Summary of Product Characteristics

1. Name of the Medicinal Product

Zemtard 300 XL.
Angiozem 300 XL.
Uard 300 XL.

2. Qualitative and Quantitative Composition

Diltiazem hydrochloride EP 300mg.
International non-proprietary name (INN): Diltiazem Hydrochloride.
Chemical names:

\(+\)-cis-3-Acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride

or

\((2S,3S)\)-5-(2-Dimethylaminoethyl)-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-3-yl acetate hydrochloride.

3. Pharmaceutical Form

Hard gelatin capsule containing prolonged release diltiazem hydrochloride beads.

4. Clinical Particulars

4.1. Therapeutic Indications

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

4.2. Posology and Method of Administration

Capsules should be swallowed whole (not chewed) with half a glass of fluid.

Adults:
The recommended dose in adults is between 180 and 300mg given once daily. Doses of up to 360mg/day in hypertension and 480mg/day in angina may be of benefit in some patients.

Elderly and patients with impaired renal or hepatic function:
In the elderly or renally or hepatically impaired a starting dose of 120mg daily is recommended. The dose should not be increased if the heart rate falls below 50bpm.
4.3. Contra-indications

Diltiazem depresses atioventricular node conduction and is therefore contra-indicated in patients with marked bradycardia, sick sinus syndrome, left ventricular failure with stasis or second or third degree AV block, except in the presence of a functioning pacemaker. Because of the risk of ventricular fibrillation, diltiazem should not be given with dantrolene infusion.

Diltiazem is contra-indicated in pregnancy, in women of childbearing potential and while breast-feeding. Contra-indicated in patients with hypersensitivity to diltiazem or any of the excipients.

4.4. Special Warnings and Precautions for Use

Diltiazem should be used with caution in patients with heart failure or reduced left ventricular function. Patients with mild bradycardia, first degree AV block or prolonged PR interval should be observed closely. Treatment should commence with reduced doses in elderly patients and in patients with impaired liver or kidney function. Sudden withdrawal of diltiazem might be associated with an exacerbation of angina.

4.5. Interaction with other Medicinal Products and other forms of Interaction

Potentially hazardous interactions:

- Alpha-blockers: Enhanced hypotensive effect when calcium-channel blockers are given with alpha-blockers.

- Anti-arrhythmics: Increased risk of bradycardia, AV block and myocardial depression when diltiazem is given with amiodarone.

- Antibacterials: Metabolism of diltiazem can be accelerated by rifampicin (plasma concentration significantly reduced).

- Antiepileptics: The effect of carbamazepine is enhanced by diltiazem. Diltiazem can increase the plasma concentration of phenytoin. The effect of diltiazem can be also reduced by phenytoin and probably by primidone.

- Antivirals: Plasma concentration of diltiazem increased by atazanavir (reduce dose of diltiazem); plasma concentration of calcium-channel blockers possibly increased by ritonavir.

- Barbiturates: Effects of diltiazem probably reduced by barbiturates.

- Beta-blockers: Increased risk of AV block and bradycardia when diltiazem is given with beta-blockers.
• Cardiac Glycosides: The plasma concentration of digoxin may be increased by diltiazem. The pharmacodynamic effects on heart rhythm and AV conduction of digoxin and calcium-channel blockers may also be additive.

• Ciclosporin: Diltiazem increases the plasma concentration of ciclosporin.

• Cilostazol: Diltiazem increases the plasma concentration of cilostazol - avoid concomitant use.

• Dantrolene: Lethal ventricular fibrillation is constantly observed in animals following intravenous verapamil and dantrolene administered concomitantly (see section 4.3 Contra-indications).

• Sirolimus: Diltiazem increases the plasma concentration of sirolimus.

• Tacrolimus: The plasma concentration of tacrolimus may be increased by diltiazem.

• Theophylline: Calcium-channel blockers possibly increase the plasma concentration of theophylline (enhanced effect).

Other interactions:

• In common with other calcium antagonists, when diltiazem is used with drugs that may induce bradycardia or with anti-arrhythmic drugs (e.g. amiodarone) or other antihypertensive drugs, the possibility of an additive effect should be borne in mind.

• Anaesthetics, General: Enhanced hypotensive effect when calcium-channel blockers are given with general anaesthetics.

