IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0282/070/001
Case No: 2065611

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

Norton Healthcare Limited T/A IVAX Pharmaceuticals UK

Regent House, 5-7 Broadhurst Gardens, **Swiss Cottage**, **London NW6 3RZ**, **United Kingdom**

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

Cardilate 10mg Prolonged- Release Tablet

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 **14/04/2010**.

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

Cardilate 10mg Prolonged-Release Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Nifedipine 10mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-Release Tablet.
Round, slightly biconvex, pink coated film tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cardilate is indicated for the treatment of mild to moderate hypertension and for prophylaxis of chronic stable angina pectoris.

4.2 Posology and method of administration

Adults:
Cardilate is suitable for long-term treatment of hypertension and for prophylaxis of chronic stable angina pectoris. Dosage must be determined for each patient on the basis of disease severity and the patient's individual response.

The recommended starting dose of Cardilate is 10mg every 12 hours with subsequent titration of dosage according to response. The dose may be adjusted to 40mg every 12 hours.

Tablets must be swallowed whole with a glass of water and must not be broken or chewed. The tablets should be taken during or after food. Nifedipine should not be taken with grapefruit juice (see Section 4.5). Recommended intervals between doses of Cardilate is 12 hours.

Elderly and Special Populations:
The pharmacokinetics of nifedipine are altered in the elderly, so that lower maintenance doses may be required compared to younger patients. Cardilate can be given to patients with impaired renal function without adjustment of dosage.

If hepatic function is impaired, dosage requirement of nifedipine should be established before use of Cardilate. Treatment should be commenced at a dose of 5 or 10 mg nifedipine twice daily with careful monitoring of blood levels to determine the appropriate dose regimen.

Children:
Cardilate is not recommended for treatment of children.

4.3 Contraindications

Cardilate should not be given to patients with known hypersensitivity to nifedipine or other tablet constituents, nor to those in cardiogenic shock.

Cardilate is contraindicated in women of child-bearing potential and those breast-feeding their babies.

Cardilate is contraindicated in patients with advanced aortic stenosis, unstable angina or porphyria.

Cardilate should not be used for the treatment of acute attacks of angina.

It is also contraindicated during or within one month of a myocardial infarct, and for secondary prevention after myocardial infarction.

Efficacy and safety in malignant hypertension has not been established.

4.4 Special warnings and precautions for use

Cardilate should only be administered to patients with low cardiac reserve or with severe hypotension with caution. Patients at risk of hypotensive crisis should begin any therapy under close medical supervision.

In patients on haemodialysis with malignant hypertension and irreversible renal failure with hypovolaemia, nifedipine should be given with caution. An exaggerated fall in blood pressure due to vasodilation may occur.

4.5 Interaction with other medicinal products and other forms of interaction

Cardilate can be administered concomitantly with other antihypertensives including beta-receptor blockers. These may have additive antihypertensive effects and postural hypotension may therefore occur. Cardilate will not prevent the possibility that there might be a rebound effect when other antihypertensive treatment is stopped. Concomitant therapy with cimetidine may potentiate the antihypertensive action of nifedipine. Nifedipine administration may suppress serum levels of quinidine. Therefore on combination therapy monitoring of quinidine levels is recommended. Initial reports that Nifedipine may cause an increase in plasma digoxin levels due to reduced renal drug clearance are unsupported.

Cardilate should not be administered concomitantly with rifampicin, since effective plasma levels of nifedipine may not be achieved owing to enzyme induction.

Cardilate may modify insulin and glucose responses, requiring adjustment in therapy of treated diabetics.

As with other dihydropyridines, Cardilate should not be taken with grapefruit juice as its metabolism may be inhibited.

4.6 Pregnancy and lactation

Cardilate is contraindicated in pregnant women and women of child-bearing potential because fetal risks, observed in animal experiments and during human use, far outweigh the potential benefits.

Nifedipine is secreted into breast milk, so Cardilate should not be administered during lactation.

4.7 Effects on ability to drive and use machines

Infrequently, Cardilate may cause headaches, dizziness, nausea and tiredness to such a degree that reaction time is affected. These effects can be aggravated by concurrent alcohol. If this occurs, the patient should not be allowed to drive or operate machines.

