ZALDEM ® CR
CONTROLLED RELEASE CAPSULES
Diltiazem HCl

DESCRIPTION

ZALDEM® CR (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist).

ZALDEM® CR is available as 120 mg, 180 mg and 240 mg capsules for oral administration.

Inactive ingredients: sucrose, povidone, talc, shellac, ethylcellulose.

INDICATIONS AND USAGE

Hypertension: ZALDEM® CR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

Angina: ZALDEM® CR is indicated for the management of chronic stable angina and angina due to coronary artery spasm.

CONTRAINDICATIONS

ZALDEM® CR is contraindicated in the following patients:

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 pacemaker.

3- Patients with hypotension (less than 90 mm Hg systolic).

4- Patients who have demonstrated hypersensitivity to diltiazem.

5- Patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

Cardiac Conduction: ZALDEM® CR 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. Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction.

Congestive Heart Failure: Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of ZALDEM® CR in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

Hypotension: Decrease in blood pressure associated with ZALDEM® CR therapy may occasionally result in symptomatic hypotension.

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, SGPT, and other phenomena consistent with acute hepatic injury have been reversible upon discontinuation of drug therapy.

PRECAUTIONS

General

ZALDEM® CR 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.

Dermatological events may be transient and may disappear despite continued use of ZALDEM® CR . 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 ZALDEM® CR concomitantly with other agents known to affect cardiac contractility and/or conduction. Pharmacological studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with ZALDEM® CR .

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem undergoes biotransformation by cytochrome P-450 3A4. Coadministration of ZALDEM® CR with other agents which follow the same route of biotransformation may result in competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin or simvastatin, particularly those of low therapeutic ratio in patients with renal and hepatic impairment may require adjustment when starting or stopping concomitantly administered ZALDEM® CR to maintain therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled studies suggest that concomitant use of ZALDEM® CR with 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 with propranolol resulted in increased propranolol levels and the bioavailability of propranolol was increased by 50%.If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in propranolol dose may be warranted.

Cimetidine: A one week course of 1200 mg per day of cimetidine increased the plasma level of a single dose of 60 mg diltiazem by 58%. Ranitidine produced smaller nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450. 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: It is recommended that digoxin levels be monitored when initiating, adjusting and discontinuing ZALDEM® CR therapy to avoid possible over or under digitalization.

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 and Impairment of Fertility

Two-year studies with doses of 100 mg/Kg/day in mice and rats failed to show any evidence of carcinogenic potential.

Studies in rats have revealed no impairment of fertility.

Pregnancy

Category C. There are no well controlled studies in pregnant women. Use ZALDEM® CR 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 ZALDEM® CR 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

In clinical studies, the most common adverse events 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 less than 1%:

Cardiovascular: angina, arrhythmia, AV block (second or third degree 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 SGPT, LDH and alkaline phosphatase, 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.

OVERDOSAGE

The toxic dose in man is not known. Events observed following diltiazem overdose included bradycardia, hypotension, and cardiac failure.

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. Based on the known pharmacological effects of diltiazem and reported clinical experiences the following measures may be considered:

Bradycardia: Administer atropine (0.6 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 (isoproterenol, dopamine, dobutamine) and diuretics.

Hypotension: Vasopressors (dopamine, levarterenol).

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 safely switched to ZALDEM® CR capsules at the nearest equivalent total daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted.

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.

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 up to 480 mg once daily. When necessary, titration may be carried out over 7 to 14 day period.

Concomitant use with other cardiovascular agents:

Sublingual nitroglycerin may be taken as required to abort acute anginal attacks during ZALDEM® CR therapy.

Prophylactic nitrate therapy: ZALDEM® CR may be safely administered with short and long acting nitrates.

Beta-blockers: See WARNINGS and PRECAUTIONS.

Antihypertensives: ZALDEM® CR has an additive antihypertensive effect when used with other antihypertensives. Therefore, the dosage of ZALDEM® CR or the concomitant antihypertensive may need to be adjusted when adding one to the other.

Packaging quantities: Capsules 120 mg - Blister pack of 30's
Capsules 180 mg - Blister pack of 30's
Capsules 240 mg - Blister pack of 30's

THIS IS A MEDICAMENT

- A Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

KEEP MEDICAMENT OUT OF REACH OF CHILDREN

Pharmaceutical precautions: Store below 30 °C in a dry place.

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