Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dilzem XL 240mg Prolonged-release Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Dilzem XL 240mg capsule contains diltiazem hydrochloride 240mg.

Excipients: Each capsule contains sucrose.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release capsules, hard

Product imported from Germany
White, hard gelatin capsules, printed with 'D240 mg' and containing roughly spherical white to off-white beads.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis and treatment of angina pectoris.

Treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Oral *use* only.

Adults:
Hypertension: The usual initial dose is one 180mg capsule per day (corresponding to 180mg of diltiazem hydrochloride). Depending upon clinical response the patient's dosage may be increased stepwise to 360mg/day if required.

Angina Pectoris: The usual initial dose is one 180mg capsule per day (corresponding to 180mg of diltiazem hydrochloride once daily). Depending upon clinical response the patient's dosage may be increased stepwise to 360mg/day if required.

Elderly patients and those with renal or hepatic impairment:
Dosage should commence at the lower level of 120mg once-daily and be increased slowly. Do not increase the dose if the heart rate falls below 50 beats per minute.

Children:
This product is not recommended for use in children.

4.3 Contraindications

- Use in women of child-bearing potential.
- Concomitant administration of dantrolene infusion due to the risk of ventricular fibrillation.
- Shock.

- Acute cardiac infarct with complications (bradycardia, severe hypotension, left heart insufficiency).
- Bradycardia (pulse rate, at rest, of less than 50 per minute), hypotension (less than 90mm Hg systole), second or third degree heart block or sick sinus syndrome, except in the presence of a functioning ventricular pacemaker.
- Atrial fibrillation/flutter and simultaneous presence of a WPW (Wolff- Parkinson-White) syndrome (increased risk of triggering a ventricular tachycardia).
- Manifest myocardial insufficiency.
- Left ventricular failure with stasis.
- Hypersensitivity to diltiazem or any of the excipients.

4.4 Special warnings and precautions for use

- Capsules should not be sucked or chewed.
- The use of diltiazem hydrochloride in diabetic patients may require adjustment of their control.
- Prior to general anaesthesia, the anaesthetist must be informed of ongoing diltiazem treatment (see section 4.5).
- 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.
- The product should be used with caution in patients with hepatic dysfunction. Abnormalities of liver function may occur during therapy. Very occasional reports of abnormal liver function have been received; these reactions have been reversible upon discontinuation of therapy.
- First degree AV block or prolonged PR interval. DILZEM 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 (see section 4.5 interactions section for information concerning beta-blockers and digitalis).
- Close observation is necessary in patients with reduced left ventricular function and bradycardia (risk of exacerbation) (see section 4.3).
- Diltiazem is not recommended for use in patients with acute porphyria unless other safer alternatives are not available.
- There have been literature reports of calcium-channel blockers, including diltiazem, exacerbating muscle weakness in patients with myasthenia gravis, with potentially clinically significant consequences such as respiratory failure.
- 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.
- Residues from slow release formulations of the product may pass into the patient's stools; however, this finding has no clinical relevance.
- Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression.
- Owing to the presence of sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals.

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).

Concomitant use requiring caution:
Anaesthetics: Anaesthetists should be warned that a patient is taking diltiazem. The depression of cardiac contractility, conductivity and automaticity as well as the vascular dilation associated with anaesthetics may be potentiated by calcium channel blockers.
When used concomitantly, anaesthetics and calcium channel blockers should be titrated carefully.

Statins: Due to metabolic interaction via CYP3A4, treatment with HMG CoA reductase inhibitors such as simvastatin, atorvastatin or lovastatin, in combination with diltiazem, should be started at the lowest possible dose and titrated upwards. If a patient is already taking an HMG CoA reductase inhibitor a reduction in that dose should be considered and retitration against serum cholesterol concentrations carried out. Patient monitoring for signs and symptoms of rhabdomyolysis and myopathy is recommended. CYP3A4 is not involved in the metabolism of fluvastatin, pravastatin and rosuvastatin.

