

DILTIAZEM HYDROCHLORIDE- diltiazem hydrochloride capsule, extended release
Rebel Distributors Corp

DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP

DESCRIPTION

Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). 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. It has a molecular weight of 450.98. Diltiazem hydrochloride is formulated as a once-a-day extended release capsule containing either 120 mg, 180 mg, 240 mg, or 300 mg diltiazem hydrochloride.

Each diltiazem extended-release capsule, for oral administration, contains the following inactive ingredients:

120 mg — ammonio methacrylate copolymer NF, type A, ammonio methacrylate copolymer NF, type B, ammonium hydroxide, black iron oxide, gelatin, hydroxypropyl cellulose, pharmaceutical glaze, propylene glycol, silicon dioxide, simethicone, sodium lauryl sulfate, sugar spheres, talc, titanium dioxide, triethyl citrate

180 mg — ammonio methacrylate copolymer NF, type A, ammonio methacrylate copolymer NF, type B, ammonium hydroxide, D&C yellow #10, FD&C blue #1, FD&C green #3, gelatin, hydroxypropyl cellulose, pharmaceutical glaze, propylene glycol, silicon dioxide, simethicone, sodium lauryl sulfate, sugar spheres, talc, titanium dioxide, triethyl citrate

240 mg — ammonio methacrylate copolymer NF, type A, ammonio methacrylate copolymer NF, type B, ammonium hydroxide, D&C yellow #10, FD&C green #3, gelatin, hydroxypropyl cellulose, pharmaceutical glaze, propylene glycol, silicon dioxide, simethicone, sodium lauryl sulfate, sugar spheres, talc, titanium dioxide, triethyl citrate

300 mg — ammonio methacrylate copolymer NF, type A, ammonio methacrylate copolymer NF, type B, ammonium hydroxide, black iron oxide, D&C yellow #10, FD&C green #3, gelatin, hydroxypropyl cellulose, pharmaceutical glaze, propylene glycol, silicon dioxide, simethicone, sodium lauryl sulfate, sugar spheres, talc, titanium dioxide, triethyl citrate

This drug product conforms to USP Drug release test #11.

CLINICAL PHARMACOLOGY

The therapeutic effects 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 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 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 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.

In hypertensive patients, diltiazem hydrochloride extended-release produces antihypertensive effects both in the supine and standing positions. In a double-blind, parallel, dose-response study utilizing doses ranging from 90 to 540 mg once daily, diltiazem lowered supine diastolic blood pressure in an apparent linear manner over the entire dose range studied. The changes in diastolic blood pressure, measured at trough, for placebo, 90 mg, 180 mg, 360 mg, and 540 mg were -2.9, -4.5, -6.1, -9.5, and -10.5 mm Hg, respectively. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects. Diltiazem 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 produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem 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 a double-blind, parallel dose-response study of doses from 60 mg to 480 mg once daily, diltiazem increased time to termination of exercise in a linear manner over the entire dose range studied. The improvement in time to termination of exercise utilizing a Bruce exercise protocol, measured at trough, for placebo, 60 mg, 120 mg, 240 mg, 360 mg, and 480 mg was 29, 40, 56, 51, 69 and 68 seconds, respectively. As doses of diltiazem were increased, overall angina frequency was decreased. Diltiazem, 180 mg once daily, or placebo was administered in a double-blind study to patients receiving concomitant treatment with long-acting nitrates and/or beta-blockers. A significant increase in time to termination of exercise and a significant decrease in overall angina frequency was observed. In this trial the overall frequency of adverse events in the diltiazem treatment group was the same as the placebo group.

Intravenous diltiazem hydrochloride in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of diltiazem hydrochloride in six normal volunteers, the average maximum PR

prolongation was 14% with no instances of greater than first-degree AV block. 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).

Chronic oral administration of diltiazem hydrochloride to patients in doses of up to 540 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation. (See WARNINGS.)

Pharmacokinetics And Metabolism: Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. Diltiazem undergoes extensive metabolism in which only 2% to 4% of the unchanged drug appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

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 is 70% to 80% bound to plasma proteins. Competitive in vitro ligand binding studies have also shown diltiazem binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Minimum therapeutic plasma diltiazem concentrations appear to be in the range of 50 to 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. A single study in 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: When compared to a regimen of diltiazem hydrochloride tablets at steady-state, more than 95% of drug is absorbed from the diltiazem hydrochloride extended-release capsules formulation. A single 360-mg dose of the capsule results in detectable plasma levels within 2 hours and peak plasma levels between 10 and 14 hours; absorption occurs throughout the dosing interval. When diltiazem hydrochloride extended-release capsules were coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected. Dose-dumping does not occur. The apparent elimination half-life after single or multiple dosing is 5 to 8 hours. A departure from linearity similar to that seen with diltiazem hydrochloride tablets and diltiazem hydrochloride sustained-release capsules is observed. As the dose of diltiazem hydrochloride extended-release capsules is increased from a daily dose of 120 mg to 240 mg, there is an increase in the area-under-the-curve of 2.7 times. When the dose is increased from 240 mg to 360 mg there is an increase in the area-under-the-curve of 1.6 times.

