IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0282/070/003
Case No: 2069219

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 XL 40mg 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 **08/09/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cardilate XL 40 mg Prolonged-Release Tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Prolonged-Release Tablet contains 40mg Nifedipine

Excipients: Each tablet contains 30.0g lactose

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-Release Tablet.
Red-brownish, round, biconvex film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Adults:
Patients should be treated individually depending on the severity of the disease and the therapeutic response. The following recommendations for dosing in adults **and adolescents over 14 years** are applicable:

The recommended starting dose is one Cardilate XL Tablet every 24 hours. If necessary this dose can be increased to 80 mg (two tablets) every 24 hours.

The modified release tablets are to be taken after meals, e.g. breakfast, with some liquid. The modified release tablets should be swallowed whole with half a glass of water, and must not be broken or chewed. Nifedipine should not be taken with grapefruit juice *(see Section 4.5, Interaction with other medicinal products and other forms of interaction).*

Elderly Hepatic and Renal Impairment:
The pharmacokinetics of nifedipine are altered in the elderly so that lower maintenance doses of nifedipine may be required compared to younger patients.

Nifedipine is primarily metabolised in the liver and therefore patients with liver dysfunction should be carefully monitored.

Treatment should be commenced at a dose of 5mg to 10mg nifedipine twice daily with careful monitoring of blood levels to determine the appropriate dose regimen. Patients with renal impairment should not require adjustment of dosage.

Children:
Nifedipine is not recommended for use in children **under 14 years of age**.

4.3 Contraindications

Cardilate XL should not be administered to patients with an allergy to nifedipine or other tablet constituents, nor to patients with cardiogenic shock.

Cardilate XL is contra-indicated in women with child-bearing potential and those breast-feeding their babies.

Cardilate XL is contra-indicated in patients with clinically significant aortic stenosis, unstable angina or with porphyria.

Efficacy and safety in malignant hypertension has not been established.

Cardilate XL should not be used for the treatment of acute attacks of angina or within one month of a myocardial infarct or for the secondary prevention of myocardial infarction.

4.4 Special warnings and precautions for use

Cardilate XL 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.

Ischaemic pain has been reported in a small proportion of patients following the introduction of nifedipine therapy. Although a 'steal' effect has not been demonstrated, patients experiencing this effect should discontinue nifedipine therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Cardilate XL can be administered concomitantly with other antihypertensives including beta-receptor blockers. These may have additive antihypertensive or potentiating effects and postural hypotension may therefore occur. Concomitant treatment of nifedipine with a beta-blocker occasionally results in the occurrence of heart failure. For this reason a combination with a beta-blocker is only recommended in patients with a sufficient ventricular function. After discontinuation of the beta-blocker a deterioration with regard to the symptoms of angina pectoris may occasionally occur, due to the abrupt withdrawal of the beta-blocker. Therefore, it is not recommended to switch abruptly from a beta-blocker to nifedipine.

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

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

Cardilate XL should not be taken with grapefruit juice as its metabolism may be inhibited.

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

Nifedipine may cause headache, 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 be advised not to drive or operate machines.

4.8 Undesirable effects

Undesirable effects, usually mild and transient in nature, may occur and are more frequent at the beginning of therapy. Frequently, headache, flush (facial reddening), dizziness, as well as oedema, due to vasodilation, may occur. Less common side effects include rash, nausea, lethargy and urinary frequency. In rare cases, in acute studies, a transient increase in glucose has been observed. This should be considered particularly in patients with diabetes mellitus. Nifedipine has no diabetogenic effect. Rarely gingival hyperplasia has been observed which was reversible after discontinuation of therapy. In elderly patients, very rarely a gynaecomastia has been observed which was reversible after discontinuation of therapy.

Additionally, uncommon and rare undesirable effects were also reported:

Uncommon (> 0.1% < 1%)

Body as a whole:	Abdominal pain; chest pain: malaise; pain
Cardiovascular:	Postural hypotension: syncope; tachycardia
Digestive:	Constipation, diarrhoea, dry mouth, Dyspepsia,vomiting
Musculo-sketal:	Arthralgia: myalgia
Nervous:	Insomnia: nervousness: paraesthesia; Somnolence; tremor; vertigo
Respiratory;	Dyspnoea
Skin;	Pruritus; rash skin disorder; sweating
Urogenital system:	Nocturia; polyuria

Exacerbation of angina pectoris may occur at the initial stage of treatment with sustained release formulations of nifedipine.

Rare (>0.01% < 0.1%)

Body as a whole:	Enlarged abdomen; allergic reaction; Photosensitivity reactions; hypersensitivity-type jaundice
Cardiovascular:	Hypotension
Digestive:	Flatulence; gastrointestinal disorder; GGTP increase; liver function test abnormalities.
Haemic and Purpura	Lymphatic system;
Nervous;	Hyperaesthesia; mood changes
Skin;	Urticaria
Special senses;	Abnormal vision, ambylopia
Urogential;	Impotence

The following undesirable effects were reported very rarely worldwide (> 0.01%): gingival hyperplasis, agranulocytosis, erythromelalgia, exfoliative dermatitis and anaphylactic reaction. There has also been reports of gymaecomastia in older men of long-term therapy, but this usually regresses upon withdrawal of therapy.

