Diltiazem HCl has been shown to produce increases in exercise capacity (see CLINICAL PHARMACOLOGY).

**INDICATIONS AND USAGE**

Diltiazem is indicated in the management of hypertension. Oral diltiazem prolonged-release capsules, in combination with a thiazide diuretic, are indicated in the management of patients with mild to moderate hypertension who are considered to be at increased risk for side effects of thiazide diuretics (see CLINICAL PHARMACOLOGY).

**PRECAUTIONS**

**Drug Interactions**

Multiple reports of patients (predominantly those with heart failure) who developed sinus bradycardia, atrioventricular (AV) block, and second-degree or third-degree AV block while receiving coadministration of diltiazem and a beta-blocker have been reported. 

Diltiazem prolongs the atrioventricular conduction time and decreases the heart rate-blood pressure product for any given work load. Therefore, when diltiazem is coadministered with beta-blockers, caution and careful monitoring of the patient are warranted in order to avoid possible over- or under-digitalization and to avoid asymptomatic sinus bradycardia or AV block. Diltiazem should be used with caution in patients who are taking drugs that may affect the sinus node function or heart rate. For example, in patients receiving cardioactive drugs, including digitalis, increases in serum digitalis levels and digitalis toxicity have been reported. The monitoring of digitalis toxicity in such patients is suggested (see WARNINGS).

Diltiazem is a strong inhibitor of the cytochrome P450 3A4 family of enzymes (CYP3A4) and is a substrate for this enzyme family, as evidenced by the findings of significant increases in plasma concentrations of multiple drugs metabolized by CYP3A4, including erythromycin, midazolam, nifedipine, and simvastatin. Diltiazem is also a substrate for CYP2C9 and is metabolized by CYP2C9. Therefore, concomitant administration of diltiazem with other drugs that are substrates of CYP2C9 (e.g., clopidogrel) may result in increased plasma concentrations and increased adverse effects of both diltiazem and the other drug(s). Concurrent use of diltiazem by the CYP2C19 wild-type allele is associated with a more significant increase in the plasma concentration of midazolam than in the case of diltiazem. Diltiazem is a substrate for CYP2D6, with plasma concentrations of diltiazem increased by 20% to 42% in subjects who are extensive metabolizers of diltiazem compared with poor metabolizers. Diltiazem is a weak inhibitor of CYP3A4 and CYP2C19 enzyme activity (as evidenced by the findings of increases in minimal clearance and decreases in plasma concentrations of fluvastatin). Therefore, concomitant use of diltiazem with other drugs that are metabolized by these enzymes (e.g., warfarin, fluoxetine, escitalopram, and linezolid) may result in increased plasma concentrations and increased adverse effects of both diltiazem and the other drug(s). The use of diltiazem in patients who are taking drugs that are substrates of CYP3A4 (e.g., digoxin, tacrolimus, and HIV protease inhibitors) may result in increased plasma concentrations and increased adverse effects of both diltiazem and the other drug(s) unless the dosing of one or both drugs is adjusted to account for this interaction. Although diltiazem is a weak inhibitor of CYP2C19 enzyme activity, it is a moderately strong inhibitor of CYP2D6 enzyme activity (as evidenced by the findings of increases in plasma concentrations of midazolam). Therefore, concomitant use of diltiazem with drugs that are substrates of CYP2D6 (e.g., warfarin and tricyclic antidepressants) may result in increased plasma concentrations and increased adverse effects of both diltiazem and the other drug(s) unless the dosing of one or both drugs is adjusted to account for this interaction. Diltiazem is a moderate inhibitor of CYP2B6 enzyme activity (as evidenced by the findings of increased plasma concentrations of midazolam). Therefore, concomitant use of diltiazem with drugs that are substrates of CYP2B6 (e.g., fluconazole and clarithromycin) may result in increased plasma concentrations and increased adverse effects of both diltiazem and the other drug(s) unless the dosing of one or both drugs is adjusted to account for this interaction. 

