SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tildiem LA 200mg Prolonged-Release Capsules
Tildiem LA 300mg Prolonged-Release Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains a combination of immediate-release and coated prolonged-release pellets with 200mg or 300mg diltiazem hydrochloride as the active ingredient.

For a full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Prolonged-release capsule

Tildiem LA 200: Opaque capsules with a grey body and pink cap, containing white to off-white pellets.

Tildiem LA 300: Opaque capsules with a white body and yellow cap, containing white to off-white pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate hypertension and angina pectoris.

4.2 Posology and method of administration

Tildiem LA 200 and Tildiem LA 300 are prolonged release products for once daily dosing. The capsules should not be 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 prolonged release formulations, Tildiem LA 200 should continue to be prescribed by brand name.

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

- 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 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 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.

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. 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.

4.5 Interactions with medicinal products and other forms of interactions

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 Contraindications).

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.

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

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\textsubscript{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\textsubscript{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.

Combinations To Be Taken Into Account:

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.
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.

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 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 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
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects
The following adverse reactions are listed by system organ class and frequency, based on data from clinical trials with diltiazem, using the following convention: very common (≥ 1/10); common (≥ 1/100 to ≤ 1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data)

Psychiatric disorders
Uncommon: nervousness, insomnia.

Nervous system disorders
Common: headache, dizziness

Cardiac disorders
Common: atrioventricular block, palpitations
Uncommon: bradycardia

**Vascular disorders**
Common: flushing
Uncommon: orthostatic hypotension

**Gastrointestinal disorders**
Common: constipation, dyspepsia, gastric pain, nausea
Uncommon: vomiting, diarrhoea
Rare: dry mouth

**Hepatobiliary disorders**
Uncommon: hepatic enzymes increase (AST, ALT, LDH, ALP increase)

**Skin and subcutaneous tissue disorders**
Common: erythema
Rare: urticaria

**General disorders and administration site conditions**
Very common: lower limb oedema
Common: malaise, asthenia/fatigue

**POST-MARKETING EXPERIENCE**
In addition to the above, the following adverse reactions have been reported during post-marketing surveillance. They are derived from spontaneous reports and, therefore, the frequency of these adverse reactions is not known.

**Blood and lymphatic system disorders**
Thrombocytopenia

**Psychiatric disorders**
Mood changes (including depression), extrapyramidal syndrome

**Cardiac disorders**
Sinoatrial block, congestive heart failure

**Vascular disorders**
Vasculitis (including leukocytoclastic vasculitis)

**Gastrointestinal disorders**
Gingival hyperplasia

**Hepatobiliary disorders**
Hepatitis

**Skin and subcutaneous disorders**
Photosensitivity (including lichenoid keratosis on sun-exposed skin areas), angioneurotic oedema, 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

Reproductive system and breast disorders
Gynaecomastia

4.9 Overdose

The clinical effects of acute overdose can involve pronounced hypotension leading to collapse, sinus bradycardia with or without isorhythmic dissociation, and atrioventricular conduction disturbances.

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 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.

Tildiem LA 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 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

Pregnancy: Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 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

Tildiem LA 200:
Microcrystalline cellulose,
Acrylic and methacrylic esters co-polymer,
Ethylcellulose, sodium carboxymethylcellulose,
Diacetylated monoglycerides,
Magnesium stearate.

In the capsule:
Gelatin,
Black iron oxide (E172),
Titanium dioxide (E171),
Red iron oxide (E172).

Tildiem LA 300:
Microcrystalline cellulose,
Acrylic and methacrylic esters copolymer,
Ethylcellulose,
Carmellose sodium,
Diacetylated monoglycerides
Magnesium stearate.

In the capsule:
Gelatin,
Titanium dioxide (E171),
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Tildiem LA 200: 3 years
Tildiem LA 300: 2 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Tildiem LA 200: 28 capsules, in a PVC/foil blister strip.
Tildiem LA 300: 28 capsules, in a PVC/foil blister strip.

6.6 Special precautions for disposal

No special requirements
7. MARKETING AUTHORISATION HOLDER

Sanofi-aventis
One Onslow Street
Guildford
Surrey
GU1 4YS
UK

8. MARKETING AUTHORISATION NUMBER

Tildiem LA 200: PL 04425/0639
Tildiem LA 300: PL 04425/0638

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

200mg: Date of first authorisation: 17 February 1995
        Date of latest renewal: 23 September 2005
300mg: Date of first authorisation: 9 April 1992
        Date of latest renewal: 28 August 2003

10. DATE OF REVISION OF THE TEXT

23 April 2011

LEGAL CATEGORY

POM