Diltiazem hydrochloride. Diltiazem 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 is available as a once-daily extended release capsule containing either 120 mg, 180 mg, 240 mg, or 330 mg diltiazem hydrochloride.

Each diltiazem extended-release capsule, for oral administration, contains the following inactive ingredients:
- 120 mg — ammonium methylacrylate copolymer NF, type A, ammonium methylacrylate copolymer NF, type B, ammonium hydroxide, D&C yellow #10, FD&C green #3, gelatin, hydroxypropyl cellulose, pharmaceutical grade, propylene glycol, silicon dioxide, simethicone, sodium lauryl sulfate, sugar spheres, talc, titanium dioxide, triethyl citrate
- 180 mg — ammonium methylacrylate copolymer NF, type A, ammonium methylacrylate copolymer NF, type B, ammonium hydroxide, D&C yellow #10, FD&C green #3, gelatin, hydroxypropyl cellulose, pharmaceutical grade, propylene glycol, silicon dioxide, simethicone, sodium lauryl sulfate, sugar spheres, tcalcium, titanium dioxide, triethyl citrate
- 240 mg — ammonium methylacrylate copolymer NF, type A, ammonium methylacrylate copolymer NF, type B, ammonium hydroxide, D&C yellow #10, FD&C green #3, gelatin, hydroxypropyl cellulose, pharmaceutical grade, propylene glycol, silicon dioxide, simethicone, sodium lauryl sulfate, sugar spheres, tcalcium, titanium dioxide, triethyl citrate
- 330 mg — ammonium methylacrylate copolymer NF, type A, ammonium methylacrylate copolymer NF, type B, ammonium hydroxide, D&C yellow #10, FD&C green #3, gelatin, hydroxypropyl cellulose, pharmaceutical grade, propylene glycol, silicon dioxide, simethicone, sodium lauryl sulfate, sugar spheres, tcalcium, titanium dioxide, triethyl citrate

This drug product contains USP Drug Release test #11.

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

Mechanism of Action
Hypertension: Diltiazem hydrochloride produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. This effect is only slightly reduced by the administration of propranolol, which suggests that, although sympathetic nervous system activity is important, it is not the sole determinant of cardiac contractility. The effect of diltiazem on blood pressure is usually maximal at about 1 hour. There is some evidence that tachyphylaxis occurs with chronic administration of diltiazem hydrochloride.

In the intact animal, prolongation of the AH interval can be seen at higher doses. This effect is predominantly due to a decrease in ventricular rate, and is not associated with prolongation of the His-Purkinje conduction time. In vitro, diltiazem has been shown to inhibit AV nodal conduction and, to a lesser extent, ventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. Diltiazem reduces the rate of spontaneous Ca++ release from sarcoplasmic reticulum in skinned cardiac muscle fibers. Diltiazem decreases contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function have not shown a reduction in cardiac index nor consistent negative effects on left ventricular ejection fraction.

Hemodynamic and Electrophysiologic Effects
Like other calcium antagonist blockers, diltiazem decreases sinoatrial and atrioventricular conduction. Its effect on atrioventricular conduction is of importance in isolated preparations. In intact animals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the 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 clinical results 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.

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 60 mg to 480 mg once daily, diltiazem hydrochloride 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 480 mg were -2.5, -6.1, -9.5, and -15.0 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 hydrochloride may cause an initial decrease in pulse rate (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. Therapy with diltiazem hydrochloride produces a 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. Hypotensive animal models respond to diltiazem hydrochloride with a reduction in renal blood flow and glomerular filtration rate, and natriuresis without a change in urinary sodium/potassium ratio.

In a double-blind, parallel-dose response study of dosing at 60 mg to 480 mg once daily, diltiazem hydrochloride increased AUC by 2-fold, compared to placebo. The elimination half-life may be increased up to 3-fold in patients who are extensively metabolized by the cytochrome P-450 enzymes. Diltiazem hydrochloride is a substrate and an inhibitor of the cytochrome P-450 enzymes. Diltiazem hydrochloride is a substrate and an inhibitor of the cytochrome P-450 enzymes. Diltiazem hydrochloride is a substrate and an inhibitor of the cytochrome P-450 enzymes. Diltiazem hydrochloride is a substrate and an inhibitor of the cytochrome P-450 enzymes. Diltiazem hydrochloride is a substrate and an inhibitor of the cytochrome P-450 enzymes.

WARNINGS
Cardiac Conduction: Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in aberrant low heart rates (particularly in patients with sick sinus syndrome). Concomitant use of diltiazem with beta-blockers or digoxin 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).

