IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA1488/002/001
Case No: 2056957

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

Sam McCauley Chemists Limited

Unit 11, Ardcavan Business Park, **Wexford**, **Ireland**

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

Istin Tablets 5 mg

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 **13/02/2009**.

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

Istin Tablets 5 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Amlodipine Besilate equivalent to 5 mg Amlodipine.
For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Product imported from the UK:
White, emerald shaped tablets with the imprints AML-5 on one side and "Pfizer" as logo on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. In the management of essential hypertension and can be used as the sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single antihypertensive may benefit from the addition of Istin, which has been used in combination with a thiazide diuretic, alpha-blocker, beta-adrenoceptor blocking agent, or an angiotensin-converting enzyme inhibitor.

2. In the prophylaxis of angina pectoris associated with myocardial ischaemia whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal or variant angina) of the coronary vasculature.

3. It may also be used where the clinical presentation suggests a possible vasospastic / vasoconstriction component but where vasospasm / vasoconstriction has not been confirmed.

4. It may be used as monotherapy, or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta-adrenoceptor blocking agents.

5. Istin is well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease.

4.2 Posology and method of administration

In Adults: For both hypertension and angina, the usual initial dose is 5 mg amlodipine once daily which may be increased to a maximum dose of 10 mg depending on the individual patient’s response.

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers and angiotensin-converting enzyme inhibitors.

In children: Not recommended.

Use in Elderly: Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Therefore the normal dosage regimen is recommended.

Patients with Renal Impairment: Changes in amlodipine plasma concentration are not correlated with the degree of renal impairment therefore the normal dosage is recommended.

Patients with Hepatic Impairment: See section 4.4 Special Warnings and Precautions for Use.

4.3 Contraindications

Patients with a known hypersensitivity to dihydropyridines, amlodipine, or any of the inert ingredients.

Istin should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina).

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Use in patients with Heart Failure: In a long-term, placebo controlled study (PRAISE-2) of Istin in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. See section 5.1 “Pharmacodynamic Properties”.

Patients with Hepatic Impairment: As with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients. There are no data to support the use of Istin alone, during or within one month of a myocardial infarction.

The safety and efficacy of Istin in hypertensive crisis has not been established.

See section 4.8 Undesirable effects.

4.5 Interaction with other medicinal products and other forms of interaction

Amlodipine has been safely administered with thiazide diuretics, alpha-blockers, beta blockers, angiotensiveconverting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

Amlodipine will not protect against the effects of withdrawal of beta-adrenoceptor blocking agents or the rebound effects seen with various hypertensive agents.

Special Studies: Effect of other agents on amlodipine

Cimetidine: Co-administration of Istin with cimetidine did not alter the pharmacokinetics of Istin.

Grapefruit juice: Co-administration of 240ml of grapefruit juice with a single oral dose of Istin 10mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of Istin.

Aluminium/magnesium (antacid): Co-administration of aluminium/magnesium antacid with a single dose of Istin had no significant effect on the pharmacokinetics of Istin.

Sildenafil: A single 100mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of Istin. When Istin and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of amlodipine on other agents.

Atorvastatin: Co-administration of multiple 10mg doses of Istin with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of Istin with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): Single and multiple 10mg doses of Istin had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Co-administration of Istin with warfarin did not change the warfarin prothrombin response time.

Ciclosporin: Pharmacokinetic studies with ciclosporin have demonstrated that Istin does not significantly alter the pharmacokinetics of ciclosporin.

Drug/Laboratory test Interaction: None known.

4.6 Pregnancy and lactation

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy or lactation. Accordingly, Istin should not be administered during pregnancy, or lactation, or to women of childbearing potential unless effective contraception is used.

4.7 Effects on ability to drive and use machines

Clinical experience with Istin indicates that it is unlikely to impair a patient's ability to drive or use machinery, however see Section 4.8 Undesirable effects.

4.8 Undesirable effects

The frequency of these adverse effects have been classified as very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000 ,< 1/1,000) and very rare (<1/10,000), and also includes isolated reports, where appropriate.

