IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1363/003/002
Case No: 2079004

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

Selana Healthcare Ltd

Garadice House, **3-4 Fairview**, **Dublin 3**

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

Felodipine 10 mg prolonged release tablets

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 **26/05/2010**.

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

Felodipine, 10 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains 10 mg of felodipine.
Excipient: Each prolonged release tablet contains 20.38 mg lactose.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet
Reddish brown, round, biconvex, film-coated prolonged release tablet with imprint 10.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Essential hypertension.

4.2 Posology and method of administration

Felodipine 5mg and Felodipine 10mg should usually be administered as follows:
The recommended starting dose is 5 mg felodipine once daily.
If necessary the dose may be increased to 10 mg felodipine once daily or another antihypertensive agent added. Dose increases should occur at intervals of at least 2 weeks. The usual maintenance dose is 5-10mg once daily.
The maximum daily dose is 10 mg felodipine.
The dose should be adjusted to the individual requirements of the patient.

Elderly
The recommended starting dose should be adapted in the elderly. Subsequent dose increases should be undertaken with particular caution.

Impaired hepatic function
In patients with mild to moderate hepatic impairment, the recommended starting dose should be lowered to the minimal therapeutic effective dose of felodipine. The dose should only be increased after carefully balancing the benefits against the risks (see 5.2). It is contraindicated in patients with severe hepatic impairment.

Impaired renal function
The pharmacokinetics are not significantly affected in patients with mild to moderate impaired renal function. Caution should be taken in patients with severe renal impairment (see sections 4.4 and 5.2).

Children
The safety and efficacy of felodipine in children has not been established.

Administration
The prolonged release tablets should be taken in the morning with a sufficient amount of fluid (e.g. a glass of water, but it should NOT be taken with grapefruit juice!) (see 4.5).

The prolonged release tablets should be swallowed whole and not chewed or crushed.
The tablets may be taken on empty stomach or with a light meal; however a high-fat meal should be avoided (see 5.2).

4.3 Contraindications

Felodipine is contra-indicated in patients with:
- Hypersensitivity to felodipine (or other dihydropyridines) or to any of the excipients.
- Cardiogenic shock.
- Severe aortic or mitral stenosis.
- Obstructive hypertrophic cardiomyopathy.
- Unstable angina pectoris.
- Acute myocardial infarction (within 4-8 weeks of a myocardial infarction).
- Decompensated heart failure.
- Severe hepatic impairment.
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Felodipine should be used with caution in patients with:
- Onduction disorders, compensated heart failure, tachycardia and aortic and or mitral valve stenosis.
- Mild to moderate hepatic impairment, as the anti-hypertensive effect may be enhanced. Adjustment of the dosage should be considered.
- Severe renal impairment (GFR < 30 ml/min).
- AV block of the second or third degree.

If treatment with felodipine is discontinued abruptly, a hypertensive crisis may occur in individual cases.

Felodipine could cause significant hypotension (vasodilation effect) with consecutive tachycardia, leading to myocardial ischaemia in sensitive patients, therefore predisposed patients may suffer from myocardial infarction (see section 5.1).

Dihydropyridines may cause acute hypotension. In some case there is a risk of hypoperfusion accompanied by reflex tachycardia (paradoxical angor) (see section 5.1).

Felodipine is metabolised by CYP3A4 enzymes. Therefore, combination with medicinal products which are potent CYP3A4 inhibitors or inducers should be avoided (see section 4.5). Due to the same reason the concomitant intake of grapefruit juice should be avoided (see section 4.5).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Felodipine is a CYP3A4 substrate. Drugs that induce or inhibit CYP3A4 will have large influence on felodipine concentrations.

The anti-hypertensive effect of felodipine may be enhanced by other anti-hypertensives and tricyclic antidepressants.

The concomitant intake of felodipine and drugs which inhibit the cytochrome P450 isoenzyme 3A4 of the liver (such as cimetidine, azole antifungals [itraconazole, ketoconazole], macrolide antibiotic [erythromycin] or HIV protease inhibitors leads to increased felodipine plasma levels (see section 4.4). Grapefruit juice results in increased peak plasma levels and bioavailability possibly due to interaction with flavonoids in the fruit juice. Therefore grapefruit juice should not be taken together with felodipine.

Concomitant treatment with drugs such as carbamazepine, phenytoin and barbiturates (e.g. phenobarbital) and rifampicin reduces the plasma levels of felodipine via enzyme induction in the liver (cytochrome P450-System). A similar effect is expected with St. John’s Wort. Therefore a dose increase of felodipine may be necessary.

