# 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.

Excipient with known effect

Sucrose 50.4mg in each XL 240mg capsule.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Prolonged-release capsule, hard.

White, hard gelatin capsules, printed with e240 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

Posology

*Adults*

Hypertension: The usual initial dose is one 180mg capsule per day (corresponding to 180mg of diltiazem hydrochloride once daily). Depending upon the clinical response the 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 the clinical response the 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.

*Paediatric population*

*Children*

This product is not recommended for use in children.

Method of administration

Oral use only.

## 4.3 Contraindications

Hypersensitivity to diltiazem or to any of the excipients listed in section 6.1

- Use during pregnancy, in women of child-bearing potential and lactation (see section 4.6)
- Concomitant administration of dantrolene infusion due to the risk of ventricular fibrillation (see section 4.5).
- Shock
- Acute cardiac infarct with complications (bradycardia, severe hypotension, left heart insufficiency)
- Severe bradycardia (less than 40 beats per minute)
- Bradycardia (pulse rate, at rest, of less than 50 bpm), hypotension (less than 90 mm 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 pulmonary congestion
- Combination with ivabradine (see section 4.5)

## 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.
- Plasma diltiazem concentrations can be increased 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
- Prior to general anaesthesia, the anaesthetist must be informed of ongoing diltiazem treatment (see section 4.5). The 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.
- 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. Diltiazem 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).

- Close observation is necessary in patients with reduced left ventricular function and bradycardia (risk of exacerbation) or with a 1st degree AV block detected on the electrocardiogram (risk of exacerbation and rarely of complete block) or prolonged PR interval (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 reports of calcium-channel blockers exacerbating muscle weakness in patients with myasthenia gravis. Diltiazem should be used with caution in such patients.
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- 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.
- Diltiazem does not affect the glucose or endogenous insulin responses to hypoglycaemia.
- 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).

Ivabradine

Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of diltiazem to ivabradine (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

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.

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 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 beta-blockers are co-administered with diltiazem.

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 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.

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.

**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.

Oral administration of diltiazem can raise the plasma concentration of drugs exclusively metabolised by CYP3A4. The concomitant therapy of diltiazem and such drugs may increase the risk of adverse reactions (e.g. muscular disorders with statins).

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 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 and rabbit). Diltiazem is therefore not recommended during pregnancy, as well as in women of child bearing potential not using effective contraception (see section 4.3).

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.

## 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

Tabulated list of adverse reactions

The frequencies of adverse reactions are ranked according to the following: *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 |

| | Very common | Common | Uncommon | Rare | Not known |
|---|---|---|---|---|---|
| *Cardiac disorders* | | Atrioventricular block (may be of first, second or third degree; bundle branch block may occur), palpitations | Bradycardia | | Sinoatrial block, development or aggravation of congestive heart failure, arrhythmia, angina |
| *Vascular disorders* | | Flushing | Orthostatic hypotension | | Vasculitis (including leukocytoclastic vasculitis), The manifestations of vasodilatation (headache, flushing and in particular oedema of the lower limbs) are dose-dependent and appear more frequent in elderly subjects and related to the pharmacological activity of the product, hypotension |
| *Gastrointestinal disorders* | | Constipation, dyspepsia, gastric pain, nausea | Vomiting, diarrhoea | Dry mouth | Gingival hyperplasia, gingivitis |
| *Hepatobiliary disorders* | | | Hepatic enzymes increase (AST, ALT, LDH, ALP increase) Moderate and transient elevation of liver transaminases have been observed at the start of treatment. | | Hepatitis |

| | Very common | Common | Uncommon | Rare | Not known |
|---|---|---|---|---|---|
| *Skin and subcutaneous tissue disorders* | | Erythema | | Urticaria | Allergic skin reactions, photosensitivity (including lichenoid keratosis at sun exposed skin areas) have been reported and recovering when the treatment is discontinued,, 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/fatigue, malaise | | | |
| *Eye disorders* | | | | | Amblyopia, eye irritation |
| *Investigations* | | | Hepatic enzymes increase (AST, ALT, LDH, ALP increase) | | CK elevation, weight increase |
| *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 |

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 website: 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 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. Conduction disturbances may be managed by temporary cardiac pacing. 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 under hospital supervision and activated charcoal administered to reduce diltiazem absorption.