Congestive Heart Failure: Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and with severe congestive heart failure have not demonstrated consistent negative effects on left ventricular function. Decreases in cardiac index have not been observed. In patients with chronic congestive heart failure, diltiazem has produced at least a temporary increase in exercise tolerance and reduction in angina frequency. In one trial conducted in patients with impaired ventricular function, there was only a modest fall in blood pressure in normotensive patients. 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 60 mg to 480 mg once daily, diltiazem hydrochloride 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 480 mg were -2.5, -6.1, -9.5, and -15.0 mm Hg, respectively. Postural hypotension is infrequently noted upon suddenly assuming an upright position.

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

Diastolic: Administration of diazepam, propranolol, and 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-digitization (see WARNINGS).

Quinidine: Diltiazem significantly increases the AUC of quinidine by 51%, T1/2 by 38%, and Cmax by 33% and causing for quinidine adverse effects may be warranted and the dose adjusted accordingly.

Ritanserin: Coadministration of ritanserin with diltiazem lowered the diltiazem plasma concentrations. Administration of diltiazem with ritanserin in any known CYP3A4 inducer should be avoided when possible, and alternative therapy considered.

Statin: 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 symptoms of any statin related adverse events. In a healthy volunteer cross-over study (N=10), coadministration of a single 20 mg dose of simvastatin at the end of a 14 days with 120 mg BID diltiazem sustained-release 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 AUC and Cmax by 300 and 2577 on both cap and body in white ink contains 180 mg hydrochloride tablets, and diltiazem hydrochloride sustained-release capsules involving extended-release capsules up to 360 mg with rates in placebo patients shown for be recognized that patients with impaired ventricular function and cardiac conduction disturbances may have an increased risk of adverse effects. Serious adverse reactions have been rare in studies carried out to date, but it should be noted that patients with impaired ventricular function and cardiac conduction disturbances may have an increased risk of adverse effects.

Nitrate: The following postmarketing reports have been reported frequently in patients receiving diltiazem hydrochloride: acute generalized exanthematous pustulosis, allergic reactions (urticaria, angioedema (including facial or periorbital edema), asthema, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extramammary syringomata, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, photosensitivity, purpura, retinopathy, myopathy 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 in mice and rats range from 415 to 740 mg/kg and from 560 to 10 mg/kg, respectively. The intravenous LD50 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 550 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 predicting toxicity.

There have been reports of diltiazem overdose in amounts ranging from <1 g to 18 g. Of cases with known outcome, most patients recovered and in cases with a fatal outcome, the major cause of death was cardiac arrest.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical management 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.

The effectiveness of intravenous calcium administration to reverse the pharmacological effect of diltiazem overdose has been inconsistent. In a few reported cases, overdose with calcium channel blockers associated with hypotension and bradycardia that was initially refractory to atropine became more responsive to atropine after the patients received intravenous calcium. In some cases, intravenous calcium has been administered to patients with cardiac arrest, with marked improvement in blood pressure and heart rate; in other cases, intravenous calcium has been administered with little or no effect.

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 block, administer isoproterenol cautiously.

High-dose AV Block: Treat as for bradycardia above. Fixed high-dose 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.

DOSAGE AND ADMINISTRATION
Patients controlled on diltiazem alone or in combination with other medications may be switched to Diltiazem Hydrochloride Extended-Release Capsules, USP 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.

Hyponatremia: Dosage needs to be adjusted by titration to individual patient needs. When used as monotherapy, reasonable starting doses are 180 to 240 mg daily, although some patients may respond to lower doses. Maximum hypotensive 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.

Concomitant Use With Other Cardiovascular Agents
1. Sublingual NTS — May be taken as required to abort acute anginal attacks during diltiazem hydrochloride extended-release capsules therapy.

HOW SUPPLIED
Diltiazem Hydrochloride Extended-Release Capsules, USP are supplied as follows:

120 mg — Each #2 capsule with light grey opaque cap and body printed with 120 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 39844-829-11), 90 (NDC 39844-829-09) and 500 (NDC 39844-829-05).

180 mg — Each #0 capsule with dark green opaque cap and aqua blue opaque body printed with 180 and 2578 on both cap and body in white ink contains 180 mg of diltiazem hydrochloride, USP Capsules are supplied in bottles of 30 (NDC 39844-830-11), 90 (NDC 39844-830-09) and 500 (NDC 39844-830-05).

240 mg — Each #0EL capsule with dark green opaque cap and body printed with 240 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 39844-831-11), 90 (NDC 39844-831-09) and 500 (NDC 39844-831-05).

300 mg — Each #0 capsule with dark grey opaque cap and light grey opaque body printed with 300 and 2579 on both cap and body in white ink contains 300 mg of diltiazem hydrochloride, USP Capsules are supplied in bottles of 30 (NDC 39844-832-11), 90 (NDC 39844-832-09) and 500 (NDC 39844-832-05).

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

Store at 25°C (77°F); excursions permitted to 15° to 38°C (59° to 86°F). Avoid excessive humidity.

Manufactured for:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977 U.S.A.

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