Lithium: Risk of increase in lithium-induced neurotoxicity.

Warfarin: There have been reports in the literature of diltiazem interactions with warfarin.

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. It is recommended that the plasma theophylline concentrations be assayed and that the dose should be adjusted if necessary.

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.

Amiodarone in combination with diltiazem may also cause AV block and myocardial depression.
It is recommended that the plasma digoxin concentrations be assayed and that the dose should be adjusted if necessary.

Cardiac glycosides may cause a greater degree of AV blocking, reduce the heart rate or induce a hypotensive effect.

Beta-blockers: Possibility of rhythm disturbances (pronounced bradycardia, sinus arrest), sino-atrial and atrioventricular 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.

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.

Diuretics, ACE inhibitors or other antihypertensive agents:
Patients should be carefully monitored when taking diltiazem concomitantly with these agents.

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.

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 Pglycoprotein: The patient should be monitored when initiating methylprednisolone treatment. An adjustment in the dose of methylprednisolone may be necessary.

Clopidogrel: A literature report has suggested an interaction between clopidogrel and calcium channel blockers (including diltiazem) which may reduce the effectiveness of clopidogrel. However the clinical significance of this interaction is unknown.

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.

Simultaneous administration with enzyme inducers such as rifampicin and phenobarbital may lead to reduced activity of diltiazem.

Antihypertensives: Diltiazem hydrochloride should only be administered with great care to patients receiving concurrent treatment with antihypertensives or other hypotensive agents including halogenated anaesthetics or drugs with moderate protein binding.

Diltiazem hydrochloride will not protect against effects of withdrawal of ß-adrenoceptor blocking agents, nor the rebound effects seen with various antihypertensives.

There may be an additive effect when diltiazem is used with drugs which may induce bradycardia or with other antihypertensives.

4.6 Fertility, pregnancy and lactation

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 should not be used during pregnancy, as well as in women of child bearing potential not using effective contraception (see section 4.3).
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.

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, lymphadenopathy, eosinophilia
Psychiatric disorders			Nervousness, insomnia		Hallucinations, mood changes (including depression), personality change
Nervous system disorders		Headache, dizziness			Extrapyramidal syndrome, gait abnormality, syncope, amnesia, paraesthesia, somnolence, tremor, myasthenia gravis aggravated
Cardiac disorders		Atrioventricular block (may be of first, second or third degree; bundle branch block may occur), palpitations	Bradycardia		Sinoatrial block, congestive heart failure, arrhythmia, angina
Vascular disorders		Flushing	Orthostatic hypotension		Vasculitis (including leukocytoclastic vasculitis), hypotension
Gastrointestinal disorders		Constipation, dyspepsia, gastric pain, nausea	Vomiting, diarrhoea	Dry mouth	Gingival hyperplasia, gingivitis
Hepatobiliary disorders					Hepatitis
Skin and subcutaneous tissue disorders		Erythema		Urticaria	Allergic skin reactions, 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, occasionally desquamative erythema with or without fever, petechiae, pruritus
Reproductive system and breast disorders					Gynecomastia, sexual difficulties
General disorders and administration site conditions	Peripheral oedema	Oedema, asthenia, malaise			
Eye disorders					Amblyopia, eye irritation
Investigations			Hepatic enzymes increase (AST, ALT, LDH, ALP increase)		CK elevation, weight increase , bleeding time prolonged
Respiratory, thoracic and mediastinal disorders					Dyspnoea, epistaxis, nasal congestion
Metabolism and nutrition disorders					Anorexia, hyperglycaemia
Renal and urinary disorders					Nocturia, polyuria
Musculoskeletal and connective tissue disorders					Osteoarticular pain, muscle pain, muscle weakness

Ear and labyrinth disorders					Tinnitus

4.9 Overdose

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.

Experience of overdosage in man is limited but cases of spontaneous recovery have been reported. However, it is recommended that patients with suspected overdose, should be placed under observation in a coronary care unit with facilities available for treatment of any possible hypotension and conduction disturbances that may occur.

