SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Slozem 240mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Slozem 240mg Capsules each contain 240mg diltiazem hydrochloride

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsule, hard.

Slozem 240mg Capsules have a natural transparent cap with a scarlet opaque body and contain white-grey to light yellow approximately spherical pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate hypertension. Angina pectoris.

4.2 Posology and method of administration

Posology

Adults

240mg once daily

Dosage titration in 60mg to 120mg steps at 2-weekly intervals may be required to obtain satisfactory clinical response (usually 240mg to 360mg daily will suffice). Dosage should be reduced in the presence of adverse reactions or if the pulse rate falls below 50 per minute.

Older people and patients with hepatic or renal impairment

Starting dose 120mg once daily.

Paediatric population

Not recommended

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
- Second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
- Severe bradycardia (below 40 bpm)
- Left ventricular failure with pulmonary congestion
- Concomitant use of dantrolene infusion (see section 4.5).
- Additionally, for the intravenous forms, patients known to have an accessory bypass (Wolf-Parkinson-White syndrome or short PR syndrome), and who develop atrial fibrillation or flutter, should not be administered intravenous diltiazem.
- Combination with ivabradine (see section 4.5)
- Concurrent use with lomitapide (see section 4.5)
- Concurrent use with asunaprevir (see section 4.5)
- Lactation

4.4 Special warnings and special precautions for use

Close observation and caution is necessary in patients with reduced left ventricular function, bradycardia (risk of exacerbation) or with first degree AV block or prolonged PR interval detected on the electrocardiogram (risk of exacerbation and rarely, of complete block).
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.
Prior to general anaesthesia, the anaesthesist 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. Early recognition of relevant symptoms is important, especially in predisposed patients. In such cases, drug discontinuation should be considered.

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.

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.

Sucrose
As Slozem contains sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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).

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 evaluation 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).

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. Care should be exercised in patients taking these drugs.

Alpha-antagonists
Increased antihypertensive effects. Concomitant treatment with alpha-antagonists such as prazosin 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, small increases in plasma levels of digoxin. Caution is required when these are combined with diltiazem, particularly in elderly subjects and when high doses are used.

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.

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.

Ciclosporin
Increase in circulating cyclosporin levels. It is recommended that the cyclosporin dose be reduced, renal function be monitored, circulating cyclosporin levels be assayed and that the dose should be adjusted during combined therapy and after its discontinuation.

Tricyclic antidepressants
Diltiazem increases plasma concentration of imipramine. Diltiazem possibly increases plasma concentration of tricyclic antidepressants.

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.

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.

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

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 metabolized by the CYP3A4 pathway in patients using diltiazem.

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
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 (e.g. atorvastatin, fluvastatin and simvastatin) may be increased with concomitant use of diltiazem. When possible, a non CYP3A4-metabolised statin (e.g. pravastatin) should be used together with diltiazem, otherwise close monitoring for signs and symptoms of a potential statin toxicity is required.

Oral administration of diltiazem can raise blood levels of drugs exclusively metabolised by the iso-enzyme CYP3A4 – this can lead to increased plasma levels for carbamazepine, tacrolimus, sirolimus, and erythromycin.

Grapefruit juice
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.

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

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 (teratogenic) in some animal species (rat, mice, rabbit). In the absence of adequate evidence of safety in human pregnancy, diltiazem is therefore not recommended during pregnancy as well as in women of child- bearing potential not using effective contraception.

Breast-feeding
Diltiazem hydrochloride is excreted in breast milk at low concentrations. One report suggests that concentrations in breast milk reach similar levels to those in serum. Breast-feeding while taking this drug is contra-indicated. If use of diltiazem is considered medically essential, an alternative method of infant feeding should be instituted.

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 (≥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).

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

	Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders					Thrombocytopenia
Metabolism and nutrition disorders					Hyperglycemia
Psychiatric disorders			Nervousness, insomnia		Mood changes (including depression)
Nervous system disorders		Headache, dizziness			Extrapyramidal syndrome. Drug-induced Parkinsonism
Cardiac disorders		Atrioventricular block (may be of first, second or third degree; bundle branch block may occur), palpitations	Bradycardia		Sinoatrial block, sinus arrest, congestive heart failure, cardiac arrest
Vascular disorders		Flushing	Orthostatic hypotension		Vasculitis (including leukocytoclastic vasculitis)
Respiratory, thoracic and mediastinal disorders					Bronchospasm (including asthma aggravation)
Gastrointestinal disorders		Constipation, dyspepsia, gastric pain,	Vomiting, diarrhea	Dry mouth	Gingival hyperplasia

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 generalized exanthematous pustulosis and hyperpigmentation in sun-exposed areas have also been reported
Reproductive system and breast disorders					Gynecomastia
General disorders and administration site conditions	Peripheraloedema	Malaise			

Hepatic enzymes increase (AST, ALT, LDH, ALP increase) typically observed at the start of the treatment.