INDICATIONS AND USAGE

Diltiazem hydrochloride extended-release capsules are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive medications.

Diltiazem hydrochloride extended-release capsules are indicated for the management of chronic stable angina and angina due to coronary artery spasm.

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 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 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 3,290 patients or 0.40%). 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. (See ADVERSE REACTIONS section.)

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 $24\% \pm 6\%$) 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 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 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 is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General

Diltiazem 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 section) may be transient and may disappear despite continued use of diltiazem. 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 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 diltiazem. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of diltiazem with other agents which follow the same route of biotransformation 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, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem 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 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.)

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

Digitalis: Administration of diltiazem 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 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 blockers should be titrated carefully.

Cyclosporine: A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted or discontinued.

The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine: Concomitant administration of 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.

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 five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use diltiazem 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 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 have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving diltiazem hydrochloride extended-release capsules up to 360 mg with rates in placebo patients shown for comparison.

DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULE PLACEBO-CONTROLLED ANGINA AND HYPERTENSION TRIALS COMBINED

Adverse Reaction	Diltiazem Hydrochloride Extended-Release Capsules n=607	Placebo n=301
HEADACHE	5.4%	5.0%
DIZZINESS	3.0%	3.0%
BRADYCARDIA	3.3%	1.3%
AV BLOCK FIRST-DEGREE	3.3%	0.0%
EDEMA	2.6%	1.3%
ECG ABNORMALITY	1.6%	2.3%
ASTHENIA	1.8%	1.7%

In clinical trials of diltiazem hydrochloride extended-release capsules, diltiazem hydrochloride tablets, and diltiazem hydrochloride sustained-release capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).

In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

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, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase

Dermatological: Petechiae, photosensitivity, pruritus, urticaria

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving diltiazem hydrochloride: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, 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, some characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem therapy is yet to be established.

OVERDOSAGE

The oral LD₅₀'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD₅₀'s in these species were 60 and 38 mg/kg, respectively. The oral LD₅₀ 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 g to 10.8 g. Sixteen of these reports involved multiple drug ingestions.

Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 g to 10.8 g. 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, gastric lavage, 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. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose. 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 blockade, administer isoproterenol cautiously.

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

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

Hypotension: Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION

Patients controlled on diltiazem alone or in combination with other medications may be switched to diltiazem hydrochloride extended-release capsules at the nearest equivalent total daily dose. Higher doses of diltiazem hydrochloride extended-release capsules may be needed in some patients. Patients should be closely monitored. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. There is limited general clinical experience with doses above 360 mg, but doses to 540 mg have been studied in clinical trials. The incidence of side effects increases as the dose increases with first-degree AV block, dizziness, and sinus bradycardia bearing the strongest relationship to dose.

Hypertension: Dosage needs to be adjusted by titration to individual patient needs. When used as monotherapy, reasonable starting doses are 180 to 240 mg once daily, although some patients may respond to lower doses. 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 240 to 360 mg once daily. Individual patients may respond to higher doses of up to 480 mg once daily.

Angina: Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 or 180 mg once daily. Individual patients may respond to higher 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 NTG - May be taken as required to abort acute anginal attacks during diltiazem hydrochloride extended-release capsules therapy.
2. Prophylactic Nitrate Therapy - Diltiazem hydrochloride extended-release capsules may be safely coadministered with short- and long-acting nitrates.
3. Beta-Blockers: (See WARNINGS and PRECAUTIONS).
4. Antihypertensives - Diltiazem hydrochloride extended-release capsules have an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of diltiazem hydrochloride extended-release capsules or the concomitant antihypertensives may need to be adjusted when adding one to the other.

HOW SUPPLIED

Diltiazem Hydrochloride Extended-release Capsules, USP are supplied as follows:

120 mg — Each #2 capsule with light gray opaque cap and body printed with  and 2588 on

both cap and body in white ink contains 120 mg of diltiazem hydrochloride, USP. Capsules are supplied in bottles of 30 (NDC 21695-403-30).

180 mg — Each #0 capsule with dark green opaque cap and aqua blue opaque body printed

with  and 2577 on both cap and body in white ink contains 180 mg of diltiazem hydrochloride, USP. Capsules are supplied in bottles of 30 (NDC 21695-404-30).

