Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Viazem XL 240 mg
Prolonged release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 240 mg diltiazem hydrochloride

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsule, hard.
Hard gelatin size 1 capsules with a lavender opaque cap and blue green opaque body containing white pellets. Both capsule body and cap marked viazem XL 240 in white.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

VIAZEM XL is indicated for the management of stable angina pectoris and the treatment of mild to moderate hypertension.

4.2 Posology and method of adminstration

Adults:

Dosage requirements may differ between patients with angina and patients with hypertension. In addition individual patients response may vary, necessitating careful titration. The range of strengths facilitates titration to the optimal dose.

One capsule of VIAZEM XL is to be taken before or during a meal. The dose should be taken at approximately the same time each day.

The capsule should not be chewed but swallowed whole, with a glass of water.

Due to the variability of release profile in individual patients, when changing from one type of sustained released diltiazem preparation to another, it may be necessary to adjust the dose.

Hypertension:

The usual starting dose is 180 mg once daily. The dose may be increased after 2 – 4 weeks according to the patient's response and the usual maintenance dose is 240 mg – 360 mg once daily. The maximum daily dose is 360 mg. However, the single daily doses of 300 mg and 360 mg should only be administered to patients when no satisfactory therapeutic effect has been effected with lower doses and after the benefit risk-ratio has been carefully assessed by the doctor.

Angina:

Care should be taken when titrating patients with stable angina in order to establish the optimal dose. The usual starting dose is 180 mg once daily. The dose may be increased after 2 – 4 weeks according to the patient's response. The maximum daily dose is 360 mg. However, the single daily doses of 300 mg and 360 mg should only be administered to patients when no satisfactory therapeutic effect has been effected with lower doses and after the benefit risk-ration has been assessed by the doctor.

Elderly and patients with impaired hepatic or renal function:

Plasma levels of diltiazem can be increased in the elderly, and in patients with impaired renal or hepatic function. In these cases, the starting dose should be one 120 mg capsule VIAZEM XL once daily. Heart rate should be monitored and if it falls below 50 beats per minute, the dose should be increased. Dose adjustment may be required to obtain a satisfactory clinical response.

4.3 Contraindications

Diltiazem depresses atrioventricular node conduction and is therefore contraindicated in patients with severe bradycardia (less than 50 bpm), sick sinus syndrome, congestive heart failure, and left ventricular failure with second or third degree AV or sino-atrial block, except in the presence of a functioning pacemaker. Diltiazem is also contraindicated in left ventricular failure with pulmonary stasis as diltiazem may have mild negative effects on contractility.

Diltiazem is contraindicated in acute complicated myocardial infarction (e.g. bradycardia hypotension, congestive heart failure/reduced LV function), pulmonary congestion, hypotension (<90mmHg systolic) cerebrovascular accident, cardiac shock and unstable angina pectoris.

Diltiazem is contraindicated in pre-excitation syndrome, (e.g. WPW) accompanied with atrial flutter, fibrillation and in digitalis intoxication, as diltiazem may precipitate ventricular tachycardia.

Diltiazem should not be used in patients with known hypersensitivity to diltiazem.

4.4 Special warnings and special precautions for use

Patients treated with beta-adrenoreceptor blocking drugs and patients with conduction disturbances (bradycardia, bundle branch block, first degree AV block, prolonged PR interval) should only be treated with VIAZEM XL after special consideration due to the risk of serious bradyarrhythmias.

This product should be used with caution in patients with hepatic dysfunction. Abnormalities of liver function may appear during therapy.

The higher single dose of VIAZEM XL capsules 300 mg and 360 mg should not be administered to patients with impaired renal and/or hepatic function and to elderly patients (prolonged half life of elimination) because there is no experience on the use of such high dosages in these patient categories.

In patients undergoing long-term therapy with cyclosporin, plasma levels of cyclosporin should be monitored when concurrent administration of diltiazem is initiated, or discontinued or if the dose of diltiazem is changed.

Abnormally short transit time through gastrointestinal tract could lead to incomplete release of the contents of the capsule e.g. in chronic conditions with associated diarrhoea such as Crohn's disease or ulcerative colitis.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations contraindicated as a safety measure:

In animals, fatal ventricular fibrillations are constantly seen during administration of verapamil and dantrolene via the i.v. route. The combination of a calcium antagonist and dantrolene is therefore potentially dangerous. The concurrent iv administration of beta-adrenergic blocking agents with diltiazem should be avoided because an addictive effect on SA and AV conduction and ventricular function will occur. The use of such a combination requires ECG monitoring especially at the beginning of treatment.

