SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zemtard 120XL 120mg Prolonged-release Capsules
Angiozem 120XL 120mg Prolonged-release Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diltiazem hydrochloride 120mg per capsule.

Excipient(s) with known effect: each capsule contains not more than 65.0mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard prolonged-release capsule.

Hard gelatin capsule (Size 2) with a brownish-red cap and orange body containing prolonged release diltiazem hydrochloride beads. Capsules are marked DIL 120 in black ink.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the treatment of mild to moderate hypertension. For the prophylaxis and treatment of angina pectoris.

This product is indicated in adults.

4.2. Posology and method of administration

Posology

Zemtard/Angiozem is a prolonged-release product for once daily dosing.

The dosage requirements may differ in patients with angina or hypertension.

Zemtard/Angiozem (diltiazem hydrochloride) is available in a range of strengths to enable dosage to be adjusted to meet the individual requirements of the patient. Careful titration of the dose should be considered where appropriate, as individual patient response may vary. To ensure consistency of response once established, particularly in prolonged-release formulations, Zemtard/Angiozem should be prescribed by brand name.

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. Heart rate should be monitored and if it falls below 50 beats per minute (bpm) the dose should not be increased. Plasma levels of diltiazem can be increased in this group of patients.

Paediatric population
The safety and efficacy of the product in children have not been established. This product is not recommended for use in children.

Method of administration

For oral use.

Capsules should not be crushed or chewed but swallowed whole with half a glass of fluid, ideally before or during a meal.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Diltiazem is contraindicated in patients with severe bradycardia (below 40 bpm); in sick sinus syndrome or in second- or third-degree AV block, in patients without a functioning pacemaker; in left ventricular failure with pulmonary congestion. Diltiazem should not be given concomitantly with dantrolene infusion (see section 4.5). Diltiazem is also contraindicated in combination with ivabradine (see section 4.5). Diltiazem should not be used concurrently with lomitapide (see section 4.5).

Diltiazem is contraindicated in pregnancy, in women of childbearing potential not using effective contraception and while breast-feeding (see section 4.6).

4.4. Special warnings and precautions for use

Close observation is necessary in patients with heart failure or reduced left ventricular function, bradycardia (risk of exacerbation), or with first-degree

AV block or prolonged PR interval detected on the electrocardiogram (ECG) (risk of exacerbation and rarely, of complete block).

Cases of acute renal failure secondary to decreased renal perfusion have been reported in patients with existing cardiac disease especially reduced left ventricular function, severe bradycardia or severe hypotension. Careful monitoring of renal function is advised.

Prior to general anaesthesia, the anaesthetist must be informed of ongoing diltiazem treatment. 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 closely observed and close monitoring, particularly of heart rate, should be carried out at the beginning of treatment.

Treatment with diltiazem may be associated with mood changes, including depression (see section 4.5 and 4.8). Early recognition of relevant symptoms is important, especially in predisposed patients. In such cases, drug discontinuation should be considered.

Diltiazem has an inhibitory effect on intestinal motility. Therefore, it should be used with caution in patients at risk of developing an intestinal obstruction.

Careful monitoring is necessary in patients with latent or manifest diabetes mellitus due to a possible increase in blood glucose.

The use of diltiazem may induce bronchospasm, including asthma aggravation, especially in patients with preexisting bronchial hyper-reactivity. Cases have also been reported after dose increase. Patients should be monitored for signs and symptoms of respiratory impairment during diltiazem therapy.

This product contains sucrose, therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Caution should be exercised when direct oral anticoagulants (DOACs) are co-administered with diltiazem which is a moderate CYP3A4 and a weak P-gp inhibitor, particularly in patients at high risk of bleeding (see section 4.5).

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant use contraindicated for safety reasons:

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).

Lomitapide: Diltiazem (a moderate CYP3A4 inhibitor) may increase lomitapide plasma concentrations through CYP3A4 inhibition leading to increased risk of elevations in liver enzymes (see section 4.3).

Concomitant use requiring caution:

Lithium: Risk of increase in lithium-induced neurotoxicity.

Nitrate derivatives: Increased hypotensive effects and faintness (additive vasodilation effects): In all 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.

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 strict monitoring of 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. 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.

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 diltiazem is co-administered with beta-blockers (see section 4.8).

Antiarrhythmic agents: Since diltiazem has antiarrhythmic properties, its concomitant prescription with other antiarrhythmic agents is not recommended due to the risk of increased cardiac adverse effects due to an additive effect. This combination should only be used under close clinical and ECG monitoring.