4.8 Undesirable effects

Cardilate may cause headaches, facial reddening and dizziness and leg oedema. These effects are secondary to vasodilation. Less common side-effects include rash, nausea, lethargy and urinary frequency. Rarely, gingival hyperplasia may occur; this may resolve when treatment is discontinued.

Chest pain due to myocardial ischaemia may occur 1-4 hours after ingestion of Cardilate. A ‘steal’ effect has not been observed up to now with Cardilate, but treatment should be discontinued in patients in which this does occur. Cases of hypersensitivity to nifedipine resulting in jaundice have been reported.

Exacerbation of angina pectoris may occur at the start of treatment with sustained release formulations of nifedipine. The occurrence of myocardial infarction has been described, although it is not possible to distinguish such an event from the natural course of ischaemic heart disease.

4.9 Overdose

Toxic effects arise from the three main actions of nifedipine in overdose: dilation of vascular smooth muscles (predominant effect); decreased myocardial contractility; and depression of AV nodal conduction.

Hypotension and tachycardia or bradycardia are the most likely manifestations of overdose. Other toxic effects include nausea, vomiting, drowsiness, dizziness, confusion, lethargy, flushing, coma and convulsions. Cardiac effects may include heart block, AV dissociation and asystole; metabolic disturbances include hyperglycaemia, acidosis, hypo or hyperkalaemia and hypocalcaemia; pulmonary oedema has been reported.

Primary treatment involves removal of nifedipine by gastric lavage or ipecac and administration of activated charcoal (50g adults; 10-15g children). Cardilate MR is a modified release product, therefore activated charcoal should be repeated at 4-hourly intervals (25g adults; 10g children).

The patient should be closely monitored and treated according to predominant signs:

For hypotension: The feet should be raised and plasma expanders given intravenously (calcium chloride should not be given to acidotic patients). If this fails, dopamine may be tried (large doses may be needed). Glucagon may also be of value;

For bradycardia: Treatment with atropine, isoprenaline and cardiac pacing should be given as required.

The value of extracorporeal methods of removal of nifedipine have not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Nifedipine inhibits the influx of calcium into myocardial cells, the smooth muscle cells of the coronary arteries and the peripheral capillaries. Nifedipine brings about a substantial improvement in the oxygen supply to the myocardium while reducing oxygen demand. It has been shown to exhibit anti-anginal properties. High blood pressure is normalised due to a reduction in the peripheral resistance (vasodilation).

5.2 Pharmacokinetic properties

Absorption:
Nifedipine is absorbed rapidly and almost completely following oral administration. Nifedipine can be detected in plasma 30 - 60 minutes after administration of Cardilate and reaches maximal concentration between 0.75 and 5 hours.

Distribution:
Nifedipine is more than 90% serum protein bound. Animal studies with labelled nifedipine have shown that distribution of the fraction not protein bound is throughout all organs and tissues, with higher concentrations in myocardium than in skeletal muscle. Neither nifedipine nor its metabolites are stored selectively in any tissue.

Metabolism:
Nifedipine is converted almost completely to inactive metabolites.

Elimination:
70 to 80% of administered nifedipine is excreted as metabolites by the kidneys with an elimination half-life of approximately 10 hours.

Elimination may be retarded by renal failure or insufficiency.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Carboxymethyl sodium starch
Mannitol (E421)
Colloidal anhydrous silica
Polyvidone
Magnesium stearate
Sodium Laurisulfate

Tablet coating
Hypromellose
Macrogol 6000
Macrogol 400
Red ferric oxide (E172)
Titanium dioxide (E171)
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Three years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Thermoformed blister packs of PVC/red transparent PVdC/aluminium in boxes of 56 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 MARKETING AUTHORISATION HOLDER

Norton Healthcare Ltd
T/A IVAX Pharmaceuticals UK
Regent House
5-7 Broadhurst Gardens
Swiss Cottage
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United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 282/70/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 June 1998

Date of last renewal: 26 June 2008

10 DATE OF REVISION OF THE TEXT

February 2009