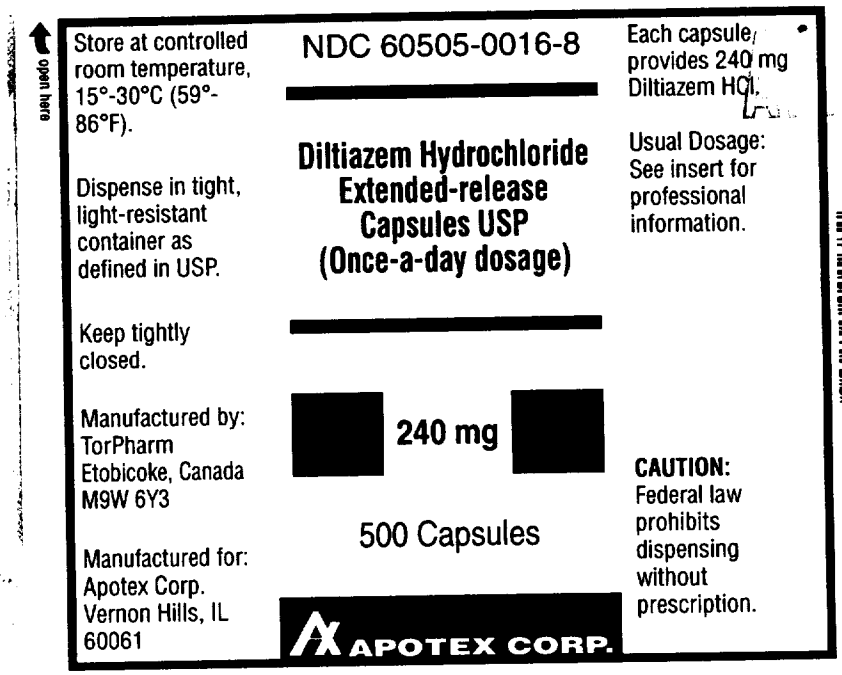
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74943

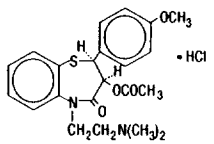
DRAFT FINAL PRINTED LABELING



DILTIAZEM HYDROCHLORIDE
EXTENDED-RELEASE CAPSULES USP
(Once-a-day dosage), 240 mg

DESCRIPTION

Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-. Its molecular formula is $C_{22}H_{26}N_2O_4S$•HCl and its molecular weight is 450.99. Its structural formula is as follows:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform.

Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) meets USP *Drug Release Test 2*.

Each Diltiazem Hydrochloride Extended-release Capsule USP (Once-a-day dosage), for oral administration contains four units of Diltiazem Hydrochloride Extended-release 60 mg tablets, resulting in a 240 mg dosage strength allowing for the controlled release of diltiazem HCl over a 24-hour period. In addition, each capsule contains the following inactive ingredients: Black SW-9008/SW9009, Colloidal Silicon Dioxide NF, D&C Red #28, D&C Yellow #10, FD&C Blue #1, FD&C Red #40, Gelatin NF, Hydroxypropyl Methylcellulose 2208 USP, Magnesium Stearate NF and Titanium Dioxide.

CLINICAL PHARMACOLOGY

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

Mechanisms of Action. Hypertension. Diltiazem HCl produces its antihypertensive effect primarily by relaxation of vascular smooth muscle with a 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 spasm are inhibited by diltiazem.

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

Hemodynamic and Electrophysiologic Effects. Like other calcium 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. In exercise tolerance studies in patients with ischemic heart disease, diltiazem reduces the double product (HR X SBP) 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. Increased heart failure has, however, been reported in occasional patients with pre-existing 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.

Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) produce antihypertensive effects both in the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. Diltiazem decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate. No reflex tachycardia is associated with the chronic antihypertensive effects.

During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually reduced. Heart rate at maximum exercise does not change or is slightly reduced.

Diltiazem antagonizes the renal and peripheral effects of angiotensin II. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Chronic therapy with diltiazem produces no change or an increase in plasma catecholamines. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in the 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 approximately 20%.

In two short-term, double-blind, placebo-controlled studies, 303 hypertensive patients were treated with once-daily Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) in doses of up to 540 mg. There were no instances of greater than first-degree atrioventricular block, and the maximum increase in the PR interval was .08 seconds. No patients were prematurely discontinued from the medication due to symptoms related to prolongation of the PR interval.