**Adverse Reactions**

The incidence of adverse effects associated with diltiazem therapy depends on the drug dosage, patient population, and the method of monitoring. Generally, the adverse events associated with diltiazem therapy are not drug-related or tend to be dose-dependent. They may represent side effects of the underlying disease or its therapy, and it is difficult to attribute them specifically to diltiazem therapy. Adverse reactions in patients taking extended-release capsules occur with a frequency comparable to those in patients taking immediate-release capsules (see CLINICAL PHARMACOLOGY). In healthy volunteers, the incidence of adverse reactions was less with sustained-release capsules compared with immediate-release capsules (see CLINICAL PHARMACOLOGY). 

The most common adverse reactions (that can occur in any patient) are headaches, flushing, diarrhea, and nausea. Other adverse reactions that have been associated with diltiazem therapy include:

- GI: Constipation, diarrhea, flatulence, nausea, dry mouth, vomiting
- GU: Hematuria, proteinuria, hemodialysis
- Respiratory: Sinusitis, rhinitis, cough
- Dermatologic: Rash, skin irritation, pruritus
- Cerebrovascular: Dizziness, syncope, vertigo
- Other: Headache, edema

**WARNINGS**

**Heart-Rate-Lowering Effects**

Diltiazem has significant negative chronotropic effects. Patients with underlying sinus node dysfunction or heart block are at increased risk for bradycardia or heart block. These patients also have a higher risk for sinus bradycardia and heart block. The incidence of heart block in clinical studies was higher in patients taking extended-release capsules (31%) than in patients taking immediate-release capsules (17%); however, heart block occurred more frequently in patients with a history of heart block or who were taking concomitant use of beta-blockers (36% compared with 1% in patients without heart block). 

**Concomitant Use of Other Agents That May Affect Cardiac Conduction**

Concomitant use of agents that can prolong the AH or AV conduction time should be used with caution. The conduction times for diltiazem may be additive with other agents that are used to treat supraventricular and ventricular arrhythmias (e.g., beta-blockers, calcium channel blockers). The conduction times for diltiazem may also be additive with other agents that are used to treat supraventricular and ventricular arrhythmias (e.g., beta-blockers, calcium channel blockers). 

**Asystole and Sudden Death**

Asystole and sudden death have been reported in patients with ventricular tachycardia or ventricular fibrillation receiving diltiazem. In patients with ventricular tachycardia or ventricular fibrillation, caution is warranted in using diltiazem to avoid precipitating ventricular arrhythmias. In patients with left ventricular dysfunction, the use of diltiazem may be associated with deterioration of left ventricular function (see CLINICAL PHARMACOLOGY). 

**Cardiovascular Effects**

Diltiazem reduces the heart rate-blood pressure product for any given work load. 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 normotensive patients. This lowering effect is dose-related. Diltiazem reduces the heart rate-blood pressure product for any given work load. 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 normotensive patients. This lowering effect is dose-related. 

**Hepatic and Renal Effects**

The plasma elimination half-life of diltiazem is increased in patients with hepatic impairment, and total plasma radioactivity is decreased in proportion to the degree of hepatic impairment. Therefore, the dose of diltiazem should be reduced in patients with hepatic impairment (see CLINICAL PHARMACOLOGY).

**Renal Elimination**

The plasma elimination half-life is increased in patients with decreased renal function (see CLINICAL PHARMACOLOGY). In patients with renal insufficiency, the dose of diltiazem should be reduced (see CLINICAL PHARMACOLOGY).

**Porphyria**

Porphyria is a rarely occurring inherited metabolic disorder. Severe cases of porphyria may be associated with intense pain in the abdomen, chest, and back. The porphyrins are excreted in the urine and can cause porphyria cutanea tarda (PCT), an inherited disorder that is characterized by skin photosensitivity and scarring; porphyria variegata (PV), an inherited disorder that is characterized by skin photosensitivity, neurological symptoms, and organ damage; and acute intermittent porphyria (AIP). The involvement of different porphyria forms can be difficult to determine, and the outcomes can be severe. However, these conditions are rare. Diltiazem should be used with caution in patients with a history of porphyria or in patients who may develop porphyria. 

