# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Zemret 180 XL Capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 180 mg diltiazem hydrochloride

For the full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Modified release capsule.

Size “1” hard gelatine capsule with a pink cap and grey body, marked 180, containing white and whitish pellets

## 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

*Posology*

Patients should be advised that the capsule membrane may pass through the gastro-intestinal tract unchanged.

Zemret 180 XL is a prolonged release product for once daily dosing. The dosage requirements may differ in patients with angina or hypertension.

Zemret XL (diltiazem hydrochloride) is available in a range of presentations 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. When changing from one type of Zemret XL formulation to another it may be necessary to adjust the dosage until a satisfactory response is obtained. To ensure consistency of response once established, particularly in the prolonged release formulations, Zemret 240 and 300 XL should continue to be prescribed by brand name.

**Adults**:
Angina and hypertension:
The usual starting dose is Zemret XL 180 once daily. This dose may be increased to Zemret XL 300 once daily, or 2 capsules of Zemret XL 180 daily (360mg), and if clinically indicated a higher dose of one Zemret XL 300 plus one Zemret XL 180 capsule (total 480mg) may be considered.

**Elderly and patients with impaired hepatic or renal function**:
Heart rate should be monitored and if it falls below 50 beats per minute the dose should not be increased. Plasma levels of diltiazem can be increased in this group of patients.

Angina and hypertension:
The initial dose should be one Zemret XL 180 capsule daily. This dose may be increased to one capsule of Zemret XL 300 daily if clinically indicated.

**Paediatric population:**
Safety and efficacy in children have not been established. Therefore, diltiazem is not recommended for use in children.

*Methods of administration*
Oral use. The capsules should not be crushed or chewed but swallowed whole with water, ideally before or during a meal.

## 4.3 Contraindications

Hypersensitivity to diltiazem or to any of the excipients listed in section 6.1.
Sick sinus syndrome, 2nd or 3rd degree AV block in patients without a functioning pacemaker.
Severe bradycardia (less than 50 beats per minute).
Left ventricular failure with pulmonary stasis.
Lactation.
Concurrent use with dantrolene infusion (see section 4.5).
Combination with ivabradine (see section 4.5).
Concurrent use with lomitapide (see section 4.5).
Concurrent use with asunaprevir (see section 4.5).

## 4.4 Special warnings and precautions for use

Close observation is necessary in patients with reduced left ventricular function, bradycardia (risk of exacerbation) or with a 1st degree AV block or prolonged PR interval detected on the electrocardiogram (risk of exacerbation and rarely, of complete block).

Increase of plasma concentrations of diltiazem may be observed 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.

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.

In the case of general anaesthesia, the anaesthetist must be informed that the patient is taking diltiazem. The depression of cardiac contractility, conductivity and automaticity as well as the vascular dilatation associated with anaesthetics may be potentiated by calcium channel blockers.

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 pre-existing 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.

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 anti-coagulants (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

**Combination 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).

Asunaprevir
Diltiazem (a moderate CYP3A4 inhibitor) may increase asunaprevir plasma concentrations through CYP3A4 inhibition (see section 4.3).

**Combinations requiring caution:**
Alpha-antagonists
Increased anti-hypertensive 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.

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).

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.

Antiarrhythmic agents
Since diltiazem has antiarrhythmic properties, its concomitant prescription with other antiarrhythmic agents are 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.

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.

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.

Phenytoin
When co-administered with phenytoin, diltiazem may increase phenytoin plasma concentration.

It is recommended that the phenytoin plasma concentrations be monitored.

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.

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.

Theophylline
Increase in circulating theophylline levels.

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.

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.

Lithium
Risk of increase in lithium-induced neurotoxicity.

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.

**Combinations to be taken into account:**
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.

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.

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.

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.

Direct oral anti-coagulants (DOACs)
Diltiazem which is a moderate CYP3A4 and weak P-gp inhibitor may increase the plasma concentration of DOACs when co-administered with diltiazem.

QT prolongation
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.

**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.

## 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 (see section 5.3) in certain animal species (rat, mice, rabbit). Diltiazem is therefore not recommended during pregnancy, as well as in women of child-bearing potential not using effective contraception.

*Breast-feeding*
As this drug is excreted in breast milk, breast feeding 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), 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), palpitations | Bradycardia | | Sinoatrial block congestive heart failure<br><br>Sinus arrest, cardiac arrest (asystole) |
| *Vascular disorders* | | Flushing | Orthostatic hypotension | | Vasculitis (including leukocytoclastic vasculitis) |
| *Gastrointestinal disorders* | | Constipation, dyspepsia, gastric pain, nausea | Vomiting, diarrhoea | Dry mouth | Gingival hyperplasia |
| *Metabolism and nutrition disorders* | | | | | Hyperglycaemia |
| *Hepatobiliary disorders* | | | Hepatic enzymes increase (AST, ALT, LDH, ALP increase) | | Hepatitis |

| | Very common | Common | Uncommon | Rare | Not known |
|---|---|---|---|---|---|
| *Skin and subcutaneous tissue disorders* | | Erythema | | Urticaria | Photosensitivity (including lichenoid keratosis at sun exposed skin areas), angioneurotic oedema, rash, erythema multiforme (including Steven-Johnson's syndrome and toxic epidermal necrolysis), sweating, exfoliative dermatitis, acute generalised exanthematous pustulosis, occasionally desquamative erythema with or without fever<br><br>Lupus-like syndrome, Lichenoid drug eruption |
| *Reproductive system and breast disorders* | | | | | Gynecomastia |
| *General disorders and administration site conditions* | Peripheral oedema | Malaise | | | |

**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 at: 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, under hospital supervision, will include gastric lavage, 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-monodesmethyl 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

Diltiazem is well absorbed (90%) in healthy volunteers following oral administration.

The prolonged release capsule provides prolonged absorption of the active constituent, producing steady state plasma concentrations between 2 - 14 hours post-dose, during which time peak plasma levels occur.

Bioavailability of this formulation of diltiazem relative to diltiazem 60mg formulation is approximately 80%. The mean apparent plasma half-life is 8 hours.

Diltiazem in plasma is 80 to 85% protein bound and is poorly dialysed. It is extensively metabolised by the liver.

The major circulating metabolite, N-monodesmethyl diltiazem accounts for approximately 35% of the circulating diltiazem.

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

Twenty-four hours after intake, plasma concentrations remain, even after the 200 mg dose administration, at the level of 50 ng/ml, in patients. During long term administration in any one patient, plasma concentrations of diltiazem remained constant.

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.

Diltiazem and its metabolites are poorly dialysed.

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.

### 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 foetal lethality. These studies revealed, in one species or another, a propensity to cause foetal 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), acetone, ammonio methacrylate copolymers types ‘A’ and ‘B’, paraffin, talc, gelatin, methylene chloride, titanium dioxide (E171), black and red iron oxide (E172), erythrosine (E127).

### 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. Store in the original package in order to protect from light.

### 6.5 Nature and contents of container

Blister packs composed of 250 µm PVC/40 $gm^2$ PVDC sealed to 25 µm aluminium/20 $gm^2$ PVDC containing 28, 30, 56, 60 or 100 capsules.

Not all packs sizes may be marketed.

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

220 Butterfield
Great Marlings
Luton
LU2 8DL
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 11311/0449

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

Date of first authorisation:15/08/2008

## 10 DATE OF REVISION OF THE TEXT

18/02/2026