**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

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

**(S.I. No.540 of 2007)**

**PA0711/135/001**
Case No: 2037713

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

**Rowex Ltd**

**Bantry**, **Co. Cork**, **Ireland**

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

**Felodipine 2.5 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 **22/08/2008** until **21/08/2013**.

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

Felodipine 2.5 mg prolonged release tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged release tablet contains 2.5 mg felodipine.

Excipient: lactose monohydrate 48.77 mg/prolonged release tablet

For a full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Prolonged release tablet

Round, biconvex film-coated-tablets, pale yellow; embossment “2.5” on one side of the tablet.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Essential hypertension

### 4.2 Posology and method of administration

For oral administration

The dose should be adjusted to the individual requirements of the patient. Felodipine should usually be administered as follows: The recommended initial 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 5-10 mg once daily.
The maximum daily dose is 10 mg felodipine. In elderly patients an initial treatment with 2.5 mg daily should be considered. Subsequent dose increases should be undertaken with particular caution.

Impaired renal function
The pharmacokinetics is 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).

Impaired hepatic function
In patients with mild to moderate hepatic impairment, the recommended initial 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 section 5.2). It is contraindicated in patients with severe hepatic impairment.

Children and adolescents (less than 18 years of age)
Felodipine is not recommended for use in children and adolescents (less than 18 years of age) due to insufficient data or safety and efficacy.

Method of administration
The prolonged release tablets should be taken in the morning with a sufficient amount of fluid (e.g. a glass of water, but should NOT be taken with grapefruit juice!) (see section 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 section 5.2).

## 4.3 Contraindications

Felodipine is contraindicated in patients:
- with hypersensitivity to felodipine (or other dihydropyridines) or to any of the excipients
- with cardiogenic shock (as with other calcium channel blockers, treatment should be discontinued in patients who develop cardiogenic shock)
- with severe aortic or mitral stenosis
- with obstructive hypertrophic cardiomyopathy
- with unstable angina pectoris
- who have had an acute myocardial infarction (within 4-8 weeks of a myocardial infarction)
- with decompensated heart failure
- with severe hepatic impairment
- during pregnancy

## 4.4 Special warnings and precautions for use

Felodipine should be used with caution in patients with:
- conduction disorders, compensated heart failure, tachycardia and aortic or mitral valve stenosis
- severe left ventricular dysfunction
- 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 susceptible patients. This may lead to myocardial infarction (see section 5.1).

Dihydropyridines may cause acute hypotension. In some cases there is a risk of hypoperfusion accompanied by reflex tachycardia (paradoxical angina pectoris) (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).

As with the use of other calcium antagonists, in patients with serious gingivitis or periodontitis there have been reports of mild gingival hyperplasia. This hyperplasia can be avoided or at least mitigated by careful attention to dental hygiene.

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

## 4.5 Interaction with other medicinal products and other forms of interaction

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

The concomitant intake of felodipine and medicinal products which inhibit the cytochrome P450 isoenzyme 3A4 of the liver (such as cimetidine, azole antifungals (itraconazole, ketoconazole), macrolide antibiotics (erythromycin), telithromycin or HIV protease inhibitors) leads to increased felodipine plasma levels (see section 4.4). During concomitant administration of felodipine with itraconazole, $C_{max}$ increased 8-fold and AUC 6-fold. During concomitant administration of felodipine with erythromycin, $C_{max}$ and AUC increased approximately 2.5-fold. Combination with potent CYP 3A4 inhibitors should be avoided.

Grapefruit juice inhibits cytochrome P450 3A4. Concomitant administration of felodipine with grapefruit juice increased felodipine $C_{max}$ and AUC approximately 2-fold. The combination should also be avoided.

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). During concomitant administration of felodipin with carbamazepin, phenytoin, phenobarbital, AUC decreased by 93 % and $C_{max}$ by 82 %. A similar effect is expected with St. John`s wort. Therefore a dose increase of felodipine may be necessary. Combination with CYP3A4 inducers should be avoided.

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

Due to an initial saliuretic effect, felodipine can enhance a pre-existing hypokalemia when added to diuretic therapy.

Hydrochlorothiazide may enhance the anti-hypertensive effect of felodipine.

Felodipine can induce an increase of $C_{max}$ of cyclosporine. Additionally, cyclosporine may inhibit felodipine metabolism which may create a potential risk to felodipine toxicity. Concomitant administration of cyclosporine and felodipine increased felodipine $c_{max}$ 2.5 fold and AUC 1.6 fold.

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

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 does not appear to affect the unbound fraction of other extensively plasma protein bound drugs such as warfarin.

## 4.6 Pregnancy and lactation

Felodipine is contraindicated throughout pregnancy, as animal experiments have demonstrated foetal damage (see section 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 totally 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. In individual cases felodipine can influence a patients reactions to such extent that the
ability to drive or to operate machines or to work without suitable safeguards may be impaired. This is particularly the case at the start of therapy or when the dose is increased, or when the dose is changed as well as after concomitant ingestion of alcohol.