**Hypersensitivity Reactions**

Hypersensitivity reactions can occur with diltiazem therapy, generally with a similar frequency as with other calcium channel blockers. These reactions include rash, pruritus, fever, urticaria, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, and exfoliative dermatitis. Should a rash or other signs of hypersensitivity develop, diltiazem should be discontinued. 

**Hyperkalemia**

Hyperkalemia can occur during diltiazem treatment, generally with a similar frequency as with other calcium channel blockers. The incidence of hyperkalemia is related to the degree of renal impairment. In patients with normal renal function, the incidence of hyperkalemia is low. In patients with moderate renal impairment, the incidence of hyperkalemia is higher. In patients with severe renal impairment, the incidence of hyperkalemia is higher. Therefore, the dose of diltiazem should be reduced in patients with renal impairment (see CLINICAL PHARMACOLOGY). 

**Drug Interactions**

Diltiazem may interact with other drugs that are metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme system. These drugs may include, but are not limited to, quinidine, nifedipine, diltiazem, verapamil, fluoxetine, saquinavir, ritonavir, midazolam, itraconazole, astemizole, clarithromycin, and warfarin. The concomitant use of diltiazem with other drugs that are metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentrations and increased adverse effects of both diltiazem and the other drug(s) unless the dosing of one or both drugs is adjusted to account for this interaction. 

**Impaired Ventricular Function**

Diltiazem is a potent negative inotropic agent and is not recommended for use in patients with impaired ventricular function or congestive heart failure. 

**Antihypertensive Effects**

Diltiazem is a potent antihypertensive agent and should be used with caution in patients with malignant hypertension. An elevation in serum creatinine level has been reported in patients with congestive heart failure who were treated with diltiazem. Diltiazem should be used with caution in patients with congestive heart failure. 

**Drug/Lab Test Interactions**

Diltiazem is a substrate for CYP2C19 and is metabolized by CYP2C19. Therefore, concomitant use of diltiazem with other drugs that are metabolized by CYP2C19 (e.g., clopidogrel) may result in increased plasma concentrations and increased adverse effects of both diltiazem and the other drug(s). 

**Lactation**

It is not known if diltiazem is excreted in human milk. Caution should be exercised when diltiazem is administered to a nursing woman. 

**Children**

Safety and effectiveness in children have not been established.
Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If the mother is breast-feeding, advise the mother of the potential risk to the fetus.

In clinical trials (480 mg/day or 8 mg/kg/day for a 60 kg patient) resulted in evidence of impaired fertility was observed in a study performed in male rats. A pharmacokinetic interaction between diltiazem and rifampin occurs.

Coadministration of diltiazem with rifampin or any known CYP3A4 inducer should be avoided when possible, and alternative therapy should be considered.

Geriatric Use.

The toxic dose in man is not known. Due to extensive metabolism, blood levels may be markedly influenced by concomitant disease or other drug therapy.

Coadministration of rifampin with diltiazem lowered the AUC and Cmax was observed during diltiazem coadministration.

A pharmacokinetic interaction between diltiazem and midazolam and triazolam can result in increased clinical effects (e.g., prolonged sedation) of both drugs.

Increased (1.5-2.5 fold) during coadministration with diltiazem. These increases may result in an increased risk for serious adverse reactions (e.g., symptoms of central nervous system depression, decreased blood pressure, bradycardia).

High-Degree AV Block: In cases of high-degree AV block should be treated with cardiac pacing.

In the event of overdose or exaggerated response, appropriate supportive care may be required.

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

Angina, arrhythmia, AV block (second- or third-degree), palpitations, syncope, tachycardia, ventricular extrasystoles, hypertension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Other.

Albuminuria, allergic reaction, amblyopia, asthenia, CPK increase, dermatological.

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

Angina, arrhythmia, AV block (second- or third-degree), palpitations, syncope, tachycardia, ventricular extrasystoles.

In addition, events such as myoglobinuria, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocar-