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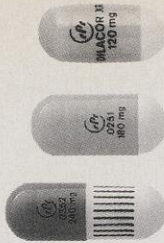
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Now, for hypertension
Once-a-day

DILACOR™ XR

(diltiazem HCl) EXTENDED
RELEASE
CAPSULES



120 mg

180 mg

240 mg

24-HOUR DELIVERY FOR 24-HOUR SECURITY



BRIEF SUMMARY

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% \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 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 the 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 Dilacor™ XR 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 Dilacor™ XR.

Information for Patients. Dilacor™ XR capsules should be taken on an empty stomach. Patients should be cautioned that the Dilacor™ XR capsules 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 biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem hydrochloride to maintain optimum therapeutic blood levels.

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 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.

References:

- Graney WF: Clinical experience with a once-daily, extended-release formulation of diltiazem in the treatment of hypertension. *Am J Med* 1992;93(Suppl 2A): 565-645.
- 1992 Drug Topics® Red Book® Update. Oradell, NJ, Medical Economics Co. Inc.; December 1992.

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 children have not been established.

ADVERSE REACTIONS

Severe adverse reactions to diltiazem hydrochloride have been rare in studies with other formulations, as well as with Dilacor™ XR. It should be recognized, however, that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The most common adverse events (frequency \geq 1%) in placebo-controlled, clinical hypertension studies with Dilacor™ XR 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)	Dilacor™ XR 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 Dilacor™ XR.

The following additional events (COSTART Terms), listed by body system, were reported infrequently in all subjects and hypertensive patients who received Dilacor™ XR (n=425): 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 Systems: Lymphadenopathy; Body as a Whole: Pain, unevaluable reaction, neck pain, neck rigidity, fever, chest pain, malaise; Special Senses: Amblyopia (blurred vision), ear pain.

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 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 (dopamine or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g. dopamine or levarterenol bitartrate).

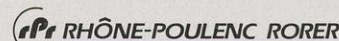
Actual treatment and dosage should depend on the severity of the clinical situation as well as the judgment and experience of the treating physician.

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.

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

Please see product circular for full prescribing information.



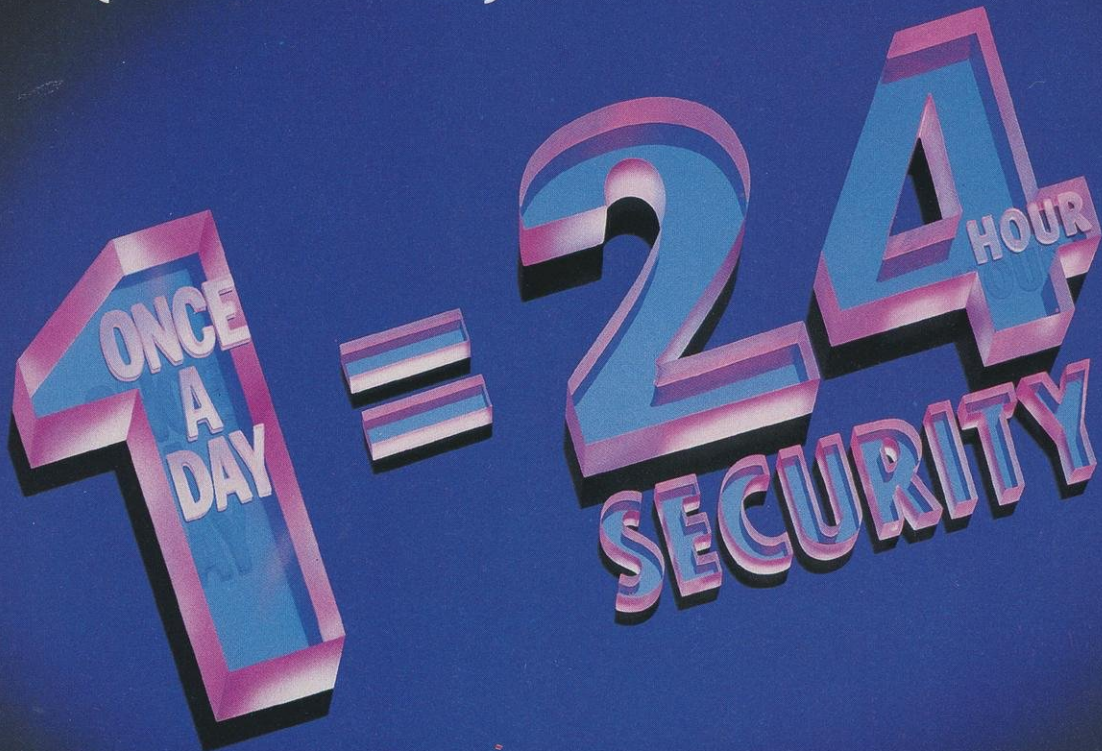
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COLLEGEVILLE, PA 19426

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120-mg strength
for patients who need the
lowest starting dose

Now, for hypertension
Once-a-day

DILACOR™ XR

(diltiazem HCl) EXTENDED
RELEASE
CAPSULES



DILACOR XR effectively lowers blood pressure
for 24 hours in the majority of patients¹

DILACOR XR offers the classic diltiazem safety
profile across the entire dosing range¹

DILACOR XR makes diltiazem a cost-effective
choice for the treatment of hypertension²

Please see adjacent page for brief summary of prescribing information.