## 4.8 Undesirable effects

The following terminologies have been used in order to classify the occurrence of undesirable effects:

Very common (≥ 1/10)

Common (≥ 1/100 to < 1/10)

Uncommon (≥ 1/1000 to < 1/100)

Rare (≥ 1/10,000 to < 1/1,000)

Very rare (< 1/10,000), not known (cannot be estimated from the available data)

Cardiac disorders
*Common:* Particularly at the beginning of treatment, angina pectoris attacks may occur, or in patients with pre-existing angina pectoris there may be an increase in the frequency, duration and severity of the attacks.
*Uncommon:* Palpitations, tachycardia, hypotension.
*Very rare:* Myocardial infarction

Nervous system disorders
*Very common:* Headache (particularly at the beginning of treatment, when the dose is increased or when high doses are administered). Generally, this effect subsides on continued treatment.
*Uncommon:* Paraesthesia, dizziness, fatigue, syncope, 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, this effect subsides on continued treatment.

Respiratory, thoracic and mediastinal disorders
*Uncommon:* Dyspnoea

Gastrointestinal disorders
*Uncommon:* Nausea, vomiting, diarrhoea, constipation

Renal and urinary disorders
*Uncommon:* Pollakiuria (increased urinary frequency)

Skin and subcutaneous tissue disorders
*Very common:* Flushing (particularly at the beginning of treatment, when the dose is increased or when high doses are administered). Generally, this effect subsides on continued treatment.
*Uncommon:* Skin and hypersensitivity reactions such as pruritus, urticaria, exanthema, photosensitisation.
Gingival hyperplasia and gingivitis
*Very rare:* Exfoliative dermatitis

Musculoskeletal and connective tissue disorders
*Uncommon:* Myalgia, arthralgia, tremors

Vascular disorders
*Rare:* Leucocytoclastic vasculitis

General disorders and administration site conditions
*Common:* Peripheral oedema (The degree of ankle swelling is dose related.)
*Uncommon:* Weight gain, sweating
*Very rare:* Angiooedema, fever

Hepatobiliary disorders
*Very rare:* Hepatic function disorders (elevated transaminase levels)

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

## 4.9 Overdose

Symptoms of overdose
Overdose may lead to excessive peripheral vasodilation and then marked hypotension and in rare cases bradycardia.

Management of overdose
The therapeutic measures should be focused on the elimination of the active ingredient and the restoration of the circulation.

Activated charcoal, induction of vomiting or gastric lavage if appropriate or indicate should be considered.
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 $\alpha_1$-adrenoreceptor (such as dobutamine, dopamine, norepinephrine or adrenaline) may also be given. Dosage depends on the efficacy obtained.

Felodipine is only dialysable to minimal extent (approx. 9 %).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 1,4-dihydropyridine derivative/calcium antagonist
ATC code: C08C A02

Felodipine is a calcium antagonist of the dihydropyridine class. 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 vasodilation.

Felodipine is a vasoselective calcium antagonist: it has a stronger effect on the vascular smooth muscle than the myocardial muscle. Felodipine selectively dilates arterioles with no effect on venous vessels.

Felodipine leads to a dose-related lowering of the blood pressure via vasodilation and consequently a reduction of peripheral vascular resistance. It reduces both systolic and diastolic blood pressure. The hemodynamic effect of felodipine is accompanied by reflex (baroreceptor-mediated) tachycardia. Reflex tachycardia is uncommon in this prolonged release product, in particular during chronic use.

In therapeutic doses, felodipine has no direct effect in either cardiac contractility or cardiac conduction. Felodipine reduces renal vascular resistance. The glomerular filtration rate remains unchanged.

Felodipine has 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.

## 5.2 Pharmacokinetic properties

Absorption
Felodipine is completely absorbed following oral administration. With the extended release tablets the absorption phase is prolonged. This results in even felodipine plasma concentrations within the therapeutic range over 24 hours. Peak plasma levels are reached after 3-5 hours. Steady-state is reached approximately 3 days after starting treatment. Due to an excessive first-pass effect, only approximately 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 a large tissue distribution. There is no significant accumulation during long-term treatment.

Metabolism
Felodipine is extensively metabolised in the liver by CYP 3A4. 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 feces.
The mean plasma clearance is 1100 ml/min and depends on the hepatic blood flow.

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
According to studies performed with felodipine tablets a high-fat meal may have an impact on pharmacokinetic parameters.

## 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 dental phalanges was found. The significance of these observations for humans is unknown.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

*Tablet core:*
Lactose monohydrate
Sodium laurilsulfate
Hypromellose
Microcrystalline cellulose
Magnesium stearate

*Tablet coating:*
Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Macrogol 4000
Iron oxide, yellow (E172)

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf Life

Blister and tablet container
5 years

Tablet container
Shelf life after first opening: 6 months.

## 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Tablet container: Storage condition after first opening: Do not store above 25 °C.

## 6.5 Nature and contents of container

PVC/Aluminium blisters with 7, 14, 20, 28, 30, 50, 56, 60, 100 and 112 prolonged-release tablets

Polyethylene containers with polyethylene closures containing 100 and 250 prolonged-release tablets

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

No special requirements

# 7 MARKETING AUTHORISATION HOLDER

Rowex Ltd.,
Bantry,
Co.Cork

## 8 MARKETING AUTHORISATION NUMBER

PA 711/135/1

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd August 2008

## 10 DATE OF REVISION OF THE TEXT