For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

DILZEM SR
(Diltiazem Hydrochloride Sustained Release Tablets)

COMPOSITION
Each uncoated sustained release tablet contains:
Diltiazem Hydrochloride I.P. ….90mg

DOSAGE FORM
Sustain Release tablet

INDICATION
For the management of angina pectoris. For the treatment of mild to moderate hypertension.

DOSE AND METHOD OF ADMINISTRATION
Angina
Adults: the usual initial dose is 90 mg twice daily. Dosage may be increased gradually 180 mg twice daily if required. Patients' responses may vary and dosage requirements can differ significantly between individual patients.
Paediatric population
The safety and efficacy in children has not been established. Therefore, diltiazem is not recommended for use in children.
Dosage in the elderly and patients with impaired hepatic or renal function
Angina
Dosage should commence at 90 mg once daily and the dose carefully titrated as required.
Hypertension
Dosage should commence at the lower level of 90 mg once daily and be increased slowly in order to achieve the required level of control. The daily dose should not exceed 90 mg twice daily. Do not increase the dose if the heart rate falls below 50 beats per minute.
Method of administration
For oral use.
It should be swallowed whole with water and should not be sucked, chewed or crushed.

USE IN SPECIAL POPULATIONS
Pregnancy
There is very limited data from the use of diltiazem in pregnant patients. Diltiazem has been shown to have reproductive toxicity in certain animal species (rat, mice, rabbit). Diltiazem is contraindicated during pregnancy, as well as in women of child-bearing potential not using effective contraception.

Breast-feeding
Diltiazem is excreted in breast milk at low concentrations. Breast-feeding while taking this drug should be avoided. If use of diltiazem is considered medically essential, an alternative method of infant feeding should be instituted.

CONTRAINDICATIONS
- Hypersensitivity to diltiazem hydrochloride or to any of the excipients
- Pregnancy and in women of child bearing potential

- Severe bradycardia (below 40 bpm)
- Second- or third-degree AV block except in the presence of a functioning ventricular pacemaker
- Sick sinus syndrome except in the presence of a functioning ventricular pacemaker
- Cardiac failure after myocardial infarction
- Left ventricular failure with pulmonary congestion
- Concomitant administration of dantrolene infusion
- Combination with ivabradine

WARNINGS AND PRECAUTIONS

Rare instances of hyperglycaemia have been reported in association with diltiazem hydrochloride. The use of diltiazem in diabetic patients may require adjustment of their control.
Precaution should be taken in patients with reduced left ventricular function. Patients should be observed closely if they have bradycardia (risk of exacerbation), first degree AV block detected on the electrocardiogram (risk of exacerbation and rarely, of complete block) or prolonged PR interval.
Diltiazem is considered unsafe in patients with acute porphyria.
Prior to general anaesthesia, the anaesthetist must be informed of ongoing diltiazem treatment.
Depression of cardiac contractility, conductivity and automaticity, as well as the vascular dilatation associated with anaesthetics may be potentiated by calcium channel blockers.
Increase of plasma concentrations of diltiazem may be observed in the elderly and in patients with renal or hepatic insufficiency. The contraindications and precautions should be carefully observed and close monitoring, particularly of heart rate, should be carried out at the beginning of treatment.
Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression.
Like other calcium channel antagonists, diltiazem has an inhibitory effect on intestinal motility. Therefore, it should be used with caution in patients at risk to develop an intestinal obstruction.
Tablet residues from slow release formulations of the product may pass into the patient's stools; however, this finding has no clinical relevance.

Effects on ability to drive and use machines

On the basis of reported adverse drug reactions, i.e. dizziness (common), malaise (common), the ability to drive and use machines could be altered. However, no studies have been performed.

DRUG INTERACTIONS

Concomitant use contraindicated:
Dantrolene (infusion): Lethal ventricular fibrillation is regularly observed in animals when intravenous verapamil and dantrolene are administered concomitantly. The combination of a calcium antagonist and dantrolene is therefore potentially dangerous.
Concomitant use requiring caution:
Lithium: Risk of increase in lithium-induced neurotoxicity.
Nitrate derivatives: Increased hypotensive effects and faintness (additive vasodilatating effects): In all the patients treated with calcium antagonists, the prescription of nitrate derivatives should only be carried out at gradually increasing doses.
Theophylline: Increase in circulating theophylline levels.
Alpha-antagonists: Increased antihypertensive effects:

