SUMMARY OF PRODUCT CHARACTERISTICS

1 TRADE NAME OF THE MEDICINAL PRODUCT

Tildiem 60mg Modified-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 60mg of the active substance diltiazem hydrochloride

Also contains 125.5mg of lactose monohydrate and 28mg of hydrogenated castor oil.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified release tablet

White, round, biconvex tablets engraved with `TILDIEM 60' or `DILT 60' or `DTZ 60' on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis and treatment of Angina Pectoris

4.2 Posology and Method of Administration

Adults: The usual dose is one tablet (60mg) three times daily. However, patient responses may vary and dosage requirements can differ significantly between individual patients. If necessary the divided dose may be increased to 360mg/day. Higher doses up to 480mg/day have been used with benefit in some patients especially in unstable angina. There is no evidence of any decrease in efficacy at these high doses.

Elderly and patients with impaired hepatic or renal function: The recommended starting dose is one tablet (60mg) twice daily. The heart rate should be measured regularly in these groups of patients and the dose should not be increased if the heart rate falls below 50 beats per minute.

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 interactions).

Hypersensitivity to diltiazem or to any of the excipients.

### 4.4 Special Warnings and Special Precautions for Use

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

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 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 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-H₂ 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-H₂ 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:**

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. 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.

**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

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.

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
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<tr>
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<td></td>
<td>Thrombocytopenia</td>
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<td>Psychiatric disorders</td>
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<td></td>
<td>Nervousness, insomnia</td>
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<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness</td>
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<td>Extrapyramidal syndrome</td>
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<td>Cardiac disorders</td>
<td>Atroventricular block (may be of first, second or third degree; bundle branch block may occur), palpitations</td>
<td>Bradycardia</td>
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<td></td>
<td></td>
<td>Sinoatrial block, congestive heart failure</td>
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<td>Vascular disorders</td>
<td>Flushing</td>
<td>Orthostatic hypotension</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation, dyspepsia, gastric pain, nausea</td>
<td>Vomiting, diarrhea</td>
<td>Dry mouth</td>
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<td>Gingival hyperplasia</td>
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<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatic enzymes increase (AST, ALT, LDH, ALP increase)</td>
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<td>Hepatitis</td>
</tr>
</tbody>
</table>
### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
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</thead>
<tbody>
<tr>
<td>Erythema</td>
<td></td>
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<td>Urticaria</td>
<td>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 generalized exanthematous pustulosis, occasionally desquamative erythema with or without fever</td>
</tr>
</tbody>
</table>

### Reproductive system and breast disorders

| General disorders and administration site conditions | Peripheral oedema | Malaise | | Gynecomastia |

### 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

Tildiem is a calcium antagonist. It restricts the slow channel entry of calcium into the cell and so reduces the liberation of calcium from stores in the sarcoplasmic reticulum. This results in a reduction of the amount of available intracellular...
calcium reducing myocardial oxygen consumption. It increases exercise capacity and improves all indices of myocardial ischaemia in the angina patient. Tildiem relaxes large and small coronary arteries and relieves the spasm of vasospastic (prinzmetal's) angina and the response to catecholamines but has little effect on the peripheral vasculature. There is therefore no possibility of reflex tachycardia. A small reduction in heart rate occurs which is accompanied by an increase in cardiac output, improved myocardial perfusion and reduction of ventricular work. In animal studies, Tildiem protects the myocardium against the effects of ischaemia and reduces the damage produced by excessive entry of calcium into the myocardial cell during reperfusion.

5.2 Pharmacokinetic Properties

Diltiazem hydrochloride is effective in angina, protecting the heart against ischaemia, vasodilating coronary arteries and reducing myocardial oxygen requirements. It is well tolerated and does not generally give rise to side effects associated with peripheral vasodilators, nor cause significant myocardial depression.

Diltiazem is well absorbed (90%) in healthy volunteers following oral administration. Peak plasma concentrations occur 3 to 4 hours after dosing.

Due to a first pass effect, the bioavailability of the 60 mg tablet is about 40%.

The mean apparent plasma half-life is 4 - 8 hours.

Diltiazem is 80 to 85% bound to plasma proteins. 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.

There is a linear relationship between dose and plasma concentration. During long term administration to any one patient, plasma concentrations of diltiazem remain constant.

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

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 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

Lactose monohydrate
Macrogol 6000
Hydrogenated caster oil
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years

6.4 Special Precautions for Storage

This medicinal product does not require any special storage conditions.

6.5 Nature and Contents of Container

PVC/foil blister packs of 90 tablets

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

PL 04425/0640

9 DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

Date of first authorisation: 8 March 1984
Date of latest renewal: 23 September 2005

10 DATE OF REVISION OF THE TEXT

13 April 2011
LEGAL CATEGORY

POM