Hypotension should be corrected with plasma expanders, intravenous calcium gluconate and inotropic agents (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.

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

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel Blocker, ATC code: C08D B01

Mechanism of action

Diltiazem is a calcium channel antagonist which restricts the entry of calcium ions into the cell through the slow voltage dependent channels and reduces the liberation of calcium from the endoplasmic reticulum. This results in a reduced amount of available intracellular calcium. The haemodynamic actions of diltiazem are:

- Peripheral and coronary vasodilatation.

- Decrease in myocardial oxygen consumption.

- Reduction of blood pressure particularly in hypertension.

- Increase in renal blood flow and urinary sodium excretion.

Diltiazem has pharmacologic actions similar to those of other calcium channel blocking agents such as nifedipine or verapamil. The principal physiologic action of diltiazem is to inhibit the transmembrane influx of extracellular calcium ions across the membranes of myocardial cells and vascular smooth muscle cells.

Calcium plays important roles in the excitation-contraction coupling processes of the heart and vascular smooth muscle cells and in the electrical discharge of the specialised conduction cells of the heart. The membranes of these cells contain numerous channels that carry a slow inward current and that are selective for calcium.

By inhibiting calcium influx, diltiazem inhibits the contractile processes of cardiac and vascular smooth muscle, thereby dilating the main coronary and systemic arteries. Dilation of systemic arteries by diltiazem results in a decrease in total peripheral resistance, a decrease in systemic blood pressure and a decrease in the afterload of the heart. The reduction in afterload, seen at rest and with exercise, and its resultant decrease in myocardial oxygen consumption are thought to be responsible for the beneficial effects of diltiazem in patients with chronic stable angina pectoris. In patients with prinzmetal variant angina, inhibition of spontaneous and ergonovine-induced coronary artery spasm by diltiazem results in increased myocardial oxygen delivery.

## 5.2 Pharmacokinetic properties

a) General Characteristics

Absorption

When taken orally diltiazem is almost completely absorbed. Despite this, the absolute bioavailability is 40% due to extensive first pass metabolism. Bioavailability is not affected by age. Diltiazem is 78-87% bound to plasma proteins but only 35-40% to albumin. The peak plasma concentration is reached in about three hours after single dose of diltiazem 90 mg CR tablets. The $C_{max}$ value was 50-65 ng/ml. Capsules seem to have a similar bioavailability to tablets (30-40%), with peak concentrations for the prolonged 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, propranolol, salicylic acid or digoxin.

Metabolism

Diltiazem hydrochloride is extensively metabolised in the liver by deacetylation and N-demethylation followed by O-demethylation or deacetylation. N-monodesmethyl diltiazem is the predominant metabolite followed quantitatively by the desacetyl metabolite, which has some hypotensive potency. 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. Diltiazem is mainly excreted as metabolites in the urine and faeces and only 1-3% of the dose is excreted as the parent compound in urine. 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 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 20 mg/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
Sugar spheres (containing sucrose and maize starch)
Ammonio methacrylate copolymer Type B
Ammonio methacrylate copolymer Type A

The capsule shell contains:
Gelatin
Titanium dioxide (E171)

The printing ink contains:
Shellac
Black iron oxide (E172)
Propylene glycol (E1520)

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

Two years from the date of manufacture.

## 6.4 Special precautions for storage

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

### 6.5 Nature and contents of container

PVC/PVDC blister pack, containing 4, 28 or 30 capsules.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Not applicable.

## 7. MARKETING AUTHORISATION HOLDER

Cephalon UK Limited
Ridings Point
Whistler Drive
Castleford
West Yorkshire
WF10 5HX
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

Dilzem XL 240 mg – PL 16260/0022

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 April 2011

## 10. DATE OF REVISION OF THE TEXT

29/12/2020