Concomitant treatment with alpha-antagonists may produce or aggravate hypotension. The combination of diltiazem with an alpha-antagonist should be considered only with the strict monitoring of the blood pressure.
Amiodarone, digoxin: Increased risk of bradycardia:
Caution is required when these are combined with diltiazem, particularly in elderly subjects and when high doses are used. Diltiazem hydrochloride may cause small increases in plasma levels of digoxin, requiring careful monitoring of AV conduction.
Beta-blockers: Possibility of rhythm disturbances (pronounced bradycardia, sinus arrest), sino-atrial and atrio-ventricular conduction disturbances and heart failure (synergistic effect). Patients with pre-existing conduction defects should not receive the combination of diltiazem and beta- blockers Such a combination must only be used under close clinical and ECG monitoring, particularly at the beginning of treatment.
Other hypertensive drugs:Enhanced antihypertensive effect may occur with concomitant use of other hypertensive drugs (e.g. beta-blockers, diuretics, ACE-inhibitors) or drugs that cause hypotension such as aldesleukin and antipsychotics.
Combination with beta-adrenoceptor blockers having significant "first pass" loss, e.g. propranolol, may require a decrease in their dose. Diltiazem will not protect against effects of withdrawal of beta-adrenoceptor blocking agents, nor the rebound effects seen with various antihypertensives.
Other antiarrhythmic agents:
Since diltiazem has antiarrhythmic properties, its concomitant prescription with other antiarrhythmic agents is not recommended (additive risk of increased cardiac adverse effects). This combination should only be used under close clinical and ECG monitoring.
Carbamazepine: Increase in circulating carbamazepine levels:
It is recommended that the plasma carbamazepine concentrations be assayed and that the dose should be adjusted if necessary.
Rifampicin: Risk of decrease of diltiazem plasma levels after initiating therapy with rifampicin:
The patient should be carefully monitored when initiating or discontinuing rifampicin treatment.
Anti-H2 agents (cimetidine, ranitidine): Increase in plasma diltiazem concentrations.
Patients currently receiving diltiazem therapy should be carefully monitored when initiating or discontinuing therapy with anti-H2 agents. An adjustment in diltiazem daily dose may be necessary.
Protease inhibitors (e.g. atazanavir, ritonavir): Increase in plasma diltiazem concentrations.
Ciclosporin: Increase in circulating ciclosporin levels:
It is recommended that the ciclosporin dose be reduced, renal function be monitored, circulating ciclosporin levels be assayed and that the dose should be adjusted during combined therapy and after its discontinuation.
General information to be taken into account:
Diltiazem has been continued in anaesthesia without problems, but the anaesthetist should be made aware that the patient is taking this medication because of the potential for synergism or interactions with other agents used in anaesthesia.
Due to the potential for additive effects, caution and careful titration are necessary in patients receiving diltiazem concomitantly with other agents known to affect cardiac contractility and/or conduction.
Diltiazem is metabolized by CYP3A4. A moderate (less than 2-fold) increase of diltiazem plasma concentration in cases of co-administration with a stronger CYP3A4 inhibitor has been documented. Diltiazem is also a CYP3A4 isoform inhibitor. Co-administration with other CYP3A4 substrates may result in an increase in plasma concentration of either co-administered drug (e.g. cilostazol, ivabradine, sirolimus, tacrolimus). Care should be exercised in patients

taking these drugs. Concomitant use of diltiazem with cilostazol should be avoided. Co-administration of diltiazem with a CYP3A4 inducer may result in a decrease of diltiazem plasma concentrations.
Concomitant use of diltiazem with ivabradine is contraindicated due to the additional heart rate lowering effect of diltiazem to ivabradine.
Barbiturates (phenobarbital, primidone) serum levels of diltiazem may be decreased by concomitant usage of CYP34A inducers.
Phenytoin: serum levels of diltiazem may be decreased by concomitant use of CYP34A inducers.
Benzodiazepines (midazolam, triazolam): Diltiazem significantly increases plasma concentrations of midazolam and triazolam and prolongs their half-life. Special care should be taken when prescribing short-acting benzodiazepines metabolised by the CYP3A4 pathway in patients using diltiazem.
Diltiazem may increase bioavailability of tricyclic antidepressants.
Corticosteroids (methylprednisolone): Inhibition of methylprednisolone metabolism (CYP3A4) and inhibition of P-glycoprotein: The patient should be monitored when initiating methylprednisolone treatment. An adjustment in the dose of methylprednisolone may be necessary.
Statins (simvastatin, atorvastatin, lovastatin): Diltiazem is an inhibitor of CYP3A4 and has been shown to significantly increase the AUC of some statins. The risk of myopathy and rhabdomyolysis due to statins metabolised by CYP3A4 may be increased with concomitant use of diltiazem. When possible, a non CYP3A4-metabolised statin should be used together with diltiazem, otherwise close monitoring for signs and symptoms of a potential statin toxicity is required.
Diltiazem tablets should not be taken at the same time as alcohol, as it may increase the rate of release of diltiazem from the sustained release preparation. In addition, the combination of alcohol and diltiazem may have an additive vasodilatory effect.