• Antidepressants: Diltiazem may increase the plasma concentration of imipramine and possibly other tricyclics, possibly accompanied by undesirable ECG changes. Enhanced hypotensive effect when calcium-channel blockers are given with MAOIs.

• Anti-fungals: Negative inotropic effect possibly increased when calcium-channel blockers are given with itraconazole.

• Antimalarials: Possible increased risk of bradycardia when calcium-channel blockers are given with mefloquine.

• Anxiolytics and hypnotics: Enhanced hypotensive effect when calcium-channel blockers are given with anxiolytics and hypnotics.

• Corticosteroids: The hypotensive effect of calcium-channel blockers may be antagonised by concurrent administration with corticosteroids.

• Lipid-regulating Drugs: Possible increased risk of myopathy when diltiazem is given with simvastatin. Diltiazem may lead to increased plasma concentrations of atorvastatin, simvastatin and lovastatin.
• Other calcium-channel blockers: Plasma concentration of both drugs may increase when diltiazem is given with nifedipine.

• Lithium: Neurotoxicity may occur when diltiazem is given with lithium without an increase in the plasma concentration of lithium.

• Nitrate derivatives: Increased hypotensive and lipothymic effects (additive vasodilating effects) when calcium-channel blockers are given with nitrates.

• Ulcer-healing drugs: The metabolism of calcium-channel blockers may be inhibited by ulcer-healing drugs such as cimetidine, leading to increased plasma diltiazem concentrations.

4.6. Pregnancy and Lactation

Diltiazem hydrochloride is teratogenic in some animal species. In the absence of adequate evidence of safety in human pregnancy, diltiazem should not be used in pregnancy or in women of childbearing potential. If use of the drug is considered essential in nursing mothers, an alternative method of feeding should be instituted, since diltiazem is excreted in breast milk.

4.7. Effects on Ability to Drive and Use Machines

Diltiazem may cause hypotension and dizziness. Patients should be warned not to drive or operate machinery until the effect of diltiazem has been established.

4.8. Undesirable Effects

Adverse effects are generally mild and transient and are most commonly related to the vasodilatory action of the drug. Reported adverse events have included, in decreasing order of frequency: lower limb oedema, headache, hypotension, dizziness, flushing, asthenia/fatigue, palpitations, malaise, nausea and other gastrointestinal disturbances (anorexia, vomiting, constipation, diarrhoea, taste disturbances and weight gain) and skin rash. Events related to the vasodilatory action of diltiazem are dose-dependent and may be more frequent in elderly patients. Symptomatic bradycardia and sino-atrial block and atrioventricular block are rare. Skin rashes are usually localised and limited to erythema and urticaria, or occasionally desquamative erythema, and regress after treatment cessation. Cases of erythema multiforme, exfoliative dermatitis and acute generalised exanthematous pustulosis (AGEP) have also been reported. Photosensitivity, namely photodistributed hyperpigmentation, has been reported. Gynaecomastia, gum hyperplasia, extrapyramidal symptoms and depression have been reported. Isolated cases of moderate but transient elevation of liver transaminases have been described at the start of treatment. Isolated cases of clinical hepatitis have been noted; these resolved on treatment discontinuation.
4.9. **Overdose**

In overdosage diltiazem can cause 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 given in those with severe hypotension. Calcium gluconate may help reverse the effects of calcium entry blockade. The bradycardia and / or conduction disturbance may be managed by atropine and temporary cardiac pacing.

5. **Pharmacological Properties**

5.1. **Pharmacodynamic Properties**

The cardiovascular activity of diltiazem is based upon its ability to inhibit the entry of calcium from extra-cellular fluid into the muscle cells and the release of intracellular calcium stores inhibiting the contractile mechanism. In vascular tissues diltiazem relaxes arterial smooth muscle, reducing peripheral resistance in both systemic and coronary circulation. The reduction in blood pressure that accompanies vasodilation with diltiazem is usually accomplished without reflex tachycardia – probably because it suppresses sinoatrial node stimulation. In cardiac muscle, diltiazem reduces contractility and has a mild negative inotropic effect, although *in vivo* its potent vasodilatory activity leads to decreases in peripheral resistance and blood pressure, with a resultant increase in cardiac output due to decreased afterload. In angina, diltiazem reduces O$_2$ consumption by decreasing afterload and decreasing heart rate. It also increases O$_2$ supply to coronary arteries and improves O$_2$ utilisation. Diltiazem neither reduces renal blood flow nor alters glomerular filtration rate.