Pharmacodynamics. In one short-term, double-blind, placebo-controlled study, Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) 120, 240, 360 and 480 mg/day demonstrated a dose-related antihypertensive response among patients with mild to moderate hypertension. Statistically significant decreases in trough mean supine diastolic blood pressure were seen through four weeks of treatment: 120 mg/day (-5.1 mmHg); 240 mg/day (-6.9 mmHg); 360 mg/day (-6.9 mmHg); and, 480 mg/day (-10.6 mmHg). Statistically significant decreases in trough mean supine systolic blood pressure were also seen through four weeks of treatment: 120 mg/day (-2.6 mmHg); 240 mg/day (-6.5 mmHg); 360 mg/day (-4.8 mmHg); and, 480 mg/day (-10.6 mmHg). The proportion of evaluable patients exhibiting a therapeutic response (supine diastolic blood pressure <90 mmHg or decrease >10 mmHg) was greater as the dose increased: 31%, 42%, 48% and 69% with the 120, 240, 360 and 480 mg/day diltiazem groups, respectively. Similar findings were observed for standing systolic and diastolic blood pressures. The trough (24 hours after a dose) antihypertensive effect of Diltiazem Hydrochloride Extended-release Capsule USP (Once-a-day dosage) retained more than one-half of the response seen at peak (3-6 hours after administration).

Significant reductions of mean supine blood pressure (at trough) in patients with mild to moderate hypertension were also seen in a short-term, double-blind, dose-escalation, placebo-controlled study after 2 weeks of once-daily Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) 180 mg/day (diastolic: -6.1 mmHg; systolic: -4.7 mmHg) and again, 2 weeks after escalation to 360 mg/day (diastolic: -9.3 mmHg; systolic: -7.2 mmHg). However, a further increase in dose to 540 mg/day for 2 weeks provided only a minimal further increase in the antihypertensive effect (diastolic: -10.2 mmHg; systolic: -6.7 mmHg).

Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage), given at 120 mg, 240 mg, and 480 mg/day, in a randomized, multicenter, double-blind, placebo controlled, parallel group, dose-ranging study, in 189 patients with chronic angina, demonstrated a dose-related increase in exercise time by Exercise Tolerance Test (ETT) and a reduction in rates of anginal attacks (based on individual patient diaries). The improvement in total exercise time (using the Bruce protocol), measured at trough exercise periods, for placebo, 120 mg, 240 mg, and 480 mg, was 20, 37, 49, and 56 seconds, respectively.

Pharmacokinetics and Metabolism. Diltiazem is well-absorbed from the gastrointestinal tract, and is subject to an extensive first-pass effect. When given as an immediate release oral formulation, the absolute bioavailability (compared to intravenous administration) of diltiazem is approximately 40%. Diltiazem undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites which attain higher concentrations than those of diltiazem and are more slowly eliminated; half-life of total radioactivity is about 20 hours compared to 2 to 5 hours for diltiazem. *In-vitro* binding studies show 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. The plasma elimination half-life of diltiazem is approximately 3.0 to 4.5 hours. Desacetyldiltiazem, the major metabolite of diltiazem, which is also present in the plasma at concentrations of 10% to 20% of the parent drug, is approximately 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of diltiazem hydrochloride appear to be in the range of 40-200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose.

A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. Patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) contain a degradable controlled-release tablet formulation designed to release diltiazem over a 24-hour period. Controlled absorption of diltiazem begins within 1 hour, with maximum plasma concentrations being achieved 4 to 6 hours after administration. The apparent steady-state half-life of diltiazem following once-daily administration of Diltiazem HCl Extended-release Capsules ranges from 5 to 10 hours. This prolongation of half-life is attributed to continued absorption of diltiazem rather than to alterations in its elimination.

The absolute bioavailability of diltiazem from a single dose of diltiazem extended-release capsules (compared to intravenous administration) is 41% (±14). This value was shown to be similar to the 40% systemic availability reported following administration of an immediate release diltiazem HCl formulation.

As the dose of Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) is increased from a daily dose of 120 mg to 240 mg, there is an increase in the AUC of 2.3 fold. When the dose is increased from 240 mg to 360 mg, AUC increases 1.6 fold and when increased from 240 mg to 480 mg, AUC increases 2.4 fold.

It has been reported that *in-vivo* release of diltiazem occurs throughout the gastrointestinal tract, with controlled release still occurring for up to 24 hours after administration, as determined by radiolabeled methods. As the once-daily dose of Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) was increased, departures from linearity were noted. There were disproportionate increases in area under the curve for doses from 120 mg to 480 mg.

However, simultaneous presence of food did not affect the ability of diltiazem hydrochloride extended-release to maintain a controlled release of the drug and did not impact its sustained release properties over 24 hours after administration. Simultaneous administration of Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) with a high-fat breakfast resulted in increases in AUC of 13% and 19%, and in C_{max} by 37% and 51%, respectively.

INDICATIONS AND USAGE

Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) are indicated for the treatment of hypertension. Diltiazem hydrochloride may be used alone or in combination with other antihypertensive medications, such as diuretics.

Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) are indicated for the management of chronic stable angina.

