IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0126/168/002
Case No: 2071930

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

Clonmel Healthcare Limited

Waterford Road, **Clonmel**, **Co. Tipperary**, **Ireland**

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

Istamel 10 mg Tablets

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 **23/11/2009** until **11/01/2012**.

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

Istamel 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of amlodipine (as amlodipine besilate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, round tablets with a break score on one side. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Essential hypertension.

Chronic stable and vasospastic angina pectoris.

4.2 Posology and method of administration

In adults
For treatment of both hypertension and angina pectoris, the usual initial dose is 5 mg once daily. If the desired therapeutic effect cannot be achieved within 2-4 weeks, this dose may be increased to a maximum dose of 10 mg daily (as a single dose), depending on the individual patient's response. Amlodipine may be used either as monotherapy or in combination with other antianginal drugs in patients with angina.

Children and adolescents
Amlodipine is not recommended for children and adolescents below 18 years due to insufficient data on safety and efficacy (see section 4.4).

In the elderly
Normal dosage regimens are recommended in the elderly, but caution should be exercised when increasing the dosage (see section 5.2).

In patients with renal impairment
In these patients amlodipine can be used at the normal dosage (see section 5.2). Amlodipine should be administered with particular caution in patients undergoing dialysis. Amlodipine is not dialysable.

In patients with hepatic impairment
A dosage regimen for patients with hepatic impairment has not been established and therefore amlodipine should be administered with caution (see section 4.4).

The tablets should be taken with a glass of water with or without food.

4.3 Contraindications

Amlodipine is contraindicated in patients with:

- hypersensitivity to amlodipine, dihydropyridine derivates or to any of the excipients
- severe hypotension
- shock, including cardiogenic shock
- heart failure after acute myocardial infarction (during the first 28 days)
- narrowing of the left ventricular outflow tract (e.g. high grade aortic stenosis)
- unstable angina pectoris

4.4 Special warnings and precautions for use

Amlodipine should be administered with caution to patients with low cardiac reserve.

There are no data to support the use of amlodipine alone, during or within one month of myocardial infarction. The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with heart failure
Patients with heart failure should be treated with caution. In a long-term study of patients suffering from severe heart failure (NYHA grade III and IV), the reported incidence of pulmonary oedema was higher in the amlodipine-treated group than in the placebo group, but this was not associated with aggravation of the heart failure (see section 5.1).

Use in patients with impaired renal function
Amlodipine should be used with caution in patients with severe renal insufficiency (see section 5.2).

Use in patients with impaired hepatic function
The half-life of amlodipine is prolonged in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be administered with caution in these patients.

Use in elderly patients
In the elderly, caution should be exercised when increasing the dosage see section 5.2).

Use in children
Amlodipine is not recommended for use in children due to insufficient clinical experience.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on amlodipine
CYP3A4 inhibitors: A study of elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4, since plasma concentration increases by approx. 50% and the effect of amlodipine is increased. It cannot be excluded that stronger inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) increase the plasma concentration of amlodipine to a greater extent than diltiazem. Caution should be exercised when amlodipine is used in combination with CYP3A4 inhibitors.

CYP3A4-inducers: There is no information on the effect of CYP3A4 inducers (i.e. rifampicin, St. John's wort) on amlodipine. Co-administration may lead to a reduced plasma concentration of amlodipine. Caution should be exercised when amlodipine is used in combination with CYP3A4 inducers.

Effects of amlodipine on other medicinal products
Amlodipine may potentiate the effect of other antihypertensives such as beta-adrenoreceptor blocking agents, ACE-inhibitors, alpha-1-blockers and diuretics. In patients with an increased risk (for example after myocardial infarction), the combination of a calcium channel blocker with a beta-adrenoreceptor blocking agent may lead to heart failure, to hypotension and to a (new) myocardial infarction.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

Amlodipine has no effect on laboratory tests.

4.6 Pregnancy and lactation

There are no adequate data on the use of amlodipine in pregnant women.

In animal studies, effects on reproduction were found at high dosages (see section 5.3). The potential risk for humans is unknown. Accordingly, amlodipine should not be used during pregnancy unless strictly indicated.

It is not known whether amlodipine is excreted in breast milk. It is advisable to stop breast-feeding during treatment with amlodipine.

4.7 Effects on ability to drive and use machines

In patients suffering from dizziness, headache, fatigue or nausea, the ability to react may be impaired.

4.8 Undesirable effects

Very common (≥1/10)
Common (≥1/100 and <1/10)
Uncommon (≥1/1,000 and <1/100)
Rare (≥1/10,000 and <1/1,000)
Very rare (<1/10,000), including isolated reports

Blood and lymphatic system disorders:
Very rare: Leukocytopenia, thrombocytopenia.

Endocrine disorders:
Uncommon: Gynaecomastia.

Metabolism and nutrition disorders:
Very rare: Hyperglycaemia.

Psychiatric disorders:
Uncommon: Sleep disorder, irritability, depression.
Rare: Confusion, mood changes including anxiety.

Nervous system disorders:
Common: Headache (especially at the start of the treatment), fatigue, dizziness, asthenia.
Uncommon: Malaise, tremor, paraesthesia, increased sweating.
Rare: Taste changes.
Very rare: Peripheral neuropathy.

Eye disorders:
Uncommon: Visual disturbances.

