IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0743/003/002
Case No: 2059566

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

Chiesi Limited

Cheadle Royal Business Park, **Highfield**, **Cheadle**, **SK8 3GY**, **United Kingdom**

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

Monomax 40 mg prolonged-release capsules, hard

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 **23/12/2008**.

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

Monomax 40 mg prolonged-release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40 mg isosorbide mononitrate.

Excipients:
Lactose monohydrate 120 mg
Sucrose not more than 46 mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard

Each size 2 capsule contains spherical off-white microgranules.
The capsule shell has an opaque white cap and body.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the prophylactic treatment of angina pectoris and as an adjunct for the treatment of chronic heart failure.

4.2 Posology and method of administration

Route of Administration

For oral use

Dosage

Capsules may be taken with or without food, and should be swallowed whole and not chewed.

Prophylaxis of Angina

Adults: Usual dose is 40 mg per day. The dose may be taken as a single administration or in a divided dose which in order to avoid tolerance should be administered in an asymmetric regimen (dosing intervals of 7 and 17 hours). The daily dose may be increased to 60 mg.

Children: Safety and efficacy in children has not been established.

Elderly : There is no evidence of a need for routine dosage adjustment in the elderly, but special care may be needed in those with increased susceptibility to hypotension or marked hepatic or renal insufficiency.

Congestive Heart Failure

Adults: 40 mg or 60 mg every twelve hours. Isosorbide mononitrate SR capsules can be used in addition to first-line diuretic therapy.

Children: Safety and efficacy in children has not been established.

Elderly: There is no evidence of a need for routine dosage adjustment in the elderly, but special care may be needed in those with increased susceptibility to hypotension or marked hepatic or renal insufficiency.

4.3 Contraindications

This product should not be given to patients with a known sensitivity to nitrates.

Isosorbide-5-mononitrate should not be used in patients with acute myocardial infarction with low filling pressure, marked anaemia, head trauma, cerebral haemorrhage, severe hypotension or hypovolaemia.

The co-administration of isosorbide mononitrate with phosphodiesterase type 5 inhibitors is contra-indicated; it has been shown that the hypotensive effects of nitrates are potentiated by phosphodiesterase type 5 inhibitors, which is consistent with the known effects of phosphodiesterase type 5 inhibitors on the nitric oxide / cyclic guanosine monophosphate pathway.

4.4 Special warnings and precautions for use

Isosorbide mononitrate SR 40 mg capsules are not indicated for relief of acute angina attacks; in the event of an acute attack, sublingual or buccal glyceryl trinitrate tablets / sprays should be used.

Isosorbide mononitrate should be used with caution in patients who are predisposed to closed angle glaucoma.

Isosorbide mononitrate should be used with caution in patients suffering from hypothyroidism, hypothermia, malnutrition, severe liver or renal disease.

Isosorbide mononitrate should not be co-administered with sildenafil. As a result of its vasodilator properties, sildenafil can potentiate the hypotensive effects of nitrates.

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

4.5 Interaction with other medicinal products and other forms of interaction

Some of the effects of alcohol may be potentiated by this agent.

Vasodilators, antihypertensives and diuretics may potentiate the hypotension caused by nitrates particularly in the elderly.

The hypotensive effects of nitrates are potentiated by concomitant administration of phosphodiesterase inhibitors.

There is no evidence of interaction with food.

4.6 Pregnancy and lactation

Since its safety and efficacy have not been established, this product should not be used during pregnancy or lactation unless considered essential by the physician.

4.7 Effects on ability to drive and use machines

Since postural hypotension with symptoms such as dizziness has been reported, patients should be advised to be

careful when driving or operating machinery if they suffer from these symptoms.

4.8 Undesirable effects

General Disorders and Administration

Using the recommended dosage schedules there is no evidence of development of nitrate tolerance.

Nervous System Disorders

Headache may occur at the onset of treatment but may be minimised by commencing with low doses and gradually increasing the dose.

Skin and Soft Tissue Disorders

Dry skin rashes may occur oaccasionally.

Vascular Disorders

Cutaneous vasodilation and postural hypotension may occur occasionally.

4.9 Overdose

Symptoms

A pulsating headache is the commonest.

More serious symptoms are excitation, flushing, cold perspiration, nausea, vomiting, vertigo, syncope, tachycardia and a fall in blood pressure.

Management

Induce emesis. Use activated charcoal.

If pronounced hypotension, place the patient in the supine position with legs raised. If necessary, intravenous fluids should be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C01D A14

Nitrate compounds relax smooth muscle causing dilatation of the veins and arteries, and to a lesser extent the arterioles. The result is a very marked reduction of preload, accompanied by lowering of the right heart pressures and left ventricular and diastolic pressure.

The dimensions of the right and left ventricles and ejection volumes are reduced but the reflex increase of heart rate prevents any reduction of cardiac output. Myocardial oxygen consumption may thus fall by more than 50% in parallel with the reduction of left ventricular preload. At higher doses, afterload is also decreased by arterial and arteriolar dilatation; this also helps to improve cardiac function.

Nitrate compounds exert a dilatory and antispasmodic effect on the coronary vessels; they are effective against both spontaneous and induced spasms.

5.2 Pharmacokinetic properties

In man, isosorbide-5-mononitrate is absorbed completely and rapidly following oral administration.

Isosorbide-5-mononitrate is not subject to the 'hepatic first-pass' effect, and provides a low degree of inter-individual variation of blood levels.

Isosorbide-5-mononitrate SR capsules have all the pharmacokinetic characteristics of a true sustained-release dosage form. Compared with an immediate-release dosage form, the peak plasma concentration obtained is lower and occurs later, while the apparent elimination half-life is unchanged; there is less fluctuation between Cmax and Cmin, whereas bioavailability is equivalent to an immediate-release formulation.
The slow continuous diffusion of the active ingredient from the sustained-release microgranules makes it possible, at steady rate, to maintain plasma concentrations above the putative effective level of 100 ng/ml for a period of about 12 hours for the 20 mg capsules, 16 hours for the 40 mg capsules and 20 hours for the 60 mg capsules.

5.3 Preclinical safety data

Isosorbide mononitrate produces very few toxic effects and is less toxic than isosorbide dinitrate. After chronic administration at high doses (60 mg/kg), signs of toxicity have been detected in canine liver and kidneys. Tests conducted have shown no evidence of a teratogenic or mutagenic potential. The sustained-release microgranules in Monomax capsules have proven to be less toxic after single doses than isosorbide mononitrate alone (bibliographic data).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres

<u>For Microgranule Coating:</u>
Lactose monohydrate
Methacrylic acid-methyl methacrylate copolymer (1:1)
Ammonio methacrylate copolymer (type B)
Bleached Dewaxed shellac (E904)
Dewaxed Shellac (E904)
Talc

<u>For Capsule Shell</u>
Gelatin
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The capsules are enclosed in blisters composed of 20 µm aluminium foil/250 µm PVC film. The blisters are packed into folded printed cardboard cartons with a patient information leaflet. Packs contain 8 (sample packs only) 28, 30, 56 or 60 sustained release capsules.
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

Chiesi Limited
Cheadle Royal Business Park
Highfield
Cheadle
SK8 3GY
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 743/3/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th May 1996
Date of last renewal: 9th May 2006

10 DATE OF REVISION OF THE TEXT

December 2008