

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

BI-CARZEM SR 120 mg prolonged release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 120 mg diltiazem hydrochloride.

Excipients with known effect: Each capsule contains 50 mg of sucrose

For the full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsule, hard (capsule)

Size S1 opaque pink and orange hard gelatine capsule containing diltiazem hydrochloride in sustained release sugar beads.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of angina pectoris

The treatment of mild to moderate hypertension

4.2 Posology and method of administration

Posology

Patients should be advised that the capsule membrane may pass through the gastro-intestinal tract unchanged.

BI-CARZEM SR (diltiazem hydrochloride) is available in a range of presentations to enable dosage to be adjusted to meet the individual requirements of the patient. Careful titration of the dose should be considered where appropriate, as individual patient response may vary. When changing from one type of BI-CARZEM SR formulation to another it may be necessary to adjust the dosage until a satisfactory response is obtained. To ensure

consistency of response once established, particularly in the sustained release formulations, BI-CARZEM SR 90 mg and 120 mg should continue to be prescribed by brand name.

Adults

Angina and hypertension:

The usual starting dose is one capsule (90 mg or 120 mg) twice daily. Patient responses may vary and dosage requirements can differ significantly between individual patients. Higher divided doses up to 480 mg/day have been used with benefit in some angina patients especially in unstable angina. Doses of 360 mg/day may be required to provide adequate BP control in hypertensive patients.

Elderly and patients with impaired hepatic or renal function

Heart rate should be monitored in these patients and if it falls below 50 beats per minute the dose should not be increased.

Angina:

The recommended starting dose is one 60 mg capsule twice daily. This dose may be increased to one 90 mg or 120 mg capsule twice daily.

Hypertension:

The starting dose should be one 120 mg capsule daily. Dose adjustment to one 90 mg or one 120 mg capsule twice daily may be required.

Paediatric population

Safety and efficacy in children have not been established. Therefore, diltiazem is not recommended for use in children

Method of administration

Oral use. The capsule should be swallowed whole with a little water and without chewing or crushing.

4.3 Contraindications

- Hypersensitivity to diltiazem or to any of the excipients listed in section 6.1.
- Sick sinus syndrome, 2nd or 3rd degree AV block in patients without a functioning pacemaker.
- Severe bradycardia (less than 50 beats per minute).
- Left ventricular failure with pulmonary stasis.
- Lactation.
- Concurrent use with dantrolene infusion (see section 4.5).
- Combination with ivabradine (see section 4.5).
- Concurrent use with lomitapide (see section 4.5).
- Concurrent use with asunaprevir (see section 4.5).

4.4 Special warnings and precautions for use

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Close observation is necessary in patients with reduced left ventricular function, bradycardia (risk of exacerbation) or with a 1st degree AV block or prolonged PR interval detected on the electrocardiogram (risk of exacerbation and rarely, of complete block).

Increase of plasma concentrations of diltiazem may be observed in the elderly and 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.

Cases of acute renal failure secondary to decreased renal perfusion have been reported in patients with existing cardiac disease especially reduced left ventricular function, severe bradycardia or severe hypotension. Careful monitoring of renal function is advised.

In the case of general anaesthesia, the anaesthetist must be informed that the patient is taking diltiazem. The depression of cardiac contractility, conductivity and automaticity as well as the vascular dilatation associated with anaesthetics may be potentiated by calcium channel blockers.

Treatment with diltiazem may be associated with mood changes, including depression (see sections 4.5 and 4.8). Early recognition of relevant symptoms is important, especially in predisposed patients. In such cases, drug discontinuation should be considered.

Diltiazem has an inhibitory effect on intestinal motility. Therefore, it should be used with caution in patients at risk of developing an intestinal obstruction.

Careful monitoring is necessary in patients with latent or manifest diabetes mellitus due to a possible increase in blood glucose.

The use of diltiazem may induce bronchospasm, including asthma aggravation, especially in patients with pre-existing bronchial hyper-reactivity. Cases have also been reported after dose increase. Patients should be monitored for signs and symptoms of respiratory impairment during diltiazem therapy.

Caution should be exercised when direct oral anti-coagulants (DOACs) are co-administered with diltiazem which is a moderate CYP3A4 and a weak P-gp inhibitor, particularly in patients at high risk of bleeding (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Combination Contraindicated for Safety Reasons

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 (see section 4.3).

Ivabradine

Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of diltiazem to ivabradine (see section 4.3).

Lomitapide

Diltiazem (a moderate CYP3A4 inhibitor) may increase lomitapide plasma concentrations through CYP3A4 inhibition leading to increased risk of elevations in liver enzymes (see section 4.3).

Asunaprevir

Diltiazem (a moderate CYP3A4 inhibitor) may increase asunaprevir plasma concentrations through CYP3A4 inhibition (see section 4.3).