Combinations requiring safety precautions:

In common with other calcium antagonists, when diltiazem is used with drugs which may induce bradycardia or with antiarrhythmic drugs (e.g. amiodarone) or other antihypertensive drugs, the possibility of an additive effect should be borne in mind. Inhalation anaesthetics should be used with caution during diltiazem therapy. Tri/tetracyclic antidepressants and neuroleptics may increase the antihypertensive effects of diltiazem whilst the concomitant use of lithium with diltiazem may lead to neurotoxicity (extrapyramidal effects). Rifampin and other hepatic enzyme inducers may reduce the bioavailability of diltiazem and high does of vitamin D and/or high intake of calcium salts leading to elevated serum calcium levels may reduce the response to diltiazem.

Diltiazem is metabolised by CYP3A4 and could, by competitive inhibition of CYP3A4, affect the pharmacokinetics of other drugs metabolised by this enzyme. In addition inhibitors and inducers of CYP3A4 may affect the pharmacokinetics of diltiazem.

Diltiazem prolongs the sedative effect of midazolam and triazolam via metabolic interaction and decreases nifedipine clearance by 50%. Diltiazem may cause increases in the levels of digitoxin. Diltiazem has been shown to increase the bioavailability of imipramine by 30% probably due to an inhibition of its first pass metabolism.

Diltiazem has been used safely in combinations with diuretics, ACE-inhibitors and other anti-hypertensive agents. It is recommended that patients receiving these combinations should be regularly monitored. Concomitant use of diltiazem with alpha-blockers such as prazosin should be strictly monitored because of the possible synergistic hypotensive effect of this combination.

Case reports have suggested that blood levels of carbamazepine, cyclosporin, theophylline and phenytoin may be increased when given concurrently with diltiazem. Care should be exercised in patients taking these drugs. In common with other calcium antagonists diltiazem may cause small increases in plasma levels of digoxin. In patients taking H_2-antagonists concurrently with diltiazem there may be increased levels of diltiazem.

Magnification of the hypotensive and lipothymic effects (summation of vasodilator properties) of nitrate derivatives can occur. In patients on calcium inhibitors, prescription of nitrate derivatives should be made at progressively increasing doses. Diltiazem treatment has been continued without problem during anaesthesia, but diltiazem may potentiate the activity of curare-like and depolarising neuromuscular blocking agents, therefore the anaesthetist should be informed that the patient is receiving a calcium antagonist.

4.6 Pregnancy and lactation

Pregnancy:

Diltiazem may suppress the contractility of the uterus. Definite evidence that this will prolong partus in full-term pregnancy is lacking. A risk of hypoxia in the foetus may arise in the event of hypotension in the mother and reduced perfusion of the uterus due to redistribution of blood flow due to peripheral vasodilatation. In animal experiments diltiazem has exhibited teratogenic effects in some animal species. In the absence of adequate evidence of safety in human pregnancy, VIAZEM XL should not be used in pregnancy or in women of childbearing potential.

Lactation:

Diltiazem is excreted in breast milk in concentrations similar to those in serum. If the use of diltiazem is considered essential, an alternative method of infant feeding should be instituted.

4.7 Effects on ability to drive and use machines

There are no studies on the effect of diltiazem when driving vehicles or operating machines. It should be taken into account that occasionally asthenia/fatigue and dizziness may occur. Treatment of hypertension with this medicinal product requires regular monitoring. Individual different reactions may affect the ability to drive. This risk should be considered especially at the beginning of treatment, when changing the drug, or in combination with alcohol.

4.8 Undesirable effects

Certain undesirable effects may lead to suspension of treatment: sinus bradycardia, sino-atrial heart block, 2nd and 3rd degree atrioventricular heart block, skin rash, oedema of the lower limbs.

In hypertensive patients, adverse effects are generally mild and transient and are most commonly vasodilatory related events.

The following have been described in decreasing order of frequency: lower limb oedema, headache, hot flushes/flushing, asthenia/fatigue, palpitations, malaise, minor gastro-intestinal disorders (dyspepsia, abdominal pain, dry mouth, nausea, vomiting, diarrhoea, constipation) and skin rash. Vasodilatory related events (in particular, oedema) are dose-dependent and appear to be more frequent in elderly subjects.

Rare cases of symptomatic bradycardia and exceptionally sino-atrial block and atrioventricular block, hypotension, syncope, reduced left ventricular function have also been recorded. Isolated cases of hallucinations, depression, insomnia, hyperglycaemia and impotence have been reported.