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. If a patient presents early after overdose, gastric lavage should be performed and activated charcoal administered to reduce diltiazem absorption.

Hypotension should be corrected with plasma expanders, intravenous calcium gluconate and ionotropic agents (dopamine, dobutamine, 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Diltiazem is a calcium channel blocking agent. The precise mechanism of action, which is dose dependent, is unknown, but calcium channel blockers act predominantly at specific voltage-sensitive ion-selective channels, "slow calcium channels" of cardiac and smooth muscle cells whose excitation-contraction coupling requires an inward displacement of calcium.

Calcium channel blockers are vasodilators whose antihypertensive effects are associated with decreases in peripheral resistance leading to a drop in blood pressure.
The antianginal effects of diltiazem hydrochloride are probably related to its coronary artery vasodilating effect and to its haemodynamic effects.

The formulation is presented as a sustained release preparation for twice daily administration.

5.2 Pharmacokinetic properties

a) General Characteristics
Absorption: Capsules seem to have a similar bioavailability to tablets (30-40%), with peak concentrations for the sustained release product after 8-11 hours compared with 1-2 hours after the conventional release product. The relatively low bioavailability is due to first pass metabolism in the liver to an active metabolite.

Distribution: Diltiazem hydrochloride is lipophilic and has a high volume of distribution.

Typical study results are in the range of 3-8 litres/kg. Protein binding is about 80% and is not concentration dependent at levels likely to be found clinically. Protein binding does not appear to be influenced by phenylbutazone, warfarin, propanolol, salicylic acid or digoxin.

Metabolism: Diltiazem hydrochloride is extensively metabolised in the liver. N-monodesmethyl diltiazem is the predominant metabolite followed quantitatively by the desacetyl metabolite, which has some pharmacological activity.

The efficacy of the metabolites, desacetyl diltiazem and N-monodesmethyl diltiazem is 25-50% and about 20% respectively of that of diltiazem. In liver function disorders delayed metabolism in the liver is likely. These metabolites are converted to conjugates, generally the glucuronide or the sulphate.

Elimination: Diltiazem is excreted in the form of its metabolites (about 35%) and in the non-metabolised form (about 2-4%) via the kidneys while about 60% is excreted via the faeces. The average elimination half life period for diltiazem is 6-8 hours but may vary between 2 and 11 hours. Although the elimination half life period is not changed after repeated oral administration, diltiazem and also the desacetyl metabolite show a slight accumulation in the plasma.

b) Characteristics in Patients
Decreased first-pass metabolism in the elderly tends to result in increased plasma concentrations of calcium antagonists but no major changes have been found with diltiazem. Renal impairment did not cause significant changes in diltiazem pharmacokinetics. Plasma concentrations of diltiazem also tend to be higher in hepatic cirrhosis due to impaired oxidative metabolism.

5.3 Preclinical safety data

Chronic toxicity studies in rats revealed no remarkable changes at oral doses up to 125 mg/kg/day although there was a 60% mortality at this dose. In dogs chronically treated with oral doses of 20mg/kg/day, transient rises in SGPT were observed. Embryotoxicity has been reported in mice, rats and rabbits following i.p. administration of diltiazem. Main types of malformations included limb and tail defects with a small number of vertebral and rib deformities also noted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fumaric acid
Talc
Povidone
Sucrose and maize starch
Ammonio methacrylate copolymer Type A
Ammonio methacrylate copolymer Type B
Gelatin
Titanium dioxide (E171)
Black iron oxide (E172)

Shellac
Propylene Glycol (E1520)
Purifield water

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

The shelf life expiry date for this product shall be the date shown on the blister and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package to protect from light and moisture.

6.5 Nature and contents of container

PVC/PVDC Blister Pack: containing 30 capsules.

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 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1562/26/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th November 2010

10 DATE OF REVISION OF THE TEXT

February 2012