Haemodynamic effects are related to dose and to plasma levels, although the relationship between these is not simple. A minimum plasma level of 40-50ng/ml has been reported as being required for haemodynamic effects and several authors quote this value when examining plasma levels in pharmacokinetic studies of sustained release preparations. However, more recently the minimally effective concentration is being given as 100ng/ml and typical plasma levels of diltiazem observed in patients are described as between 50 and 300ng/ml. There is no consistent correlation between plasma levels of diltiazem and the magnitude of haemodynamic effects, although some studies have shown a correlation between antianginal effects and plasma levels. Standard texts do not quote an effective plasma concentration range. It should be noted that oral doses can produce a wide scatter of plasma concentrations.

The accepted effective dose ranges vary from country to country, with Japan and Asia using lower doses. For France and West Germany, oral dosages of 180-360mg/day are used in hypertension while 120-360mg/day is used in the United States. In angina the dose ranges from 120-180mg/day in France and from 120-360mg/day in the United States.
5.2. Pharmacokinetic Properties

A number of studies of the pharmacokinetics of diltiazem have been published and the work has been extensively reviewed. Studies have included both healthy subjects and patients with angina or hypertension.

5.2.1 Absorption

Oral doses of diltiazem are well absorbed (about 90% of dose) but the compound undergoes considerable first-pass metabolism.

Absorption is rapid after the conventional formulation with half-lives of around 0.25-0.5 hours being reported.

5.2.2 Distribution

In single and multiple dose studies in normal subjects and in those with coronary artery disease, diltiazem is about 78-87% bound to plasma protein. The percentage of unbound drug is independent of the concentration of diltiazem over the range tested (3-500 µg/l) and the percentage is not influenced by the metabolite desacetyldiltiazem. The mean volume of distribution is between 4 and 7 l/kg, and this relatively large volume is considered probably to result from its high lipid solubility.

5.2.3 Metabolism

Diltiazem is mainly metabolised in the liver and less than 5% of parent drug appears in the urine. It is metabolised to form at least eight metabolites via pathways that include O-deacetylation, N-demethylation and O-demethylation with oxidative deamination identified as a major route. The main metabolites are desmethyl- and desacetyl-diltiazem and these have about 20% and 50%, respectively, of the activity of the parent compound. However, the concentration in plasma is not usually more than 30-50% of the parent for desmethyldiltiazem and 10-30% for desacetyldiltiazem, and most activity is due to diltiazem itself.

5.2.4 Excretion

Only 0.2% to 4% of a single orally administered dose (60-210mg) and 1-3% of a dose following repeat oral administration (120-180mg/day for 7-15 days) is excreted unchanged in urine.

Höglund and Nilsson studied oral labelled diltiazem and found between 70-73% of label in urine with the rest of the label appearing in faeces.

5.3. Preclinical Safety Data

Not applicable.
6. Pharmaceutical Particulars

6.1. List of Excipients

Sugar spheres
Ammoniomethacrylate Copolymer type A
Ammoniomethacrylate Copolymer type B
Paraffin
Talc

Capsule Components
Indigotine E132
Titanium Dioxide E171
Gelatin

Overprint Ink Constituents
Shellac
Propylene glycol
Black iron oxide (E172)

6.2. Incompatibilities

None known.

6.3. Shelf Life

3 years.

6.4. Special Precautions for Storage

Store in a dry place below 25°C; protect from light.

6.5. Nature and Contents of Container

Blister packs composed of PVC/PVDC sealed to aluminium-PVDC containing 28, 30, 56, 60 or 100 Size 0 capsules with a light-blue cap and white body. Capsules are marked DIL 300.

6.6. Special Precautions for Disposal

None stated.
7. **Marketing Authorisation Holder**

Galen Limited  
Seagoe Industrial Estate  
Craigavon  
BT63 5UA  
UK

8. **Marketing Authorisation Number**

PL 27827/0036.

9. **Date of First Authorisation**

15 March 1996.

10. **Date of Revision of the Text**

08 November 2012.