Combinations Requiring Caution

Alpha-antagonists

Increased anti-hypertensive effects. Concomitant treatment with alpha-antagonists may produce or aggravate hypotension. The combination of diltiazem with an alpha antagonist should be considered only with strict monitoring of blood pressure.

Beta-blockers

Possibility of rhythm disturbances (pronounced bradycardia, sinus arrest), sino-atrial and atrio-ventricular conduction disturbances and heart failure (synergistic effect).

Such a combination must only be used under close clinical and ECG monitoring, particularly at the beginning of treatment.

An increased risk of depression has been reported when diltiazem is co-administered with beta-blockers (see section 4.8).

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.

Antiarrhythmic agents

Since diltiazem has antiarrhythmic properties, its concomitant prescription with other antiarrhythmic agents is not recommended due to the risk of increased cardiac adverse effects due to an additive effect. This combination should only be used under close clinical and ECG monitoring.

Nitrate derivatives

Increased hypotensive effects and faintness (additive vasodilating effects). In all patients treated with calcium antagonists, the prescription of nitrate derivatives should only be carried out at gradually increasing doses.

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.

Phenytoin

When co-administered with phenytoin, diltiazem may increase phenytoin plasma concentration.

It is recommended that the phenytoin plasma concentrations be monitored

X-Ray Contrast Media

Cardiovascular effects of an intravenous bolus of an ionic X-ray contrast media, such as hypotension, may be increased in patients treated with diltiazem.

Special caution is required in patients who concomitantly receive diltiazem and X-ray contrast media.

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.

Theophylline

Increase in circulating theophylline levels.

Anti-H₂ agents (cimetidine and 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.

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.

Lithium

Risk of increase in lithium-induced neurotoxicity.

Antiplatelet drugs

In a pharmacodynamic study, diltiazem was shown to inhibit platelet aggregation. Although the clinical significance of this finding is unknown,

potential additive effects when used with antiplatelet drugs should be considered.

Combinations to be Taken into Account

Diltiazem is metabolised 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. Grapefruit juice may increase diltiazem exposure (1.2-fold). Patients who consume grapefruit juice should be monitored for increased adverse effects of diltiazem. Grapefruit juice should be avoided if an interaction is suspected. 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. Co-administration of diltiazem with a CYP3A4 inducer may result in a decrease of diltiazem plasma concentrations.

Statins

Diltiazem is an inhibitor of CYP3A4 and has been shown to significantly increase the AUC of some statins. The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with statins metabolised by CYP3A4 (e.g. atorvastatin, fluvastatin, and simvastatin). An adjustment of the dose of statin may be necessary (see also product information of the relevant statin). When possible, it is recommended to use a statin not metabolised by CYP3A4 (e.g. pravastatin) with diltiazem.

Cilostazol

Inhibition of cilostazol metabolism (CYP3A4). Diltiazem has been shown to increase cilostazol exposure and to enhance its pharmacological activity.

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.

Corticosteroids (methylprednisolone)

Diltiazem can increase methylprednisolone levels (through inhibition of CYP3A4 and possible inhibition of P-glycoprotein). The patient should be monitored when initiating methylprednisolone treatment. An adjustment to the dose of methylprednisolone may be necessary.

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter P-glycoprotein (P-gp). Diltiazem is known to inhibit CYP3A and P-gp. When diltiazem and colchicine are administered together, inhibition of P-gp and/or CYP3A by diltiazem may lead to increased exposure to colchicine. Combined use is not recommended.

Direct oral anti-coagulants (DOACs)

Diltiazem which is a moderate CYP3A4 and weak P-gp inhibitor may increase the plasma concentration of DOACs when co-administered with diltiazem.

QT prolongation

Diltiazem may lead to QT prolongation, when administered with drugs with potential/known for prolonging the QT interval. Co-administration of diltiazem with drugs known to prolong the QT interval must be based on a careful assessment of the potential risks and benefits of the treatment.

General Information to be Taken into Account

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.

4.6 Pregnancy and lactation

Pregnancy

There is very limited data from the use of diltiazem in pregnant patients. Diltiazem has been shown to have reproductive toxicity (see section 5.3) in certain animal species (rat, mice, rabbit). Diltiazem is therefore not recommended during pregnancy as well as in women of child-bearing potential not using effective contraception.

Breastfeeding

As this drug is excreted in breast milk, breast-feeding whilst taking diltiazem is contraindicated.