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.

Phenytoin: When co-administered with phenytoin, diltiazem may increase phenytoin plasma concentration. It is recommended that the phenytoin plasma concentrations be monitored.

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-H_2 agents (cimetidine and ranitidine): Increase in plasma diltiazem concentrations. Patients currently receiving diltiazem therapy should be carefully monitored when initiating or discontinuing therapy with anti-H_2 agents. An adjustment in diltiazem daily dose may be necessary.

Immunosuppressants: 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. The plasma concentrations of sirolimus, tacrolimus and everolimus may be increased by diltiazem.

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.

X-Ray Contrast Media: Cardiovascular effects of an intravenous bolus of an ionic X-ray contrast media, such as hypotension, may be increased in patients treated with diltiazem. Special caution is required in patients who concomitantly receive diltiazem and X-ray contrast media.

Antiplatelet drugs: In a pharmacodynamic study, diltiazem was shown to inhibit platelet aggregation. Although the clinical significance of this finding is unknown, potential additive effects when used with antiplatelet drugs should be considered.

<u>Combinations to be taken into account:</u>

Diltiazem is metabolised 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. Grapefruit juice may increase diltiazem exposure (1.2-fold). Patients who consume grapefruit juice should be monitored for increased adverse effects of diltiazem. Grapefruit juice should be avoided if an interaction is suspected. 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.
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 metabolised by the CYP3A4 pathway in patients using diltiazem.

Corticosteroids (methylprednisolone): Diltiazem can increase methylprednisolone levels (through inhibition of CYP3A4 and possible inhibition of P-glycoprotein). The patient should be monitored when initiating methylprednisolone treatment. An adjustment to the dose of methylprednisolone may be necessary.

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 is increased by concomitant administration of diltiazem with statins metabolised by CYP3A4 (e.g. atorvastatin, fluvastatin, and simvastatin). An adjustment of the dose of statin may be necessary (see also product information of the relevant statin). When possible, it is recommended to use a statin not metabolised by CYP3A4 (e.g. pravastatin) with diltiazem.

Cilostazol: Inhibition of cilostazol metabolism (CYP3A4). Diltiazem has been shown to increase cilostazol exposure and to enhance its pharmacological activity.

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.

Colchicine: Colchicine is a substrate for both CYP3A and the efflux transporter P-glycoprotein (P-gp). Diltiazem is known to inhibit CYP3A and P-gp. When diltiazem and colchicine are administered together, inhibition of P-gp and/or CYP3A by diltiazem may lead to increased exposure to colchicine. Combined use is not recommended.

DOACs: Diltiazem which is a moderate CYP3A4 and weak P-gp inhibitor may increase the plasma concentration of DOACs when co-administered with diltiazem.

Diltiazem may lead to QT prolongation, when administered with drugs with potential/ known for prolonging the QT interval. Co-administration of diltiazem with drugs known to prolong the QT interval must be based on a careful assessment of the potential risks and benefits of the treatment.

<u>General information to be taken into account</u>:

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.

4.6. Fertility, 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 (see section 5.3) in certain animal species (rat, mice, rabbit). Diltiazem should not be used in pregnancy or in women of child-bearing potential not using effective contraception (see section 4.3).

Breastfeeding

As diltiazem is excreted in breast milk, breastfeeding whilst taking diltiazem is contraindicated.

4.7. Effects on ability to drive and use machines

On the basis of reported adverse drug reactions, i.e. dizziness (common) and 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
Psychiatric disorders			Nervousness, insomnia		Mood changes (including depression)
Nervous system disorders		Headache, dizziness			Extrapyramidal syndrome
Respiratory, thoracic and mediastinal disorders					Bronchospasm (including asthma aggravation)
Cardiac disorders		Atrioventricular block (may be of first, second or third degree; bundle branch block may occur),	Bradycardia		Sinoatrial block, congestive heart failure, sinus arrest, cardiac arrest (asystole)