Experience with use in other indications and with other formulations, has shown that skin rashes are usually localised and are limited to cases of erythema, urticaria or occasionally desquamative erythema, with or without fever, which regress when treatment is discontinued.

Isolated cases of moderate and transient elevations of liver transaminases have been observed at the start of treatment. Isolated cases of clinical hepatitis have been reported which resolved with cessation of therapy.

Dizziness, pruritis, nervousness, paraesthesia, articular/muscular pain, photo sensitisation, hypotension, gingival hyperplasia, and gynaecomastia, have also been observed.

4.9 Overdose

The clinical consequences of overdose can be severe hypotension leading to collapse and sinus bradycardia which may be accompanied by isorhythmic dissociation and atrioventricular conduction disturbances. Observation in a coronary care unit is advisable. Vasopressors such as adrenaline may be indicated in patients exhibiting profound hypotension. Calcium gluconate may help reverse the effects of calcium entry blockade. Atropine administration and temporary cardiac pacing may be required to manage bradycardia and/or conduction disturbances.

Glucagon can be used in cases of established hypoglycaemia.

Diltiazem and its metabolites are very poorly dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Diltiazem is classified as a calcium channel blocker, benzothiazepine derivative, C08DB01, under the ATC classification. It selectively reduces calcium entry through voltage-dependent calcium-n channels into vascular smooth muscle cells and myocardial cells. This lowers the concentration of intracellular calcium which is available to activate contractile proteins. This action of diltiazem results in dilation of coronary arteries causing an increase in myocardial oxygen supply. It reduces cardiac work by moderating the heart rate and by reducing systemic vascular resistance thus reducing oxygen demand. Diltiazem also prolongs AV conduction and has mild negative effects on contractility. Clinical data on morbidity and mortality are not available.

5.2 Pharmacokinetic properties

Multiple dose pharmacokinetic studies have shown that the kinetics of VIAZEM XL are non-linear within the 120 mg – 360 mg dosage range. Diltiazem is well absorbed, but has a highly saturable first pass effect leading to a variable absolute bioavailability, which is on average 35%. The saturable first pass effect results in higher than expected systemic exposure with increasing doses.

The protein binding is 80% to 85% and the volume of distribution is 5.0 l/kg.

Diltiazem is metabolised by CYP3A4 in the liver and 70% of the dose is excreted in urine, mainly as metabolites.

The plasma levels of the two main metabolites,
N-monodesmethyldiltiazem and desacetyldiltiazem, represent 35 % and 15% of diltiazem levels respectively. The metabolites contribute around 50% of the clinical effect. Plasma clearance of diltiazem is approximately 0.5 l/h/kg. Plasma half-life of diltiazem is approximately 5 – 7 hours.

VIAZEM XL capsules allow a prolonged absorption of diltiazem and maximum levels are reached within 6 to 12 hours. Concomitant food intake with VIAZEM XL does not influence the pharmacokinetics of diltiazem. For most patients, chronic administration of VIAZEM XL 300 mg once daily, results in therapeutic diltiazem levels (50 – 200ng/ml) over 24 hours. However, the inter-individual variability is high and individual dose adjustment based on therapeutic response is therefore necessary.

5.3 Preclinical safety data

Tests on reproductive functions in animals show that diltiazem decreases fertility in rats and that it is teratogenic in mice, rats and rabbits. Exposure during late pregnancy induces dystocia and a decrease in the number of live newborns in rats.

Results from conventional studies of genotoxicity and carcinogenic potential have not revealed any special hazards for humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose stearate
Microcrystalline cellulose (E460)
Povidone (E1201)
Magnesium stearate
Talc (E553)
Titanium dioxide (E171)
Hypromellose (E464)

Polysorbate 80 (E432)
Polyacrylate dispersion 30% (dry)
Simethicone emulsion

Capsule
Gelatin

Body
Quinoline yellow (E104)
Indigotine (E132)
Titanium dioxide (E171)

Cap
Azorubine (E122)
Indigotine (E132)
Titanium dioxide (E171)

Printing ink
Shellac (E904)
Ethyl alcohol
Isopropyl alcohol
n-Butyl
Propylene glycol (E1518)
Sodium hydroxide
Povidone (E1201)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC/aluminium blisters.
Pack size: 28 capsules per blister.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Limited
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 126/109/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th October 1998

Date of last renewal: 30th October 2003

10 DATE OF REVISION OF THE TEXT

April 2005