UNDESIRABLE EFFECTS
The following frequencies are the basis for assessing undesirable effects:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

	Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders					Thrombocytopenia
Immune system disorders			Hypersensitivity		
Psychiatric disorders			Nervousness, insomnia		Mood changes (including depression)
Nervous system disorders		Headache, dizziness			Extrapyramidal syndrome

Cardiac disorders		Atrioventricular block (may be of first, second or third degree; bundle branch block may occur), palpitations	Bradycardia		Sinoatrial block, congestive heart failure
Vascular disorders		Flushing	Orthostatic hypotension		Vasculitis (including leukocytoclastic vasculitis), hypotension
Gastrointestinal disorders		Constipation, dyspepsia, gastric pain, nausea	Vomiting, diarrhoea	Dry mouth	Gingival hyperplasia
Hepatobiliary disorders			Hepatic enzymes increase (AST, ALT, LDH, ALP increase)		Hepatitis
Skin and subcutaneous tissue disorders		Erythema, pruritus		Urticaria	Photosensitivity (including lichenoid keratosis at sun exposed skin areas), angioneurotic oedema, rash, erythema multiforme (including Steven-Johnson's syndrome and toxic epidermal necrolysis), hyperhidrosis, exfoliative dermatitis, acute generalized exanthematous pustulosis, desquamative erythema with or without fever, allergic dermatitis
Reproductive system and breast disorders					Gynaecomastia
General disorders and administration site conditions	Peripheral oedema	Malaise, fatigue			

OVERDOSE

Symptoms

The clinical effects of acute overdose can involve pronounced hypotension possibly leading to collapse, sinus bradycardia with or without isorhythmic dissociation, and atrioventricular conduction disturbances. It is recommended that patients with suspected overdose should be placed under observation in a coronary care unit.

Most patients suffering from overdosage of diltiazem become hypotensive within 8 hours of ingestion. With bradycardia and first to third degree atrioventricular block also developing, cardiac arrest may ensue. Hyperglycaemia is also a recognised complication. The elimination half-life of diltiazem after overdosage is estimated to be about 5.5-10.2 hours.

Management

Treatment, in a hospital setting, will include gastric lavage with administration of activated charcoal to reduce diltiazem absorption and/or osmotic diuresis. Conduction disturbances may be managed by temporary cardiac pacing. Proposed corrective treatments: Hypotension should be corrected with plasma expanders, vasopressors, glucagon, calcium gluconate infusion and inotropic agents (e.g. dopamine, dobutamine or isoprenaline). Symptomatic bradycardia and high grade AV block may respond to atropine, isoprenaline or occasionally cardiac pacing which may be useful if cardiac standstill occurs.

Diltiazem tablets are sustained release and effects may be slow in onset and extended, therefore, monitoring should be carried out for longer periods than following overdose with immediate-release dosage forms.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blockers with direct cardiac effects: ATC code: C08DB01

Diltiazem hydrochloride is a calcium-channel blocking agent. It is a peripheral and coronary vasodilator with some negative inotropic activity. Diltiazem inhibits cardiac conduction particularly at the sino-atrial and atrioventricular nodes. It is used in the management of classical and vasospastic angina pectoris and it is also used in the treatment of essential hypertension.

Pharmacokinetic properties

Absorption

Diltiazem is rapidly and almost completely absorbed from the gastro-intestinal tract following oral administration, but undergoes extensive first-pass hepatic metabolism. The bioavailability has been reported to be about 40%, although there is considerable inter-individual variation in plasma concentrations.

Distribution

Diltiazem is about 80% bound to plasma proteins.

Biotransformation

It is extensively metabolised in the liver; one of the metabolites, desacetyl diltiazem has been reported to have 25 to 50% of the activity of the parent compound. The half-life is reported to be about 3 to 4 hours.

Elimination
Approximately 60% of the dose is excreted in the bile and 35 to 40% in the urine, and 2 to 4% as unchanged diltiazem.
The extended-release formulation is designed for twice daily dosage.

Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the prescribing information.

EXPIRY DATE
Do not use later than the date of expiry.

PACKAGING INFORMATION
DILZEM - SR is available in blister pack of 10 tablets.

STORAGE AND HANDLING INSTRUCTIONS
Store at a temperature not exceeding 30°C, protected from light and moisture.

MARKETED BY


TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

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