Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tildiem LA 300 mg Prolonged-Release Capsules, Hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 300 mg diltiazem hydrochloride as the active ingredient in a combination of immediate-release and coated prlonged-release pellets.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release Capsule, Hard.
Opaque capsules with a white body and a yellow cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a calcium antagonist for use in the management of angina pectoris and mild to moderate hypertension.

4.2 Posology and method of administration

Dosage and administration:
Tildiem LA 200 and Tildiem LA 300 are sustained release products for once daily dosing. The capsules should not be crushed or chewed but swallowed whole with water, ideally before or during a meal. The dosage requirements may differ in patients with angina or hypertension.

Tildiem (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 Tildiem 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 sustained release formulations, Tildiem LA 200 and Tildiem LA 300 should continue to be prescribed by brand name.

Tildiem LA 300 has been used following an acute myocardial infarction initially treated with thrombolysis, in the absence of congestive heart failure (see section 5.1 Pharmacodynamics).

Adults:
Angina and hypertension:
The usual starting dose is Tildiem LA 200, one capsule once daily. This dose may be increased to Tildiem LA 300 once daily, or 2 capsules of Tildiem LA 200 daily (400mg) and if clinically indicated a higher dose of one Tildiem LA 300 plus one Tildiem LA 200 capsule (500mg) may be considered.

Elderly and patients with impaired hepatic or renal function:
Heart rate should be monitored and if it falls below 40 beats per minute, the dose should not be increased. Plasma levels of diltiazem can be increased in this group of patients.
Tildiem LA 300 mg Prolonged-Release Capsules, Hard should be used with caution in patients with renal or hepatic impairment (see Section 4.4 Special Warnings and Special Precautions for Use)

Angina and hypertension:
The initial dose should be one Tildiem LA 200 capsule daily. This dose may be increased to one capsule of Tildiem LA 300 daily if clinically indicated.

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

4.3 Contraindications

Pregnancy, women of childbearing potential (see section 4.6 Pregnancy and Lactation).

Sick sinus syndrome except in the presence of a functioning ventricular pacemaker

Second or third degree AV block except in the presence of a functioning ventricular pacemaker.

Severe bradycardia (less than 40 beats per minute).

Left ventricular failure with pulmonary congestion.

Concomitant use of dantrolene infusion (see section 4.5 Interactions With Other Medicinal Products and Other Forms of Interaction).

Hypersensitivity to diltiazem or to any of the excipients.

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 first degree AV block detected on the electrocardiogram (risk of exacerbation and rarely of complete block).

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 such as 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 carefully observed and close monitoring, particularly of heart rate, should be carried out at the beginning of treatment.

Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression

Like other calcium channel antagonists, diltiazem has an inhibitory effect on intestinal motility. Therefore, it should be used with caution in patients at risk to develop an intestinal obstruction. Tablet residues from slow release formulations of the product may pass into the patient’s stools; however, this finding has no clinical relevance.

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use contraindicated:

Dantrolene (infusion)
Lethal ventricular fibrillation is regularly observed in animals when intravenous verapamil and dantrolene are administered concomitantlyThe combination of calcium antagonist and dantrolene is therefore potentially dangerous *(see section 4.3 Contraindications).*

Concomitant use requiring caution:

Lithium:
Risk of increase in lithium-induced neurotoxicity.

Nitrate derivatives:
Increased hypotensive effects and faintness (additive vasodilatating 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 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.

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.

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.

Other Antiarrhythmic agents:
Since diltiazem has antiarrhythmic properties, its concomitant prescription with other antiarrhythmic agents is not recommended (additive risk of increased cardiac adverse effects) 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.

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.

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.

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.

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 metabolized 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. Diltiazem is also a CYP3A4 isoform inhibitor. Co-administration with other CYP3A4 substrates may result in an increase in plama concentraion of either co-administered drug. Co-administration of diltiazem with a CYP3A4 inducer may result in a decrease of diltiazem plasma concentrations.

BENZODIAZEINES (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 metabolized by the CYP3A4 pathway in patients using diltiazem.

CORTICOSTEROIDS (methylprednisolone): Inhibition of mehtylprednisolone metabolism (CYP3A4) and inhibition of P-glycoprotein. The patient should be monitored when initiating methylprednisolone treatment. An adjustment in 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 due to statins metabolised by CYP3A4 may be increased with concomitant use of diltiazem. When possible, a non CYP3A4-metabolised statin should be used together with diltiazem, otherwise close monitoring for signs and symptoms of a potential statin toxicity is required.

4.6 Fertility, pregnancy and lactation

There are very limited data from the use of diltiazem in pregnant patients. Diltiazem has been shown to have reproductive toxicity 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.

Diltiazem is excreted in breast milk at low concentrations. Breast feeding while taking this drug should be avoided. If use of Diltiazem is considered medically essential, an alternative method of infant feeding should be instituted.