Ear and labyrinth disorders:
Uncommon: Tinnitus.

Cardiac disorders:
Common: Palpitations.
Uncommon: Syncope, tachycardia, chest pains, aggravation of angina pectoris (may occur at the start of treatment), isolated cases of myocardial infarction and arrhythmias (including extra systole, ventricular tachycardia, bradycardia and atrial arrhythmias) and angina pectoris have been reported in patients with coronary artery disease, but a clear association with amlodipine has not been established.

Vascular disorders:
Uncommon: Hypotension.
Very rare: Vasculitis.
Common: Facial flushing with heat sensation, especially at the start of treatment.

Respiratory, thoracic and mediastinal disorders:
Uncommon: Dyspnoea, rhinitis.
Very rare: Cough.

Gastrointestinal disorders:
Common: Nausea, dyspepsia, abdominal pain.
Uncommon: Vomiting, diarrhoea, constipation, gingival hyperplasia, dry mouth.
Very rare: Gastritis.

Hepatobiliary disorders:
Rare: Elevated liver enzymes, jaundice, hepatitis.
Very rare: Pancreatitis.

Skin and subcutaneous tissue disorders:
Uncommon: Exanthema, pruritus, urticaria, alopecia, skin discolouration, purpura.
Very rare: Angioedema, isolated cases of allergic reactions including pruritus, rash, angioedema and erythema exsudativum multiforme, exfoliative dermatitis, Stevens Johnson syndrome and Quincke oedema have been reported.

Musculoskeletal, connective tissue disorders:
Very common: Ankle swelling.
Uncommon: Muscle cramps, back pain, myalgia and arthralgia.

Renal and urinary disorders:
Uncommon: Increased micturition frequency.

Reproductive system and breast disorders:
Uncommon: Impotence.

General disorders and administration site conditions:
Uncommon: Increase or decrease in weight.

4.9 Overdose

In humans, experience with intentional overdose is limited. Available data suggest that overdosage (>100 mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension.

Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of the extremities, and attention to circulating fluid volume and urine output.

A vasoconstrictor may be useful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of activated charcoal up to 2h after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dihydropyridine derivates.
ATC code: C08C A01
Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and smooth muscle cells. The mechanism of the antihypertensive action is due to the direct spasmolytic effect on vascular smooth muscle cells. The precise mechanism by which amlodipine relieves angina pectoris has not been fully determined, but the following two actions play a role:

1. Amlodipine dilates peripheral arterioles and thus reduces the peripheral resistance (afterload) against which the heart pumps. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2. Dilation of the main coronary arteries and the coronary arterioles also probably plays a role in its action. This dilation increases the supply of oxygen to myocardiac muscle in patients with Prinzmetal's angina.

In *patients with hypertension*, once daily dosing provides a clinically significant reduction of blood pressure (in both the supine and standing position), that persists for 24 hours.

In *patients with angina pectoris*, once daily administration of amlodipine increases total exercise time and delays the occurrence of an anginal attack and a 1-mm ST segment depression. Amlodipine decreases both the frequency of angina attacks and glyceryl trinitrate tablet consumption.

In haemodynamic studies *in patients with heart failure* and in clinical studies based on exercise tests in patients with NYHA class II-IV heart failure, amlodipine was found not to cause any clinical deterioration, as measured by exercise tolerance, left ventricular ejection fraction and clinical signs and symptoms.

5.2 Pharmacokinetic properties

Absorption and distribution
After oral administration of therapeutic doses, amlodipine is slowly absorbed from the gastrointestinal tract. The absorption of amlodipine is unaffected by the concomitant intake of food. The absolute bioavailability of the unchanged compound is estimated to be 64-80%. Peak plasma levels are reached 6-12 hours post-dose. The volume of distribution is about 20 l/kg. The pKa of amlodipine is 8.6. Plasma protein binding in vitro is approximately 98%.

Metabolism/Elimination
The plasma elimination half-life varies between 35 and 50 hours. Steady-state plasma levels are reached after 7-8 consecutive days.

Amlodipine is extensively metabolised to inactive metabolites. About 60% of the administered dose is excreted in the urine, about 10% of which is in the form of unchanged amlodipine.

In the elderly
The time to reach peak plasma concentrations is the same in elderly and younger patients. Clearance may be reduced in elderly patients so that the area under the curve (AUC) and the terminal elimination half-life are increased. The recommended dosage regimen for elderly patients is, however, the same, although caution should be exercised when increasing the dosage.

In patients with impaired renal function
Amlodipine is extensively metabolised to inactive metabolites. 10% of the substance is excreted unchanged in the urine. Changes in amlodipine plasma concentration are not correlated with the degree of renal impairment. In these patients, amlodipine may be administered at the normal dosage. Amlodipine is not dialysable.

Patients with hepatic impairment
The half-life of amlodipine is prolonged in patients with impaired hepatic function.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. In reproduction toxicity studies in rats, delayed parturition, difficult labour and impaired foetal and pup survival were seen at high doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)
Calcium hydrogen phosphate, anhydrous (E341)
Sodium starch glycolate (type A)
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Blister packs of aluminium/PVC/PE/PVDC with 7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 98 or 100 tablets.

Not all pack sizes may be marketed.

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

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA126/168/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12th January 2007

10 DATE OF REVISION OF THE TEXT

November 2009