CONTRAINDICATIONS

Diltiazem hydrochloride is contraindicated in: (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker; (2) patients with second or third degree AV block except in the presence of a functioning ventricular pacemaker; (3) patients with hypotension (less than 90 mmHg systolic); (4) patients who have demonstrated hypersensitivity to the drug; and (5) patients with acute myocardial infarction and pulmonary congestion as 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 (22 of 10,119 patients, or 0.2%); 41% of these 22 patients were receiving concomitant β-adrenoceptor antagonists versus 17% of the total group. 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 60 mg dose 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 of 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 serum 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 alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 6 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some others (see PRECAUTIONS).

PRECAUTIONS

General. Diltiazem hydrochloride is extensively metabolized by the liver and is excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters 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.

Although Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) utilizes a slowly disintegrating matrix, caution should still be used in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been no reports of obstructive symptoms in patients with known strictures in association with the ingestion of Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage).

Information for Patients. Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) should be taken on an empty stomach. Patients should be cautioned that the Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) should not be opened, chewed or crushed, and should be swallowed whole.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem hydrochloride concomitantly with any 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 diltiazem hydrochloride (see WARNINGS). As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem hydrochloride undergoes biotransformation by cytochrome P-450 mixed function oxidase. Co-administration of diltiazem hydrochloride with other agents which follow the same route of bio-transformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio such as cyclosporin, may require adjustment when starting or stopping concomitantly administered diltiazem hydrochloride to maintain optimum therapeutic blood levels. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated plasma levels of carbamazepine, resulting in toxicity in some cases.

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 the bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. 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 hydrochloride dose may be warranted.

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).

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and an 18-month study in mice 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 male or female rats at oral doses 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 q.d. or 8 mg/kg q.d. for a 60 kg patient) has resulted in embryo and fetal lethality. These studies have 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 diltiazem hydrochloride is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Serious adverse reactions to diltiazem hydrochloride have been rare in studies with other formulations, as well as with Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage). It should be recognized, however, that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

Hypertension: The most common adverse events (frequency ≥1%) in placebo-controlled, clinical hypertension studies with Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) using daily doses up to 540 mg, are listed in the table below with placebo-treated patients included for comparison.

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

Adverse Events (COSTART Term)	Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage)* n=303 # pts (%)	Placebo n=87 # pts (%)
rhinitis	29 (9.6)	7 (8.0)
headache	27 (8.9)	12 (13.8)
pharyngitis	17 (5.6)	4 (4.6)
constipation	11(3.6)	2 (2.3)
cough increase	9 (3.0)	2 (2.3)
flu syndrome	7 (2.3)	1 (1.1)
edema, peripheral	7 (2.3)	0 (0.0)
myalgia	7 (2.3)	0 (0.0)
diarrhea	6 (2.0)	0 (0.0)
vomiting	6 (2.0)	0 (0.0)
sinusitis	6 (2.0)	1 (1.1)
asthenia	5 (1.7)	0 (0.0)
pain, back	5 (1.7)	2 (2.3)
nausea	5 (1.7)	1 (1.1)
dyspepsia	4 (1.3)	0 (0.0)
vasodilatation	4 (1.3)	0 (0.0)
injury, accident	4 (1.3)	0 (0.0)
pain, abdominal	3 (1.0)	0 (0.0)
arthrosis	3 (1.0)	0 (0.0)
insomnia	3 (1.0)	0 (0.0)
dyspnea	3 (1.0)	0 (0.0)
rash	3 (1.0)	1 (1.1)
tinnitus	3 (1.0)	0 (0.0)

*Adverse events occurring in 1% or more of patients receiving Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage).

Angina: The most common adverse events (frequency ≥1%) in a placebo-controlled, short-term (2 week) clinical angina study with Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) are listed in the table below with placebo-treated patients included for comparison. In this trial, following a placebo phase, patients were randomly assigned to once-daily doses of either 120, 240 or 480 mg of Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage).

MOST COMMON ADVERSE EVENTS IN A DOUBLE-BLIND, PLACEBO-CONTROLLED SHORT-TERM, ANGINA TRIALS

Adverse Events (COSTART Term)	Diltiazem Hydrochloride Extended-release Caspules USP (Once-a-day dosage)* n=139 # pts (%)	Placebo n=50 # pts (%)
asthenia	5 (3.6)	2 (4.0)
headache	4 (2.9)	3 (6.0)
pain, back	4 (2.9)	1 (2.0)
rhinitis	4 (2.9)	1 (2.0)
constipation	3 (2.2)	1 (2.0)
nausea	3 (2.2)	0 (0.0)
edema, peripheral	3 (2.2)	1 (2.0)
dizziness	3 (2.2)	0 (0.0)
cough, increased	3 (2.2)	0 (0.0)
bradycardia	2 (1.4)	0 (0.0)
fibrillation, atrial	2 (1.4)	0 (0.0)
arthralgia	2 (1.4)	0 (0.0)
dream, abnormal	2 (1.4)	0 (0.0)
dyspnea	2 (1.4)	0 (0.0)
pharyngitis	2 (1.4)	1 (2.0)

*Adverse events occurring in 1% or more of patients receivlng Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage).