Hydrochlorothiazide may enhance the anti-hypertensive effect of felodipine.

Felodipine can induce an increase of Cmax of cyclosporine. Additionally, cyclosporine may inhibit felodipine metabolism, which may create a potential risk of felodipine toxicity.

Blood levels of digoxin increase during concomitant administration of felodipine. Therefore, decreasing of digoxin dosage should be taken into account when the two drugs are administered concurrently.

Felodipine may increase the concentration of tacrolimus. When used together, the tacrolimus serum concentration should be followed and the tacrolimus dose may need to be adjusted.

4.6 Pregnancy and lactation

Felodipine is contra-indicated during the entire duration of pregnancy, as animal experiments have demonstrated foetal damage (see 5.3). Pregnancy must be excluded before starting treatment with felodipine.

Felodipine is excreted in breast milk. If the breast-feeding mother is taking therapeutic doses of felodipine, a fully breast-fed infant absorbs only a very low dose of the active substance with the breast milk. There is no experience of the risk this may pose to the newborn, therefore as a precaution breast-feeding should be discontinued during treatment.

4.7 Effects on ability to drive and use machines

Treatment with felodipine requires regular medical supervision. Felodipine can influence individual reactions to such an extent that the ability to take an active part in road traffic or to operate machines or work without suitable safeguards may be impaired. This is particularly the case at start of therapy, or when the dose is increased, or medication is changed as well as after concomitant ingestion of alcohol.

4.8 Undesirable effects

Adverse reactions have been ranked under headings of frequency using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000), not known (cannot be estimated from the available data).

Nervous system disorders
Very common: Headache (particularly at the beginning of treatment, when the dose is increased or when high doses are administered. Generally, those effects subside on continued treatment).
Uncommon: Dizziness, syncope, paraesthesia, tremors, restlessness.

Ear and labyrinth disorders
Very common: Tinnitus (particularly at the beginning of treatment, when the dose is increased or when high doses are administered. Generally, those effects subside on continued treatment).

Cardiac disorders
Common: Angina pectoris (particularly at the beginning of treatment); increase in the frequency, duration and severity of angina pectoris attacks in patients with pre-existing angina pectoris.
Uncommon: Palpitations, tachycardia.
Very rare: Myocardial infarction.

Vascular disorders
Very common: Flushing (particularly at the beginning of treatment, when the dose is increased or when high doses are administered. Generally, those effects subside on continued treatment).
Uncommon: Hypotension.
Rare: Leucocytoclastic vasculitis.

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea.

Gastrointestinal disorders
Uncommon: Gastro-intestinal complaints (e.g. nausea, vomiting, diarrhoea, constipation), gingival hyperplasia and gingivitis.

Hepato-biliary disorders
Very rare: Hepatic function disorders (elevated transaminase levels).

Skin and subcutaneous tissue disorders
Uncommon: Skin and hypersensitivity reactions such as pruritus, urticaria, exanthema, and photosensitization.
Very rare: Exfoliative dermatitis.

Musculoskeletal, connective tissue and bone disorders
Uncommon: Myalgia, arthralgia.

Renal and urinary disorders
Uncommon: Pollakiuria.

Reproductive system and breast disorders
Very rare: Erection disorders, gynaecomastia, menorrhagia.

General disorders and administration site conditions
Common: Peripheral oedema (the degree of ankle swelling is dose related).
Uncommon: Fatigue, weight gain, sweating.
Very rare: Angioedema, fever.

4.9 Overdose

Symptoms of intoxication
Overdose may lead to excessive peripheral vasodilatation with marked hypotension and in rare cases bradycardia.

Management of intoxication
The therapeutic measures should focus on elimination of the active ingredient and monitoring of the vital signs. If severe hypotension occurs, symptomatic treatment should be provided, the patient should be placed supine with the legs elevated. In case of accompanying bradycardia, atropine (0.5 – 1.0 mg) should be given intravenously. Additional intravenous fluids should be cautiously administered under haemodynamic supervision to prevent cardiac overloading. Sympathomimetic drugs with predominant effect on the α_1-adrenoreceptor (such as dobutamin, dopamin, norepinephrin or adrenalin) may also be given. Dosage depends in the efficacy obtained.
Felodipine is only dialysable to a minimal extent (approx. 9 %).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Dihydropyridine derivates.

ATC code:
C08C A02.

