10.8 gm. Sixteen of these reports involved multiple drug ingestions. Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 gm to 10.8 gm. There were seven reports with a fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports.

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

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences, the following measures may be considered:

Bradycardia: Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockage, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

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

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

In a few reported cases, overdose with calcium channel blockers has been associated with hypotension and bradycardia, initially refractory to atropine but becoming more responsive to this treatment when the patients received large doses (close to 1 gram/hour for more than 24 hours) of calcium chloride.

Due to extensive metabolism, plasma concentrations after a standard dose of diltiazem can vary over tenfold, which significantly limits their value in evaluation cases of overdosage.

Charcoal hemoperfusion has been used successfully as an adjunct therapy to hasten drug elimination. Overdoses with as much as 10.8 gm of oral diltiazem have been successfully treated using appropriate supportive care.

DOSAGE AND ADMINISTRATION

Hypertension. Dosage needs to be adjusted by titration to individual patient needs. When used as monotherapy, usual starting doses are 120 to 240 mg once daily. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. The usual dosage range studied in clinical trials was 120 to 540 mg once daily. Current clinical experience with 540 mg dose is limited; however, the dose may be increased to 540 mg once daily.

Angina. Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 mg to 180 mg once daily. Individual patients may respond to higher doses of up to 540 mg once daily. When necessary, titration should be carried out over 7 to 14 days.

Concomitant use with Other Cardiovascular Agents

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

Hypertensive or anginal patients who are treated with other formulations of diltiazem can safely be switched to Tiazac capsules at the nearest equivalent total daily dose. Subsequent titration to higher or lower doses may, however, be necessary and should be initiated as clinically indicated.

Sprinkling the Capsule Contents on Food

Tiazac (diltiazem hydrochloride) Extended-release Capsules may also be administered by carefully opening the capsule and sprinkling the capsule contents on a spoonful of applesauce. The applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the capsule contents. The applesauce should not be hot, and it should be soft enough to be swallowed without chewing. Any capsule contents/applesauce mixture should be used immediately and not stored for future use. Subdividing the contents of a Tiazac (diltiazem hydrochloride) Extended-release Capsule is not recommended.

HOW SUPPLIED
Tiazac® (diltiazem hydrochloride) Extended-Release Capsules

Strength	Description	Quantity	NDC#
120 mg	#3 lavender/lavender capsule imprinted: Tiazac 120	7's	0456-2612-07
		30's	0456-2612-30
		90's	0456-2612-90
		1000's	0456-2612-00
		HUD's	0456-2612-63
180 mg	#2 white/blue-green capsule imprinted: Tiazac 180	7's	0456-2613-07
		30's	0456-2613-30
		90's	0456-2613-90
		1000's	0456-2613-00
		HUD's	0456-2613-63
240 mg	#1 blue-green/lavender capsule imprinted: Tiazac 240	7's	0456-2614-07
		30's	0456-2614-30
		90's	0456-2614-90
		1000's	0456-2614-00
		HUD's	0456-2614-63
300 mg	#0 white/lavender capsule imprinted: Tiazac 300	7's	0456-2615-07
		30's	0456-2615-30
		90's	0456-2615-90
		1000's	0456-2615-00
		HUD's	0456-2615-63
360 mg	#0 blue-green/blue-green capsule imprinted: Tiazac 360	7's	0456-2616-07
		30's	0456-2616-30
		90's	0456-2616-90
		1000's	0456-2616-00
		HUD's	0456-2616-63
420 mg	#00 white/white capsule imprinted: Tiazac 420	7's	0456-2617-07
		30's	0456-2617-30
		90's	0456-2617-90
		1000's	0456-2617-00

Storage conditions: Store at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [see USP Controlled Room Temperature]. Avoid excessive humidity.

Manufactured by:
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Carolina, PR 00983

OR

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Manufactured for:

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St. Louis, Missouri 63045

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