

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bilzem XL 240mg Prolonged-release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release capsule contains 240mg diltiazem hydrochloride.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Prolonged release, hard capsule.

Product imported from the UK:

White gelatin capsules, printed with 'e240'.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Prophylaxis and treatment of angina pectoris.
2. Treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Oral use only.

Adults

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

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

Elderly Patients and those with Renal or Hepatic Impairment

Dosage should commence at the lower level of 120 mg 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

1. Use in women of child-bearing potential.
2. Concomitant administration of dantrolene infusion due to the risk of ventricular fibrillation.
3. Shock.
4. Acute cardiac infarct with complications (bradycardia, severe hypotension, left heart insufficiency).
5. Bradycardia (pulse rate, at rest, of less than 50 per minute), hypotension (less than 90 mmHg systole), second or third degree heart block or sick sinus syndrome, except in the presence of a functioning ventricular pacemaker.
6. Atrial fibrillation/flutter and simultaneous presence of a WPW (Wolff-Parkinson-White) syndrome (increased risk of triggering a ventricular tachycardia).
7. Manifest myocardial insufficiency.
8. Left ventricular failure with stasis.
9. 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.
- 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 interactions section for information concerning beta-blockers and digitalis).
- Mild bradycardia
- Patients with reduced left ventricular function.
- Renally impaired patients.
- 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

Diltiazem undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration with other agents, which follow the same route of biotransformation, may result in competitive inhibition of metabolism. Diltiazem hydrochloride should 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 β -adrenoceptor blocking agents, nor the rebound effects seen with various antihypertensives. Combination with β -adrenoceptor blockers having a significant "first pass" loss e.g. propranolol may require a decrease in their dose and may lead to bradycardia. There may be an additive effect when used with drugs, which may induce bradycardia, or with other antihypertensives. Concomitant H_2 antagonist therapy may increase diltiazem blood levels.

Diltiazem may affect the blood levels of concomitant carbamazepine, theophylline, cyclosporin and digoxin. Careful attention should therefore be given to signs of overdose, if necessary the levels should be determined and the dose of carbamazepine, theophylline, cyclosporin A, or digoxin reduced if necessary. Patients receiving β -blockers, diuretics, ACE inhibitors or other antihypertensive agents should be regularly monitored. Use with alpha blockers should be strictly monitored.

The simultaneous administration of diltiazem with drugs such as β -blockers, antiarrhythmics or heart glycosides may cause a greater degree of AV blocking, reduce the heart rate or induce a hypotensive effect. Intravenous administration of β -blockers should be discontinued during therapy with diltiazem.

Anaesthetists should be warned that a patient is on a calcium antagonist. 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.

There have been reports in the literature of diltiazem interactions with warfarin, rifampicin and lithium.

4.6 Pregnancy and lactation

Diltiazem must not be taken during pregnancy as experimental studies have shown indications of teratogenicity. There is no experience of its effects in humans. As diltiazem is known to enter the breast milk and there is no experience of possible effects in infants, infants should be weaned if treatment of the mother with diltiazem is necessary.

4.7 Effects on ability to drive and use machines

See section 4.8 Undesirable Effects

4.8 Undesirable effects

In studies carried out to date, serious adverse reactions with diltiazem have been rare; however, it should be recognised that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

In 900 patients with hypertension, the most common adverse events were oedema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first degree AV block (3%). Only oedema and perhaps bradycardia were dose related.

The most common adverse events (>1%) observed in clinical studies of over 2100 angina and hypertensive patients receiving diltiazem were: oedema (5.4%), Headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%) and rash (1.5%).

Less common adverse events have included the following:

Cardiovascular: angina, arrhythmia, AV block (second or third degree), congestive heart failure, hypotension, palpitations, syncope.

Nervous system: Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paraesthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: anorexia, constipation, diarrhoea, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT and LDH (see Special Warnings and Precautions), vomiting, weight increase, gingivitis.

Dermatologic: petechiae, pruritus, photosensitivity, urticaria. Allergic skin reactions including erythema multiforme, vasculitis, lymphadenopathy and eosinophilia have been observed in isolated cases. Dermatological events may be transient and may disappear despite continued use of diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Other: amblyopia, CK elevation, dyspnoea, epistaxis, eye irritation, hyperglycaemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

4.9 Overdose

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 inotropic 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 once-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, propranolol, 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 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 A
Ammonio-methacrylate copolymer B

The capsule shell contains

Titanium dioxide (E171)
Gelatin
Shellac
Soya lecithin
Dimeticone
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf life expiry date of this product is the date shown on the container 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 original package.

6.5 Nature and contents of container

Blister pack of 28 capsules contained in an outer cardboard carton.

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

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
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8 Parallel Product Authorisation Number

PPA 0465/164/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2005

10 DATE OF REVISION OF THE TEXT

October 2008