Felodipine is a calcium antagonist of the dihydropyridine class of calcium channel blockers. Calcium antagonists interfere with the voltage-dependent L-type (slow) calcium channels in the plasma membranes of smooth muscle cells and reduce the inflow of calcium ions. This results in vasodilatation.

Felodipine has a greater selectivity for vascular smooth muscle than myocardial muscle. Felodipine selectively dilates arterioles with no effects on venous vessels. Felodipine leads to a dose-related lowering of blood pressure via vasodilatation and consequently a reduction of peripheral vascular resistance. It reduces both systolic and diastolic blood pressure. The haemodynamic effect of felodipine is accompanied by reflex (baroreceptor-mediated) tachycardia. In therapeutic doses, felodipine has no direct effect on either cardiac contractility or cardiac conduction. Felodipine reduces renal vascular resistance. The glomerular filtration rate remains unchanged.

Felodipine has a weak natriuretic/diuretic effect and does not provoke fluid retention.

Felodipine can be used as a monotherapy but also concomitantly with beta-blockers, diuretics and ACE inhibitors.

There is limited clinical trial experience of the use of felodipine in hypertensive paediatric patients. In a randomised, double-blind, 3-week, parallel group study in children aged 6-16 years with primary hypertension, the antihypertensive effects of once daily felodipine 2.5 mg (n=33), 5 mg (n=33) and 10 mg (n=31) were compared with placebo (n=35). The study failed to demonstrate the efficacy of felodipine in lowering blood pressure in children aged 6-16 years.
The long-term effects of felodipine on growth, puberty and general development have not been studied. The long-term efficacy of antihypertensive therapy as therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

5.2 Pharmacokinetic properties

Absorption
Felodipine is completely absorbed following oral administration. Peak plasma levels are reached with the prolonged release formulation after 3 – 5 hours and result in even felodipine plasma concentrations within the therapeutic range for 24 hours. Steady state is reached approx. 3 days after starting treatment. Due to an extensive first-pass effect, only approx. 15 % of the administered dose is systemically available.

Distribution
The plasma protein binding of felodipine is > 99 %. The volume of distribution is approximately 10 l/kg at steady state, so that felodipine is indicating large tissue distribution. There is no significant accumulation during long-term treatment.

Metabolism
Felodipine is extensively metabolised in the liver by CYP3A4. All identified metabolites are inactive.

Elimination
No unchanged parent substance is detectable in the urine. The average half-life of felodipine in the terminal phase is 25 hours. The inactive hydrophilic metabolites formed by hepatic biotransformation are mainly eliminated renally (to approx. 70 %), and the remainder is excreted in the faeces. The mean plasma clearance is 1100 ml/l and depends on the hepatic blood flow.

In a single dose (felodipine **prolonged** release 5 mg) pharmacokinetic study **with a limited number** of children aged between 6 and 16 years (**n=12**) there was no apparent relationship between the age and AUC, C_{max} or half-life of felodipine.

Elderly
Increased plasma concentrations have been measured in elderly patients.

Impaired hepatic function
Increased plasma concentrations of up to 100% have been measured in patients with impaired hepatic function.

Impaired renal function
Renal impairment does not affect the pharmacokinetics of felodipine, although accumulation of inactive metabolites occurs in renal failure.

Effect of food
The rate, but not the extent of absorption is affected by the simultaneous ingestion of fatty food. Cmax was 2 to 2.5 times higher following intake of a high-fat meal compared to a fasting state.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. In animal studies with respect to the reproduction adverse effects were found. Effects in rats (prolonged duration of pregnancy and difficult labour) and rabbits (impaired development of distal phalanges, presumably due to decreased uteroplacental perfusion) revealed no evidence of a direct teratogenic effect, but indicate secondary consequences of the pharmacodynamic effect. In monkeys an abnormal position of the distal phalanges was found. The significance of these observations for humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Hypromellose
Povidone
Propyl gallate
Colloidal anhydrous silica
Magnesium stearate

Tablet coat:
Hypromellose
Iron oxide red (E172)
Iron oxide yellow (E172)
Titanium dioxide (E171)
Talcum
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

PVC/PE/PVDC aluminium blister.

Pack sizes: 10, 14, 20, 28, 30, 50, 56, 60, 90, 98, 100, 250, 500 and 1000 prolonged release tablets.

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

Selana Healthcare Ltd.
Caradice House
3-4 Fairview
Dublin 3
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1363/3/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 May 2004

Date of last renewal: 18 January 2006

10 DATE OF REVISION OF THE TEXT

May 2010