IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0549/003/002
Case No: 2043622

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

Ethypharm SA

17-21 rue St. Matthieu, **78550 Houdan**, **France**

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

Cardox SR 40mg Prolonged-release Capsule

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 **22/04/2008**.

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

Cardox SR 40mg Prolonged-release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains: Isosorbide mononitrate 40.00 mg.

Excipients: also includes lactose monohydrate 120mg per capsule and sucrose 38.5mg per capsule.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release Capsules, hard. (Prolonged-release capsules).

Size 2, opaque white, hard gelatin capsules contains spherical off-white microgranules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Dosage recommendations:

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

- Prophylaxis of angina

Adults: the usual adult dose is 40 mg per day, taken as a single dose or in divided doses. If the dose is divided, in order to avoid tolerance, the first dose should be taken at the same time each day, followed 7 hours later by the second dose. The daily dose may be increased to 60 mg.

Children: safety and efficacy in children have 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. Cardox ™ SR capsules can be used in addition to a first-line diuretic therapy.

Children: safety and efficacy in children have 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 isosorbide mononitrate, other nitrates or to any of the excipients.

This product should not be administered concomitantly with sildenafil, or any other phosphodiesterase type-5 inhibitor (See section 4.5).

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

4.4 Special warnings and precautions for use

Isosorbide-5-mononitrate should be used with caution in patients who are predisposed to closed angle glaucoma.
Isosorbide-5-mononitrate should be used with caution in patients suffering from hypothyroidism, hypothermia, malnutrition, severe liver or renal disease.
Cardox ™ SR 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.

This medicinal product contains sucrose and lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency 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.

The hypotensive effects of other drugs such as alprostadil, aldesleukin and angiotensin II receptor antagonists may be potentiated. In particular, the hypotensive effects of nitrates are potentiated by concurrent co-administration of phosphodiesterase type-5 inhibitors e.g. sildenafil (see Section 4.3); these effects are potentially life threatening.

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

There is no evidence of interaction with food.

4.6 Pregnancy and lactation

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

Side-effects including cutaneous vasodilatation, postural hypotension and dry skin rashes may occur occasionally.
Headache may occur at the onset treatment but may be minimised by commencing with low doses and gradually increasing the dose.
Using the recommended dosage schedules there is no evidence of development of nitrate tolerance.

4.9 Overdose

Treatment should be symptomatic. The main symptom is likely to be hypotension.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C01D A14 Vasodilator used in cardiac diseases.

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

The end-diastolic volume and pressure and the ejection fraction 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.

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 prolonged release microgranules makes it possible, at steady state, 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-5-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 prolonged release microgranules in Cardox ™ SR capsules have proved to be less toxic after single doses than isosorbide-5-mononitrate alone (Bibliographic data).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Sucrose and maize starch microgranules
Shellac
Eudragit L 100
Eudragit RS 100
Talc
Gelatin
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years

6.4 Special precautions for storage

Store below 25°C. Store in the original package.

6.5 Nature and contents of container

Blister packs (20 µm aluminium / 250 µm PVC) - boxed in cardboard carton containing 28, 30, 56 or 60 capsules.

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

Ethypharm SA
17-21 rue Saint-Matthieu
78550 Houdan
France

8 MARKETING AUTHORISATION NUMBER

PA 549/3/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th October 1992
Date of last renewal: 13th October 2007

10 DATE OF REVISION OF THE TEXT

April 2008