240 mg — Each #0EL capsule with dark green opaque cap and body printed with  and 2578 on both cap and body in white ink contains 240 mg of diltiazem hydrochloride, USP. Capsules are supplied in bottles of 30 (NDC 21695-803-30).

Dispense in tight, light-resistant containers as defined in the USP.

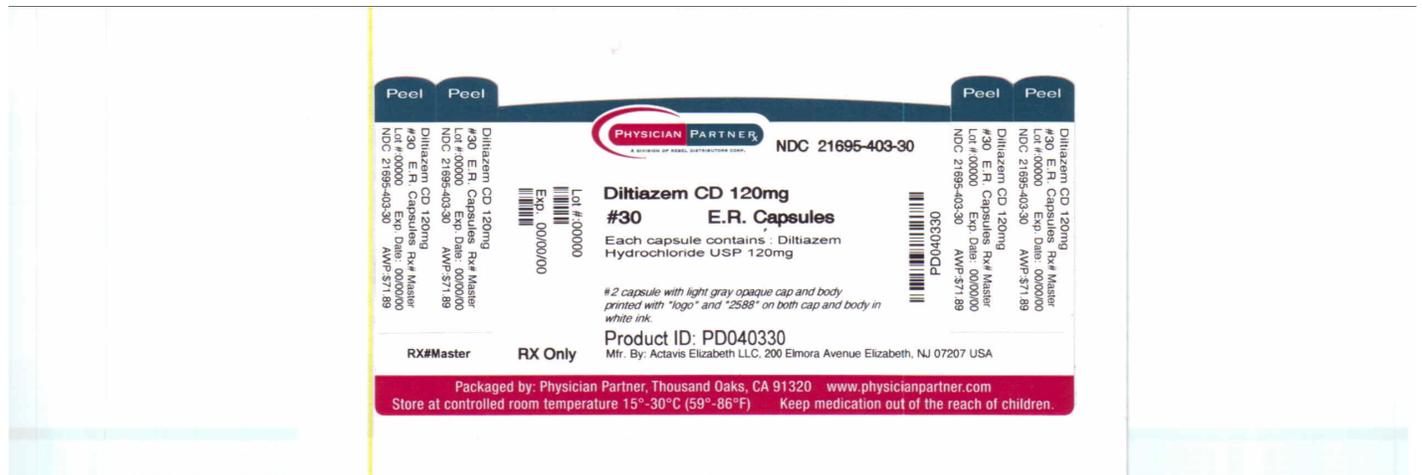
Store at controlled room temperature 15°-30°C (59°-86°F).

Avoid excessive humidity.

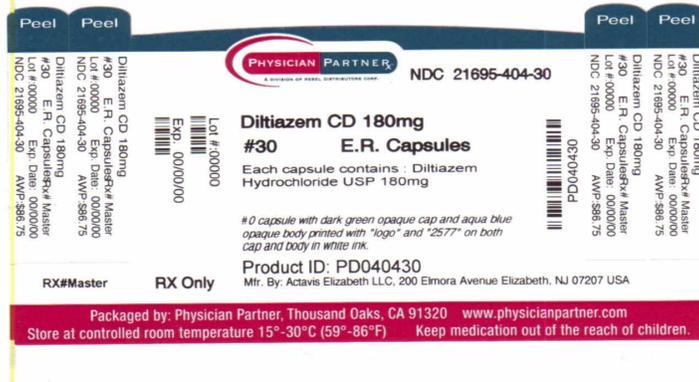
Manufactured by:
Actavis Elizabeth LLC
200 Elmora Avenue
Elizabeth, NJ 07207 USA

Repackaged by:
Rebel Distributors Corp
Thousand Oaks, CA 91320

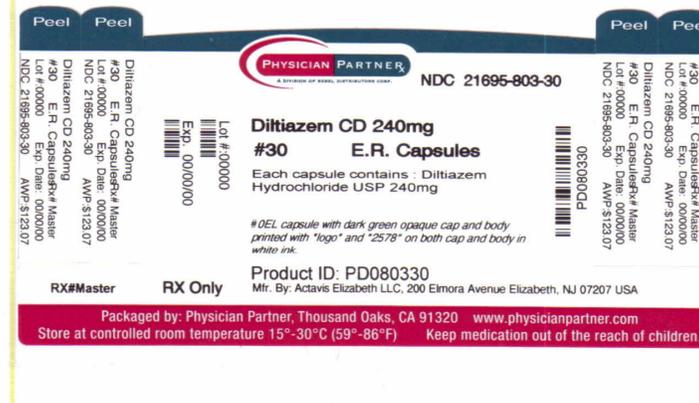
Principal Display Panel



Principal Display Panel



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DILTIAZEM HYDROCHLORIDE

diltiazem hydrochloride capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:21695-403(NDC:0228-2588)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Diltiazem Hydrochloride (UNII: OLH94387TE) (Diltiazem - UNII:EE92BBP03H)	Diltiazem Hydrochloride	120 mg