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
Cardiac disorders		Atrioventricular block (may be of first, second or third degree;	Bradycardia		Sinoatrial block, congestive heart failure

		bundle branch block may occur), palpitations			
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 disordrs					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, erythema multiforme (including Steven-Johnson's syndrome and toxic epidermal necrolysis), sweating, exfoliative dermatitis, acute generalized exanthematous pustulosis, occasionally desquamative erythema with or without fever
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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

The clinical effects of acute overdose can involve pronounced hypotension possibly leading to collapse, sinus

bradycardia with or without isorhythmic dissociation, and atrioventricular conduction disturbances.

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

Calcium antagonist, anti-anginal agent, antihypertensive agent.

Pharmacotherapeutic group: Calcium Channel Blocker, ATC code: C08 B01

Diltiazem selectively 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 the vicinity of contractile proteins.

In animals
Anti-anginal properties:
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. desacetyl diltiazem and N−monodesmethyl diltiazem, induce coronary vasodilation corresponding to 10 and 20% respectively of that of the parent compound.

Antihypertensive properties:
Diltiazem reduces arterial smooth muscle tone by reducing calcium influx in vascular smooth muscle cells, and causes vasodilation which produces a decrease in total peripheral resistance.
Diltiazem reduces blood pressure without producing reflex tachycardia in various animal models of hypertension, particularly in the spontaneously hypertensive rat.
It does not modify cardiac output and maintains renal blood flow.

Furthermore, it preferentially inhibits the vasoconstrictor effects of noradrenaline and angiotensin II. Diltiazem increases diuresis and reduces cardiac hypertrophy in the spontaneously hypertensive rat.

High doses of diltiazem lessen the development of arterial calcinosis arterialis in the rat. The two major active circulating metabolites (desacetyl diltiazem and N−monodesmethyl diltiazem) possess pharmacological activity which is approximately 50% that of diltiazem.

In humans
Anti-anginal properties:
Diltiazem increases coronary blood flow by reducing coronary resistance. Due to its moderate bradycardia-inducing activity demonstrated on heart rates greater than 75 beats/minute and the reduction in systemic arterial resistance, diltiazem reduces cardiac workload. Electrophysiologically, diltiazem causes moderate bradycardia in normal subjects, marginally prolongs intranodal conduction and has no effect on hisian and infrahisian conduction.

Antihypertensive properties:
At a vascular level, the calcium antagonist effect of diltiazem produces moderate arterial vasodilation and improves large artery compliance. This well-balanced vasodilation leads to a decrease in blood pressure in the hypertensive subject, due to lowered peripheral resistance, without producing reflex tachycardia. On the contrary, there is a bradycardia inducing activity which is more pronounced on elevated heart rates. Visceral blood flow rates, in particular

renal and coronary, are maintained or increased.
A slight natriuretic effect is observed following acute administration.

Diltiazem does not stimulate the renin-angiotensin-aldosterone system during long-term therapy, and does not cause water and sodium retention, as evidenced by the absence of body weight variation and a lack of change in the water and electrolyte balance of the plasma. Diltiazem acts as a coronary vasodilator on the heart, reducing left ventricular hypertrophy in the hypertensive subject. It has little effect on cardiac output.

Diltiazem reduces cardiac work by its moderate bradycardiac effect coupled with the lowering of systemic arterial resistance. A negative inotropic effect has not been observed in a healthy myocardium. Diltiazem slows heart rate to a moderate extent and may exert a depressant effect on a diseased sinus node. It slows atrioventricular conduction and there is thus a risk of AV block.

Diltiazem does not affect conduction at the bundle of His or at an infrahisian level.
Diltiazem does not affect glycoregulation. It does not adversely affect plasma lipoproteins or lipid metabolism.

A prospective, randomised, controlled, double-blind study versus placebo, of 6 months duration, in 874 patients following acute myocardial infarction initially treated with thrombolysis, in the absence of congestive heart failure, established that Tildiem LA 300 is well tolerated.

A favourable trend was observed on the combined endpoint (cardiac death, non-fatal reinfarction and refractory ischaemia), together with a significant reduction in non-fatal cardiac events (reinfarction combined with either refractory ischaemia or with the need for myocardial revascularisation).

5.2 Pharmacokinetic properties

Diltiazem is well absorbed (90%) in healthy volunteers following oral administration.
The sustained release capsule provides prolonged absorption of the active constituent, producing steady state plasma concentrations between 2 and 14 hours post-dose, during which time peak plasma levels occur.

Bioavailability of Tildiem LA relative to the Tildiem 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 Tildiem LA, 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

In subacute and chronic dog and rat studies designed to produce toxicity, high doses of Tildiem LA 200mg Prolonged release Capsules, Hard were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20mg/kg were alsoassociated with hepatic changes; however, these changes were reversible with continued dosing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Copolymers of acrylic and methacrylic esters
Carmellose sodium
Ethylcellulose
Diacetylated monoglycerides
Magnesium stearate
Gelatin
Yellow iron oxide (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Cartons containing 28 capsules in two blister strips of PVC blister tray and aluminium foil of 14 capsules.

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 MARKETING AUTHORISATION HOLDER

Sanofi-aventis Ireland Ltd. T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/161/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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