Blood and the Lymphatic System Disorders	thrombocytopenia leucopenia	Very Rare
Immune System Disorders	allergic reaction	Very Rare
Metabolism and Nutrition Disorders	hyperglycemia	Very Rare
Psychiatric Disorders	insomnia, mood changes	Uncommon
Nervous System Disorders	somnolence, dizziness, headache	Common
	tremor, taste perversion. syncope, hypoesthesia, paresthesia	Uncommon
	hypertonia, peripheral neuropathy	Very Rare
Eye Disorders	visual disturbances	Uncommon
Ear and Labyrinth Disorders	tinnitus	Uncommon
Cardiac Disorders	palpitations	Common
	myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Very Rare

Vascular Disorders	flushing	Common
	hypotension	Uncommon
	vasculitis	Very Rare
Respiratory, Thoracic and Mediastinal Disorders	dyspnea, rhinitis	Uncommon
	coughing	Very Rare
Gastrointestinal Disorders	abdominal pain, nausea	Common
	vomiting, dyspepsia, altered bowel habits, dry mouth	Uncommon
	pancreatits, gastritis, gingival hyperplasia	Very Rare
Hepato-biliary Disorders	hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestatis)	Very Rare
Skin and Subcutaneous Tissue Disorders	alopecia, purpura, skin discolouration, increased sweating, pruritus, rash	Uncommon
	angioedema, erythema multiforme, urticaria	Very Rare
Musculoskeletal and Connective Tissue Disorders	arthralgia, myalgia, muscle cramps, back pain	Uncommon
Renal and Urinary Disorders	micturition disorder, nocturia, increased urinary frequency	Uncommon
Reproductive System and Breast Disorders	impotence, gynecomastia	Uncommon
General Disorders and Administration Site Conditions	edema, fatigue	Common
	chest pain, asthenia, pain, malaise	Uncommon
Investigations	weight increase, weight decrease	Uncommon

Very rarely, heart block has been found in patients treated with amlodipine and causality is uncertain.

4.9 Overdose

Available data suggest that gross overdosage could result in excessive peripheral vasodilation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to Istin overdosage calls for active cardiovascular support including monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor agent may be helpful in restoring vascular tone and blood pressure, provided that there is no contra-indication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Since Istin is highly protein-bound, dialysis is unlikely to be of benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Amlodipine is a calcium ion influx inhibitor (slow channel blocker) or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of Istin is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which Istin relieves angina has not been fully determined but Istin reduces total ischaemic burden by the following two actions:

1. Amlodipine dilates peripheral arterioles and thus reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2**.** The mechanism of action of Istin probably involves dilation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine treatment.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in Patients with Heart Failure:

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and angiotensin converting enzyme (ACE) inhibitors has shown that Istin did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of Istin in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, Istin had no effect on total cardiovascular mortality. In this same population Istin was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease (CHD) risk factor, including: previous myocardial infarction or stroke (6 months prior to enrolment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI(0.90-1.07) p=0.65. Among Secondary Endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% % vs 7.7%, RR 1.38, 95% CI[1.25-1.52] p 0.001). However, there was no significant difference in all cause mortality between amlodipine-based therapy and chlorthalidone-based therapy, RR 0.96 95 % CI[0.89-1.02] p=0.20.

5.2 Pharmacokinetic properties

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6 – 12 hours post-dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21L/kg.

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after 7-8 days of consecutive dosing. Amlodipine is extensively metabolised to inactive metabolites with 0% of the parent compound and 60% of metabolites excreted in the urine.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Dibasic calcium phosphate
Sodium starch glycollate
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf life expiry date of this product is the date shown on the container and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Opaque blister calendar packs with foil backing containing 28 tablets.

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 Parallel Product Authorisation Holder

Sam McCauley Chemists Limited
Unit 11, Ardcavan Business Park
Wexford
Ireland

8 Parallel Product Authorisation Number

PPA 1488/2/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 13th February 2009

10 DATE OF REVISION OF THE TEXT