Cases of hypersensitivity to nifedipine resulting in jaundice have been reported.

List of undesirable effects to body system:

Cardiovascular System:
Tachycardia, hypotension. 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.

Central Nervous System:
Dizziness, tiredness, parasthesia, tremor.

Eyes:
Transient change in optical perception.

Gastro-Intestinal Tract:
Nausea, disturbances.

Skin:
Redness, itching, urticaria, exanthema, and exceptionally exfoliative dermatitis.

Urinary Tract:
An increase in the daily amount of urine so that nocturia may occur.

Legs:
Myalgia.

Liver:
Very rarely liver function disturbances (intrahepatic cholestatis, or increases in transaminases) have occurred which were reversible after discontinuation of therapy.

Miscellaneous:
Gingival hyperplasia, gynaecomastia, increase in glucose in particular in patients with diabetes mellitus.

4.9 Overdose

Toxic effects arise from the three main actions of nifedipine in overdose: dilatation 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 ipecacuanha and administration of activated charcoal (50g adults; 10 - 15g children). Cardilate XL is a modified release matrix tablet, 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:

Hypotension: the feet should be raised and plasma expanders given. If this is not effective, 10% calcium gluconate or chloride can be 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;

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 is a Ca-antagonist of the 1,4,-dihydropyridine type. Ca-antagonists inhibit the slow Ca-channel flux into the myocardial cells, the smooth muscle cells of the coronary arteries and the peripheral capillaries. Nifedipine brings about a substantial improvement in the oxygen supply of 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: Cardilate XL is absorbed rapidly and almost completely following oral administration. Cardilate XL reaches maximal concentrations (29.4 ± 12.0 ng/ml) approximately 5 hours after drug intake at steady state.

The release of nifedipine from the Cardilate XL modified release tablet is almost linear, this means that the drug is delivered at a constant rate.

The relative bioavailability of the modified release form compared to the slow release forms of nifedipine is not statistically different in steady state.

Trough levels after Cardilate XL (24 h post-dose) in steady state (12.0 +/- 6.5 ng/ml) are achieved after the first dose.

Based on its pharmacokinetic profile, an effect due to Cardilate XL is expected over 24 hours.

Concomitant intake of food results in higher maximum plasma concentrations of nifedipine, which occurs earlier compared to administration in fasted state, but the concentrations at the end of the dose interval are similar.

Distribution: The protein binding of Nifedipine amounts to 94 - 99%. 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 almost completely metabolised to inactive metabolites.

Elimination: An apparent half-life of 14.9 +/- 6.0 hours was found. The apparent half-life of Cardilate XL did not change after repeated dosing. Only <1% of the dose is excreted in the urine as the parent compound. 70 - 80% of the dose is excreted in the urine as metabolites. The remainder is excreted as metabolites in the faeces. Elimination may be retarded by renal failure or insufficiency.

5.3 Preclinical safety data

Studies in mice, rats and rabbits demonstrated a low intraperitoneal, subcutaneous and oral acute toxicity. No significant sensibility was detected: LD_{50} in mice p.o. was found to be 421-572 mg/kg, in rats p.o. 950-1087 mg/kg, in rabbits p.o. 250-500 mg/kg, in cats p.o. 100 mg/kg. Toxic symptoms were rapidly and completely reversible in surviving animals. No major differences have been observed between male and female animals.

Subacute, Subchronic and chronic oral toxicity studies in rats demonstrated a low toxicity of high doses of nifedipine. With the exception of a dose-dependent increase in heart and liver weights and phospholipids in the subchronic study, a no-effect dose has been evaluated to be equivalent to 75 times the human therapeutic dose. Only doses of 800 (1200 HTD) and to some extent 400 mg/kg/day, were found to be clearly toxic.

Teratogenicity studies of nifedipine in rats and rabbits demonstrated a teratogenic potential which justify it to be contraindicated in women who are, or may become pregnant.

Extensive mutagenicity studies in Ames Salmonella mutagenicity testing systems were all negative.

No carcinogenic potential has occurred during the long clinical experience with the compound and in the negative Ames.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
microcrystalline cellulose
cellulose
hypromellose
lactose
magnesium stearate
colloidal anhydrous silica

Tablet coating
Macrogol 400
Macrogol 6000
ferric oxide red (E172)
titanium dioxide (E171)
talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Four 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 red transparent, light protective PVC/PVDC-film/aluminium in boxes of 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112, and 120.

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

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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 July 1998

Date of last renewal: 26 June 2008

10 DATE OF REVISION OF THE TEXT

February 2009