Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Adizem-SR 90 mg Prolonged Release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 90 mg diltiazem hydrochloride.

Excipients: also contains sucrose 18.26 mg per capsule.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsules, hard.

Size 3, hard gelatin, capsules with an opaque white body and an opaque white cap, printed '90 mg'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the management of stable angina pectoris.
In the management of mild to moderate hypertension.

ADIZEM-SR capsules are indicated for use in adults only.

4.2 Posology and method of administration

Posology

Adults:
The usual initial dose is 90 mg twice daily. Dosage may be increased gradually to 120 mg twice daily if required, or 180 mg twice daily.

Elderly and patients with impaired renal or hepatic function
In the elderly dosage should commence at the lowest level of 90 mg twice daily and be increased very slowly.

Dosage adjustments are not necessary in the presence of renal dysfunction.

Paediatric population
Not recommended for use in children.

Route of administration
Oral.

To be taken at 12 hour intervals.

Dosage may be taken with or without food, and should be swallowed whole and not chewed.

Adizem-SR should not be taken at the same time as an alcoholic beverage (see section 4.5).

4.3 Contraindications

Patients with severe bradycardia (less than 40 beats per minute), second or third degree heart block, or sick sinus syndrome, decompensated cardiac failure or left ventricular failure with pulmonary congestion.

Concurrent use with dantrolene infusion due to the risk of ventricular fibrillation (see section 4.5).

Concurrent use with lomitapide (see section 4.5).

Pregnant women or women of child bearing potential.

Hypersensitivity to diltiazem or to any of the excipients.

4.4 Special warnings and precautions for use

Patients with bradycardia (risk of exacerbation), first degree AV block or a prolonged PR interval should be observed closely. Diltiazem should be used with caution in patients with reduced left ventricular function.

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.

Diltiazem is considered unsafe in patients with acute porphyria.

Isolated cases of moderate and transient increased liver transaminases have been observed at the start of treatment. Isolated cases of clinical hepatitis have been reported which resolved when diltiazem was withdrawn.

The use of diltiazem in diabetic patients may require adjustment of their control.

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 of developing an intestinal obstruction.

Capsule residues from prolonged release formulations of the product may pass into the patient's stools; however, this finding has no clinical relevance.

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

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 (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).

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 antihypertensive drugs: Enhanced antihypertensive effect may occur with concomitant use of other antihypertensive drugs (e.g. beta-blockers, diuretics, ACE-inhibitors) or drugs that cause hypotension such as aldesleukin and antipsychotics.

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-H_2 agents (e.g. ranitidine): Increase in plasma diltiazem concentrations. Patients currently receiving diltiazem therapy should be carefully monitored when initiating or discontinuing therapy with anti-H_2 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.

Direct Oral Anticoagulants (DOACs):
Diltiazem (an inhibitor of CYP3A4 and P-gp) may increase the plasma concentrations of DOACs (i.e. apixaban, rivaroxaban, dabigatran) metabolized through these pathways with resulting increases in pharmacodynamic effects such as bleeding risk.

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.

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. 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 and ivabradine should be avoided.

Co-administration of diltiazem with a CYP3A4 inducer may result in a decrease of diltiazem plasma concentrations.

Barbiturates (phenobarbital, primidone): serum levels of diltiazem may be decreased by concomitant usage of CYP3A4 inducers.

Phenytoin: serum levels of diltiazem may be decreased by concomitant usage of CYP3A4 inducers. Diltiazem may increase serum levels of phenytoin.

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): 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.

Adizem-SR should not be taken at the same time as alcohol, as it may increase the release of diltiazem from the prolonged release preparation. In addition the combination of alcohol and diltiazem may have an additive vasodilatory effect.

4.6 Fertility, 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 in certain animal species (rat, mice, rabbit - see section 5.3). Diltiazem is contraindicated during pregnancy (see section 4.3), 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.

Fertility
In animal studies, Diltiazem hydrochloride produced reversible effects on spermatogenesis (see section 5.3).

4.7 Effects on ability to drive and use machines

Diltiazem has been reported to cause adverse reactions such as dizziness (common) and malaise (common), which may impair patients' ability to drive or operate machinery to a varying extent depending on the dosage and individual susceptibility. However, no studies have been performed. Therefore, patients should not drive or operate machinery if affected.