Infrequent Adverse Events. The following additional events (COSTART Terms), listed by body system, were reported infrequently (less than 1%) in all subjects, hypertensive (n=425) or angina (n=318) patients who received Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage), or with other formulations of diltiazem.

Hypertension. Cardiovascular: First-degree AV block, arrhythmia, postural hypotension, tachycardia, pallor, palpitations, phlebitis, ECG abnormality, ST elevation.

Nervous System: Vertigo, hypertonia, paresthesia, dizziness, somnolence.

Digestive System: Dry mouth, anorexia, tooth disorder, eructation.

Skin and Appendages: Sweating, urticaria, skin hypertrophy (nevus).

Respiratory System: Epistaxis, bronchitis, respiratory disorder.

Urogenital System: Cystitis, kidney calculus, impotence, dysmenorrhea, vaginitis, prostate disease.

Metabolic and Nutritional Disorders: Gout, edema.

Musculoskeletal System: Arthralgia, bursitis, bone pain.

Hemic and Lymphatic System: Lymphadenopathy.

Body as a Whole: Pain, unevaluable reaction, neck pain, neck rigidity, fever, chest pain, malaise.

Special Senses: Amblyopia (blurred vision), ear pain.

Angina. Cardiovascular: Palpitations, AV block, sinus bradycardia, bigeminal extrasystole, angina pectoris, hypertension, hypotension, myocardial infarct, myocardial ischemia, syncope, vasodilatation, ventricular extrasystole.

Nervous System: Abnormal thinking, neuropathy, paresthesia.

Digestive System: Diarrhea, dyspepsia, vomiting, colitis, flatulence, GI hemorrhage, stomach ulcers.

Skin and Appendages: Contact dermatitis, pruritus, sweating.

Respiratory System: Respiratory distress.

Urogenital System: Kidney failure, pyelonephritis, urinary tract infection.

Metabolic and Nutritional Disorders: Weight increase.

Musculoskeletal System: Myalgia.

Body as a Whole: Chest pain, accidental injury, infection.

Special Senses: Eye hemorrhage, ophthalmitis, otitis media, taste perversion, tinnitus.

There have been post-marketing reports of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with the use of diltiazem hydrochloride.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem hydrochloride has been limited. The administration of ipecac to induce vomiting and activated charcoal to reduce drug absorption have been advocated as initial means of intervention. In addition to gastric lavage, the following measures should also be considered:

Bradycardia: Administer atropine (0.60 mg to 1 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 (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 as well as the judgment and experience of the treating physician.

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

Hypertensive or anginal patients who are treated with other formulations of diltiazem can safely be switched to Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) 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.

Studies have shown a slight increase in the rate of absorption of Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage), when ingested with a high-fat breakfast; therefore, administration in the morning on an empty stomach is recommended.

Patients should be cautioned that the Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) should not be opened, chewed or crushed and should be swallowed whole.

Dosage: Hypertension. Dosages must be adjusted to each patient's needs, starting with 180 mg or 240 mg once-daily. Based on the antihypertensive effect, the dose may be adjusted as needed. Individual patients, particularly ≥ 60 years of age, may respond to a lower dose of 120 mg. The usual dosage range studied in clinical trials was 180 mg to 480 mg once daily.

Current clinical experience with the 540 mg dose is limited, the dose may be increased to 540 mg with little or no increased risk of adverse reactions. Doses should not exceed 540 mg once-daily.

While a dose of Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) given once-daily may produce an antihypertensive effect similar to the same total daily dose given in divided doses, individual dose adjustment may be needed.

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

Concomitant Use with Other Cardiovascular Agents.

1. **Sublingual Nitroglycerin** may be taken as required to abort acute anginal attacks during diltiazem hydrochloride therapy.
2. **Prophylactic Nitrate Therapy** - Diltiazem hydrochloride may be safely co-administered 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.

HOW SUPPLIED

Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) are supplied as follows:

Strength	Size	NDC	Colour	Coding
240 mg	Bottles of 100	60505-0016-6	Brown opaque cap and a white opaque body	APO 016
	Bottles of 500	60505-0016-8		APO 016

STORE AT CONTROLLED ROOM TEMPERATURE, 15°-30°C (59°-86°F).

CAUTION: FEDERAL (U.S.A.) LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

TorPharm

Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage), 240 mg

Manufactured by:
TorPharm
Etobicoke, Ontario
Canada
M9W 6Y3

Manufactured for:
Apotex Corp.
Vernon Hills, Illinois
60061

Revised: December 1997

LB 0476

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