	Very common	Common	Uncommon	Rare	Not known
		palpitations			
Vascular disorders		Flushing	Orthostatic hypotension		Vasculitis (including leukocytoclastic vasculitis)
Gastrointestinal disorders		Constipation, dyspepsia, gastric pain, nausea	Anorexia, vomiting, diarrhoea, taste disturbance, weight gain	Dry mouth	Gingival hyperplasia
Metabolism and nutrition disorders					Hyperglycemia
Hepatobiliary disorders			Hepatic enzymes increase (AST, ALT, LDH, ALP increase)		Hepatitis
Skin and subcutaneous tissue disorders		Erythema		Urticaria	Photosensitivity (including lichenoid keratosis at sun exposed skin areas), angioneurotic oedema, rash, erythema multiforme (including Stevens-Johnson syndrome and toxic epidermal necrolysis), sweating, exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP), occasionally desquamative erythema with or without fever, lupus-like syndrome
Reproductive system and breast disorders					Gynecomastia
General disorders and administration site conditions	Peripheral oedema	Malaise			Fatigue

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 leading to collapse and acute kidney injury, sinus bradycardia with or without isorhythmic dissociation, sinus arrest, atrioventricular conduction disturbances and cardiac arrest.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of diltiazem overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early

resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment, in a hospital setting, will include gastric lavage and/or osmotic diuresis. Conduction disturbances may be managed by temporary cardiac pacing. Proposed corrective treatments: atropine, vasopressors, inotropic agents, glucagon and calcium gluconate infusion.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers; Benzothiazepine derivatives, ATC code: C08DB01

Calcium antagonist, antihypertensive agent.

Diltiazem restricts calcium entry into the slow calcium channel of vascular smooth muscle and myocardial muscle fibres in a voltage-dependent manner. By this mechanism, diltiazem reduces the concentration of intracellular calcium in contractile protein.

In animals: diltiazem increases coronary blood flow without inducing any coronary steal phenomena. It acts both on small, large and collateral arteries. This vasodilator effect, which is moderate on peripheral systemic arterial territories, can be seen at doses that are not negatively inotropic. The two major active circulating metabolites, i.e.
deacetyl diltiazem and N-monodemethyl diltiazem, possess pharmacological activity in angina corresponding to 10 and 20% respectively of that of the parent compound.

In humans: diltiazem increases coronary blood flow by reducing coronary resistance. Due to its moderate bradycardia-inducing activity and the reduction in systemic arterial resistance, diltiazem reduces cardiac workload.

Diltiazem does not have a significant myocardial depressant action in man.

5.2. Pharmacokinetic properties

Once daily formulations of diltiazem have been shown to have different pharmacokinetic profiles and therefore it is not advised to substitute different brands for one another.

Absorption

In healthy volunteers, oral doses of diltiazem are well absorbed (about 90% of dose).

Prolonged-release capsules provide prolonged absorption of diltiazem with steady state plasma concentrations observed between 2 to 14 hours post-dose, during which time peak plasma levels occur.

Mean plasma concentrations in the elderly and patients with renal and hepatic insufficiency are higher than in young subjects.

Food intake does not significantly affect the kinetics of diltiazem, however, when administered with food, absorption was observed to be higher in the first few hours post-dose.

Distribution

Diltiazem in plasma is about 80-85% protein bound and is poorly dialysed.

Biotransformation

Diltiazem is extensively metabolised by the liver. The major circulating metabolite, N-monodesmethyl diltiazem accounts for approximately 35% of the circulating diltiazem.

Elimination

Less than 5% of diltiazem is excreted unchanged in the urine.

Diltiazem and its metabolites are poorly dialysed.

5.3. Preclinical safety data

Pregnancy

Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 – 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) resulted in embryo and fetal lethality. These studies revealed, in one species or another, a propensity to cause fetal abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights, pup survival, as well as prolonged delivery times and an increased incidence of stillbirths.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sugar spheres (sucrose and starch)
Ammonio methacrylate copolymer (type A)
Ammonio methacrylate copolymer (type B)
Paraffin
Talc

Capsule Components
Red iron oxide (E172)
Yellow iron oxide (E172)
Erythrosine (E127)
Indigotine (E132)
Titanium dioxide (E171)
Gelatin

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

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 25°C. Store in the original package in order to protect from light and moisture.

6.5. Nature and contents of container

Blister packs composed of PVC/PVDC sealed to aluminium-PVDC containing 28, 30, 56, 60 or 100 capsules. Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Galen Limited
Seagoe Industrial Estate
Craigavon
BT63 5UA
UK

8. MARKETING AUTHORISATION NUMBER

PL 27827/0033.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 1996
Date of latest renewal: 03 May 2001

10 DATE OF REVISION OF THE TEXT

17/04/2026