4.8 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		
Metabolism and nutrition disorders					Anorexia

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 Stevens-Johnson syndrome and toxic epidermal necrolysis), hyperhidrosis, exfoliative dermatitis, acute generalised exanthematous pustulosis, occasionally desquamative erythema with or without fever, allergic dermatitis, lupus-like syndrome
Reproductive system and breast disorders					Gynecomastia
General disorders and administration site conditions	Peripheral oedema	Malaise, fatigue			

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 HPRA Pharmacovigilance at www.hpra.ie.

4.9 Overdose

The clinical effects of acute overdose can involve pronounced hypotension possibly leading to collapse, acute kidney injury, sinus bradycardia with or without isorhythmic dissociation and atrioventricular conduction disturbances. Hyperglycaemiais also a recognised complication.
Treatment in a hospital setting with include gastric lavage and/or osmotic diuresis. Conduction disturbances may be managed by temporary cardiac pacing.

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

Symptomatic bradycardia and high grade atrioventricular block may respond to atropine and isoprenaline.

The formulation employs a prolonged release system which will continue to release diltiazem for some hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blocker with direct cardiac effects.
ATC Code: C08D B01

Diltiazem is a calcium antagonist. It restricts the slow channel entry of calcium ions into the cell and so reduces the liberation of calcium from stores in the sarcoplasmic reticulum.

This results in a reduction in the amount of available intra-cellular calcium and consequently a (1) reduction of myocardial oxygen consumption, (2) dilation of small and large coronary arteries, (3) mild peripheral vasodilation, (4) negative dromotropic effects, (5) reflex positive chronotropic and inotropic effects due to reflex sympathetic activity are partially inhibited and result in a slight reduction or no change in heart rate.

The antihypertensive effect is due to the reduction in peripheral vascular resistance.

The antianginal effect is due to a reduction in the peripheral resistance, thereby decreasing the after-load, whilst a reduction in the vasomotor tone of the coronary circulation maintains the coronary blood flow. Cardiac contractility and ventricular ejection fraction are unchanged. Diltiazem increases exercise capacity and improves indices of myocardial ischaemia in the angina patient. Diltiazem relieves the spasm of vasospastic (Prinzmetal) angina.

5.2 Pharmacokinetic properties

Absorption
An oral dose of diltiazem is almost completely absorbed. Despite this, diltiazem has a low bioavailability of approximately 40% owing to hepatic first-pass metabolism.

Biotransformation
Diltiazem is extensively metabolised by the liver. The desacetyl metabolite is considered to be approximately 25% to 50% as potent as a coronary vasodilator as diltiazem and is present in plasma at concentrations of 10% to 20% of parent.

Elimination
The mean elimination half life of diltiazem is around 4 hours, but this is extended from prolonged-release formulations. Mean plasma concentrations in elderly subjects and patients with renal and hepatic insufficiency are higher than in young subjects.

Linearity/non-linearity
This process of first-pass metabolism process is saturable at higher doses of the drug. This results in a non-linear accumulation and higher blood concentrations at steady state than would be anticipated from those following a single dose. From modified-release preparations, the prolonged delivery of diltiazem can significantly reduce the degree of non-linearity associated with conventional formulations.

5.3 Preclinical safety data

Genotoxicity and Carcinogenicity
Diltiazem was not genotoxic when tested in vitro in two bacterial mutation tests with and without metabolic activation, and in two clastogenicity assays.

Diltiazem was not carcinogenic in two long term carcinogenicity studies, in rats and mice.

Reproductive and developmental toxicity
Diltiazem was toxic to the developing embryo in studies in mice, rats and rabbits when dosed to the mother at critical stages during organ development. Skeletal malformations occurred in the limbs, tail and ribs of all three species.

Diltiazem had an adverse effect upon male fertility in rats, with decreases in sperm count, sperm motility and epididymal weight, although these effects were reversible on cessation of dosing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Maize Starch
Povidone
Ethylcellulose
Dibutyl sebacate
Talc
Sodium laurilsulfate
Cetyl alcohol

Capsule shell
Titanium dioxide (E171)
Gelatin
Iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium/PVC blister packs (28, 30, 56 and 60 capsules).
Medical sample packs up to 8 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mundipharma Pharmaceuticals Limited
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8 MARKETING AUTHORISATION NUMBER

PA1688/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 16 December 2009

10 DATE OF REVISION OF THE TEXT

May 2025