IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1328/101/003
Case No: 2061333

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

B & S Healthcare

Unit 4, Bradfield Road, **Ruislip**, **Middlesex**, **HA4 0NU**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Tildiem LA 200mg Prolonged-Release Hard Capsules

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **08/05/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tildiem LA 200 mg Prolonged-Release Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200mg diltiazem hydrochloride as the active ingredient in a combination of immediate release and coated prolonged-release pellets.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release, hard capsules

Product imported from the UK:
Opaque capsules with a grey body and a pink cap containing white immediate release and prolonged-release pellets.

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 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

Pregnancy, women of childbearing potential and lactation (see section 4.6 Pregnancy and Lactation).
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.
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 detected on the electrocardiogram (risk of exacerbation and rarely of complete block) or prolonged PR interval.
Plasma diltiazem concentrations can be increased 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.
Abnormalities of liver function may appear during therapy.
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.
The risk of raised creatine kinase, myopathy and rhabdomyolisis due to statins (metabolised by CYP3A4) may be increased in case of a concomitant use of diltiazem. Closer monitoring for signs and symptoms is warranted in such case.

4.5 Interaction with other medicinal products and other forms of interaction

COMBINATION CONTRA-INDICATED FOR SAFETY REASONS:
Dantrolen (infusion)
Lethal ventricullar 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.

Cyclosporin:

Increase in circulating cyclosporin levels. It is recommended that the cyclosporin dose be reduced, renal function be monitored, circulating cyclosporin 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_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.
COMBINATIONS TO BE TAKEN INTO ACCOUNT:
Oral administration of dilitiazem can raise the plasma concentration of drugs exclusively metabolised by CYP3A4. The concomitant therapy of diltiazem and statins metabolised by the CYP3A4 group (simvostatin, atorvastatin, lovastatin) increases the risk of raised creatine kinase, myopathy and rhabdomyolisis.

4.6 Pregnancy and lactation

Pregnancy: this drug has been shown to be teratogenic in certain animal species and is therefore contraindicated in pregnancy and in women of child-bearing potential.
Breast feeding: as this drug is excreted in breast milk, breast feeding while taking diltiazem is contraindicated.

4.7 Effects on ability to drive and use machines

No effect reported to date.

4.8 Undesirable effects

Cardiovascular disorders:

The manifestations of vasodilation (hypotension, headache, flushing and in particular oedema of the lower limbs) are dose-dependent and appear more frequently in elderly subjects and are related to the pharmacological activity of the product.
Orthostatic hypotension.
Occasional cases of vasculitis.
Rare cases of symptomatic bradycardia, sino-atrial block, atrioventricular block and palpitations.
Development or aggravation of congestive heart failure.

Gastro-intestinal system disorders:

Digestive disturbances such as dyspepsia, gastric pain, nausea, constipation, dry mouth.
Gingival hyperplasia.

Platelet, bleeding and clotting disorders:

Thrombocytopenia.

Skin and appendage disorders:

Muco-cutaneous reactions such as simple erythema, urticaria, or occasionally desquamative erythema, with or without fever and photosensitivity have been reported, with patients recovering when the treatment is discontinued.
Erythema multiforme (including rare cases of Steven-Johnson's syndrome), exfoliative dermatitis, acute generalised exanthematous pustular dermatitis and angioneurotic odema have been reported. Very rare cases of Toxic Epidermal Necrolysis have also been reported.

Liver and other biliary system disorders:

Isolated cases of moderate and transient elevation of liver transaminases have been observed at the start of treatment.
Isolated cases of clinical hepatitis have been reported which resolved on cessation of diltiazem therapy.

Musculoskeletal disorders:

Arthralgia.
Others:
Malaise, dizziness, asthenia/fatigue, syncope
As with some other calcium channel blockers, exceptional cases of extrapyramidal symptoms and gynaecomastia have been reported, reversible after discontinuation of calcium antagonists.
Raised creatine kinase, myopathy and rhabdomyolisis due to statins metabolised by the CYP3A4 system when taken concomitantly with diltiazem, see section 4.5, Interactions with Other Medicinal Products and Other Forms of Interaction.

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

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

No data of therapeutic relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Carmellose sodium
Co-polymers of acrylic and methacrylic esters
Ethylcellulose
Diacetylated Monoglycerides
Magnesium stearate
Gelatine
Red Iron Oxide (E172)
Black iron oxide (E172)
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC/aluminium blisters in an overlabelled carton containing 28 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

7 Parallel Product Authorisation Holder

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8 Parallel Product Authorisation Number

PPA 1328/101/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th May 2009

10 DATE OF REVISION OF THE TEXT