Isolated cases of clinical hepatitis have been reported which resolved on cessation of therapy.
Skin reactions are generally mild and resolve on cessation of therapy.
The current literature suggests that the effects of vasodilation, particularly ankle oedema, are dose dependent and are more frequent in the elderly.

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 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

Signs and symptoms
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.

Hyperglycaemia may require treatment. Onset of symptoms may be delayed for several hours after ingestion and have been described after as little as 900mg diltiazem.

Treatment
Treatment in a hospital setting will include gastric lavage and/or osmotic diuresis

Observation in a coronary or intensive care unit is advisable if a substantial overdose has been ingested. Soon after ingestion, gastric lavage followed by activated charcoal may reduce absorption.
Profound hypotension requires plasma expanders, I V calcium gluconate and inotropic agents (e.g. dopamine, dobutamine or isoprenaline). Symptomatic bradycardia and heart block may respond to atropine, vasopressors, inotropic agents, isoprenaline, glucagon, calcium gluconate infusion or, if necessary, cardiac pacing. Slozem capsules are extended release capsules and effects may be slow in onset and prolonged.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers; Benzothdiazepine derivatives, ATC code: C08DB01

Diltiazem hydrochloride is a calcium antagonist. It selectively reduces calcium entry through voltage-dependent calcium channels into vascular smooth muscle cells and myocardial cells. This lowers the concentration of intracellular calcium which is available to active contractile proteins. In vascular tissue, diltiazem relaxes arterial smooth muscle, reducing systemic peripheral resistance and dilating the coronary arteries. In cardiac muscle diltiazem reduces contractility and slows the heart rate through its negative chronotropic and inotropic actions. Cardiac work

and oxygen demand can therefore be reduced and high blood pressure lowered without reflex tachycardia.

5.2 Pharmacokinetic properties

Diltiazem is effective in angina, protecting the heart against ischaemia, vasodilating coronary arteries and reducing myocardial oxygen requirements. It is well tolerated and does not generally give rise to side effects associated with peripheral vasodilation, nor cause significant myocardial depression.

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first- pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%.

Diltiazem in plasma is 80-85% protein bound. Plasma levels above 40-50ng/ml are associated with pharmacological activity.

Diltiazem is extensively metabolised by the liver, the plasma elimination half-life being on average 3-4.5 hours.

The two major active circulating metabolites, desacetyl-diltiazem and N-monodesmethyl diltiazem possess coronary artery vasodilatory activity equivalent to about 50% of that of diltiazem. Only 0.2 to 4% diltiazem is found unchanged in the urine.

The prolonged release pellets in this presentation usually achieve maximum plasma diltiazem levels six to eight hours after dosing and have an apparent plasma half-life of approximately 7 hours, allowing once daily dosing

The bioavailability of diltiazem from the Slozem formulation given once a day is equivalent to that obtained from a conventional release tablet given three times a day, when the same total daily dose is administered.

Data from studies in patients and healthy volunteers have also demonstrated that trough plasma levels (i.e. 24 hours post dosing) can be maintained within the minimum therapeutic range by appropriate dose titration.

Plasma concentrations in elderly patients and in hepatic failure are in general higher than in young subjects, due to an increase in apparent bioavailability. In renal failure, a reduction in dosage is only necessary as a function of the clinical response.

Diltiazem and its metabolites are poorly dialysed.

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 fetal lethality. These studies revealed, in one species or another, a propensity to cause fetal 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 increase incidence of stillbirths.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, sucrose, povidone, shellac, ethylcellulose, talc, gelatin, erythrosine (E127), indigo carmine (E132), titanium dioxide (E171) and black iron oxide (E172), shellac, propylene glycol.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

4, 28 or 56 capsules in PVC/PVDC/Aluminium blisters enclosed in a cardboard carton.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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