4.7 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.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1000$); very rare ($\leq 1/10,000$); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

	<i>Very common</i>	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>	<i>Not known</i>
Blood and lymphatic system disorders					Thrombocytopenia
Psychiatric disorders			Nervousness, insomnia		Mood changes (including depression)

	<i>Very common</i>	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>	<i>Not known</i>
Nervous system disorders		Headache, dizziness			Extrapyramidal syndrome
Respiratory, thoracic and mediastinal disorders					Bronchospasm (including asthma aggravation)
Cardiac disorders		Atrioventricular block (may be of first, second or third degree; bundle branch block may occur), palpitations	Bradycardia		Sinoatrial block, congestive heart failure, sinus arrest, cardiac arrest (asystole)
Vascular disorders		Flushing	Orthostatic hypotension		Vasculitis (including leukocytoclastic vasculitis)
Gastrointestinal disorders		Constipation, dyspepsia, gastric pain, nausea	Vomiting, diarrhoea	Dry mouth	Gingival hyperplasia
Metabolism and nutrition disorders					Hyperglycaemia
Hepatobiliary disorders			Hepatic enzymes increase (AST, ALT, LDH, ALP increase)		Hepatitis
Skin and subcutaneous tissue disorders		Erythema		Urticaria	Photosensitivity (including lichenoid keratosis at sun exposed skin areas), angioneurotic oedema, rash, erythema multiforme (including Steven-Johnson's syndrome and toxic epidermal necrolysis), sweating, exfoliative dermatitis, acute generalised exanthematous pustulosis, occasionally desquamative erythema with or without fever, Lupus-like syndrome, Lichenoid drug eruption
Reproductive system and breast disorders					Gynecomastia
General disorders and administration site conditions	Peripheral oedema	Malaise			

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The clinical effects of acute overdose can involve pronounced hypotension leading to collapse and acute kidney injury, sinus bradycardia with or without isorhythmic dissociation, sinus arrest, atrioventricular conduction disturbances and cardiac arrest.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of diltiazem overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and required ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment, under hospital supervision, will include gastric lavage, osmotic diuresis. Conduction disturbances may be managed by temporary cardiac pacing.

Proposed corrective treatments: atropine, vasopressors, inotropic agents, glucagon and calcium gluconate infusion.

There is a possibility of renal impairment in patients following diltiazem overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium Channel Blockers; Benzothiazepine derivatives, ATC Code: C08D B01

BI-CARZEM SR is a calcium antagonist. It restricts the slow channel entry of calcium into the cell and so reduces the liberation of calcium from stores in the sarcoplasmic reticulum. This results in a reduction of the amount of available intracellular calcium reducing myocardial oxygen consumption. It increases exercise capacity and improves all indices of myocardial ischaemia in the angina patient. Diltiazem relaxes large and small coronary arteries and relieves the spasm of vasospastic (Prinzmetal's) angina and the response to catecholamines but has little effect on the peripheral vasculature. There is therefore no possibility of reflex tachycardia. A small reduction in heart rate

occurs which is accompanied by an increase in cardiac output, improved myocardial perfusion and reduction of ventricular work. In animal studies, Diltiazem protects the myocardium against the effects of ischaemia and reduces the damage produced by excessive entry of calcium into the myocardial cell during reperfusion.

5.2 Pharmacokinetic properties

Diltiazem is well absorbed (90%) in healthy volunteers following oral administration.

These formulations of diltiazem hydrochloride provide prolonged absorption of the active ingredient. Peak plasma concentrations occur between 4 and 8 hours post-dose.

Bioavailability of this formulation of diltiazem is approximately 90% of that of the conventional tablet. The mean apparent plasma half-life is 7 - 8 hours.

Diltiazem is 80 to 85 % bound to plasma proteins. It is extensively metabolised by the liver.

The major circulating metabolite, N-monodesmethyl diltiazem accounts for approximately 35% of the circulating diltiazem.

Less than 5% of diltiazem is excreted unchanged in the urine.

During long term administration to any one patient, plasma concentrations of diltiazem remain constant.

Mean plasma concentrations in elderly subjects and patients with renal and hepatic insufficiency are higher than in young subjects.

Diltiazem and its metabolites are poorly dialysed.

Twice daily formulations of diltiazem have been shown to have different pharmacokinetic profiles and therefore it is not advised to substitute different brands for one another.

5.3 Preclinical safety data

Pregnancy: 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 (480mg q.d. or 8mg/kg q.d. for a 60-kg patient) resulted in embryo and foetal lethality. These studies revealed, in one species or another, a propensity to cause foetal abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights, pup survival, as well as prolonged delivery times and an increased incidence of stillbirths.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres (75% sucrose; 25% corn starch)

Povidone

Methacrylic acid copolymer

Ethylcellulose

Diethyl phthalate

Talc

Hard gelatin capsules:

containing E171 (Titanium dioxide), E172 (Red iron oxide, Yellow iron oxide)

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store below 25° C in a dry place away from heat. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

- PVC/aluminium foil blister strips containing 56 capsules
- High density, white polyethylene “tablet containers” with white polypropylene screw caps containing 100 capsules.

Both containers are enclosed in outer cardboard cartons, which also contain a patient information leaflet.

Not all packs sizes or pack types may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Ltd,
220 Butterfield
Great Marlings
Luton
LU2 8DL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 11311/0470

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

Date of first authorisation: 28/05/2010

10 DATE OF REVISION OF THE TEXT

08/05/2026