Inactive Ingredients

Ingredient Name	Strength
AMMONIO METHACRYLATE COPOLYMER TYPE A (UNII: 8GQS4E66YY)	
AMMONIO METHACRYLATE COPOLYMER TYPE B (UNII: 161H3B14U2)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSO FERRIC OXIDE (UNII: XM0M87F357)	
gelatin (UNII: 2G86QN327L)	

HYDROXYPROPYL CELLULOSE (UNII: RFW2ET671P)	
SHELLAC (UNII: 46N107B71O)	
propylene glycol (UNII: 6DC9Q167V3)	
silicon dioxide (UNII: ETJ7Z6XBU4)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
sodium lauryl sulfate (UNII: 368GB5141J)	
SUCROSE (UNII: C151H8M554)	
talc (UNII: 7SEV7J4RIU)	
titanium dioxide (UNII: 15FIX9V2JP)	
triethyl citrate (UNII: 8Z96QXD6UM)	

Product Characteristics

Color	gray (light gray opaque)	Score	no score
Shape	CAPSULE	Size	18mm
Flavor		Imprint Code	R2588
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:21695-403-30	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074984	12/20/1999	

DILTIAZEM HYDROCHLORIDE

diltiazem hydrochloride capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:21695-404(NDC:0228-2577)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Diltiazem Hydrochloride (UNII: OLH94387TE) (Diltiazem - UNII:EE92BBP03H)	Diltiazem Hydrochloride	180 mg

Inactive Ingredients

Ingredient Name	Strength
AMMONIO METHACRYLATE COPOLYMER TYPE A (UNII: 8GQS4E66YY)	
AMMONIO METHACRYLATE COPOLYMER TYPE B (UNII: 161H3B14U2)	

AMMONIA (UNII: 5138Q19F1X)
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)
gelatin (UNII: 2G86QN327L)
HYDROXYPROPYL CELLULOSE (UNII: RFW2ET671P)
SHELLAC (UNII: 46N107B71O)
propylene glycol (UNII: 6DC9Q167V3)
silicon dioxide (UNII: ETJ7Z6XBU4)
DIMETHICONE (UNII: 92RU3N3Y1O)
sodium lauryl sulfate (UNII: 368GB5141J)
SUCROSE (UNII: C151H8M554)
talc (UNII: 7SEV7J4R1U)
titanium dioxide (UNII: 15FIX9V2JP)
triethyl citrate (UNII: 8Z96QXD6UM)
FD&C BLUE NO. 1 (UNII: HBR47K3TBD)
FD&C GREEN NO. 3 (UNII: 3P3ONR6O1S)

Product Characteristics

Color	blue (aqua blue opaque) , green (dark green opaque)	Score	no score
Shape	CAPSULE	Size	22mm
Flavor		Imprint Code	R2577
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:21695-404-30	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074984	12/20/1999	

DILTIAZEM HYDROCHLORIDE

diltiazem hydrochloride capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:21695-803(NDC:0228-2578)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Diltiazem Hydrochloride (UNII: OLH94387TE) (Diltiazem - UNII:EE92BBP03H)	Diltiazem Hydrochloride	240 mg

Inactive Ingredients

Ingredient Name	Strength
AMMONIO METHACRYLATE COPOLYMER TYPE A (UNII: 8GQS4E66YY)	
AMMONIO METHACRYLATE COPOLYMER TYPE B (UNII: 161H3B14U2)	
AMMONIA (UNII: 5138Q19F1X)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
gelatin (UNII: 2G86QN327L)	
HYDROXYPROPYL CELLULOSE (UNII: RFW2ET671P)	
SHELLAC (UNII: 46N107B71O)	
propylene glycol (UNII: 6DC9Q167V3)	
silicon dioxide (UNII: ETJ7Z6XBU4)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
sodium lauryl sulfate (UNII: 368GB5141J)	
SUCROSE (UNII: C151H8M554)	
talc (UNII: 7SEV7J4R1U)	
titanium dioxide (UNII: 15FIX9V2JP)	
triethyl citrate (UNII: 8Z96QXD6UM)	
FD&C GREEN NO. 3 (UNII: 3P3ONR6O1S)	

Product Characteristics

Color	green (dark green opaque)	Score	no score
Shape	CAPSULE	Size	23mm
Flavor		Imprint Code	R2578
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:21695-803-30	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074984	12/20/1999	

Labeler - Rebel Distributors Corp (118802834)

Establishment

Name	Address	ID/FEI	Business Operations
Rebel Distributors Corp		118802834	RELABEL, REPACK