PACKAGE INSERT TEMPLATE FOR FELODIPINE EXTENDED RELEASE TABLET

Brand or Product Name
[Product name] ER Tablet 2.5mg
[Product name] ER Tablet 5mg
[Product name] ER Tablet 10mg

Name and Strength of Active Substance(s)
Felodipine 2.5mg
Felodipine 5mg
Felodipine 10mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge extended release tablets marked '10' on one side]

Pharmacodynamics
Felodipine is a vascular selective calcium antagonist which lowers arterial blood pressure by decreasing systemic vascular resistance. Due to the high degree of selectivity for smooth muscle in the arterioles, felodipine in therapeutic doses has no direct effect on cardiac contractility or conduction. Because there is no effect on venous smooth muscle or adrenergic vasomotor control, felodipine is not associated with orthostatic hypotension. Felodipine possesses a mild natriuretic/diuretic effect and fluid retention does not occur.

Felodipine is effective in all grades of hypertension. It can be used as monotherapy or in combination with other antihypertensive drugs, e.g. ß-adrenoceptor blockers, diuretics or ACE-inhibitors, in order to achieve an increased antihypertensive effect. Felodipine reduces both systolic and diastolic blood pressure and can be used in isolated systolic hypertension. Felodipine maintains its antihypertensive effect during concomitant therapy with non-steroidal anti-inflammatory drugs (NSAID).

Felodipine has anti-anginal and anti-ischaemic effects due to improved myocardial oxygen supply/demand balance. Coronary vascular resistance is decreased and coronary blood flow and myocardial oxygen supply are increased by felodipine due to dilatation of both epicardial arteries and arterioles. Felodipine effectively counteracts coronary vasospasm. The reduction in systemic blood pressure caused by felodipine leads to decreased left ventricular afterload and myocardial oxygen demand.

Felodipine improves exercise tolerance and reduces anginal attacks in patients with stable effort-induced angina pectoris. Both symptomatic and silent myocardial ischaemia are reduced by felodipine in patients with vasospastic angina. Felodipine can be used as monotherapy or in combination with ß-adrenoceptor blockers in patients with stable angina pectoris.

Felodipine is effective and well tolerated in adult patients irrespective of age and race and is also well tolerated in the presence of concomitant diseases such as congestive heart failure, asthma and other obstructive pulmonary disease, impaired renal function, diabetes mellitus, gout, hyperlipidaemia, Raynaud´s disease and in renal transplant recipients. Felodipine has no effect on blood glucose levels or lipid profile.

Site and mechanism of action
The predominant pharmacodynamic feature of felodipine is its pronounced vascular vs myocardial selectivity. Myogenically active smooth muscles in arterial resistance vessels are particularly sensitive to felodipine. Felodipine inhibits electrical and contractile activity of vascular smooth muscle cells via an effect on the calcium channels in cell membranes.

Haemodynamic effects

The primary haemodynamic effect of felodipine is a reduction of total peripheral vascular resistance which leads to a decrease in blood pressure. These effects are dose-dependent. Generally, a reduction in blood pressure is evident two hours after the first oral dose and lasts for at least 24 hours and the trough/peak ratio is usually well above 50%.

Plasma concentrations of felodipine are positively correlated to the decrease in total peripheral resistance and blood pressure.

Cardiac effects
Felodipine in therapeutic doses has no effect on cardiac contractility or atrioventricular conduction or refractoriness. In patients with heart failure, felodipine favourably affects left ventricular function, as assessed by ejection fraction or stroke volume, and does not cause neurohormonal activation. However, felodipine does not seem to affect survival. In patients with hypertension or angina pectoris, felodipine can be used also in case of impaired left ventricular function. Antihypertensive treatment with felodipine is associated with significant regression of pre-existing left ventricular hypertrophy.

Renal effects
Felodipine has a natriuretic and diuretic effect due to reduced tubular reabsorption of filtered sodium. This counteracts the salt and water retention observed with other vasodilators. Felodipine does not affect daily potassium excretion. The renal vascular resistance is decreased by felodipine. Normal glomerular filtration rate is unchanged. In patients with impaired renal function, the glomerular filtration rate may increase. Felodipine does not influence urinary albumin excretion.

In cyclosporin-treated renal transplant recipients, felodipine reduces blood pressure and improves both the renal blood flow and the glomerular filtration rate. Felodipine may also improve early renal graft function.

Paediatric population
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.

Pharmacokinetics
Absorption and distribution
Felodipine is administered as extended-release tablets, from which it is completely absorbed in the gastrointestinal tract. The systemic availability of felodipine is approximately 15% and is independent of dose in the therapeutic dose range. The plasma protein binding of felodipine is approximately 99%. It is bound predominantly to the albumin fraction.

The extended-release tablets produce a prolonged absorption phase of felodipine. This results in even felodipine plasma concentrations within the therapeutic range for 24 hours. Plasma concentrations are directly proportional to dose within the therapeutic dose range 2.5 - 10 mg.

Metabolism and elimination
Felodipine is extensively metabolised by the liver and all identified metabolites are inactive. Felodipine is a high clearance drug with an average blood clearance of 1200 ml/min. There is no significant accumulation during long-term treatment.

Elderly patients and patients with reduced liver function have on average higher plasma concentrations of felodipine than younger patients. The pharmacokinetics of felodipine are not changed in patients with renal impairment, including those treated with haemodialysis.

About 70% of a given dose is excreted as metabolites in the urine; the remaining fraction is excreted in the faeces. Less than 0.5% of a dose is recovered unchanged in urine.

Indication
Hypertension
Stable Angina pectoris

Recommended Dosage
The tablets should be taken in the morning, be swallowed with water and must not be divided, crushed or chewed. The tablets can be administered without food or following a light meal not rich in fat or carbohydrate.

Hypertension
The dose should be adjusted individually. Treatment should be started with 5 mg once daily. If necessary the dose may be further increased or another antihypertensive agent added. The usual maintenance doses are 5 mg to 10 mg once daily. In elderly patients initial treatment with 2.5 mg daily should be considered.

Stable Angina pectoris
The dose should be adjusted individually. Treatment should be started with 5 mg once daily, increasing to 10 mg once daily if needed.

Elderly patients
Initial treatment with 2.5mg daily dose should be considered.

Impaired renal function
Impaired renal function does not affect plasma concentrations of felodipine. No dose adjustment is required. However, felodipine should be used with caution in patients with severely impaired renal function.

Impaired hepatic function
Patients with impaired hepatic function may have elevated plasma concentrations of felodipine and may respond to treatment at lower doses.

Paediatric patients
Due to limited clinical experience use of felodipine to paediatric patients with hypertension should be avoided.

Mode of Administration
Oral

Contraindications
Pregnancy
Known hypersensitivity to felodipine or any other component of the product
Uncompensated heart failure
Acute myocardial infarction
Unstable angina pectoris
Haemodynamically significant cardiac valvular obstruction
Dynamic cardiac outflow obstruction

Warnings and Precautions
Felodipine, like other effective arteriolar dilators, may in rare cases precipitate significant hypotension, which, in susceptible individuals, may result in myocardial ischaemia.

Mild gingival enlargement has been reported in patients with pronounced gingivitis/periodontitis. The enlargement can be avoided or reversed by careful dental hygiene.

Felodipine is eliminated by the liver. Therefore, higher therapeutic concentrations and a higher treatment response may be expected in patients with clearly impaired hepatic function.

Effects on ability to drive and use machines
Felodipine is not likely to affect the ability to drive or use machines.

Interactions with Other Medicaments
Concomitant administration of substances which interfere with the cytochrome P450 3A4 enzyme system may affect plasma concentrations of dihydropyridine calcium antagonists such as felodipine. Enzyme inhibitors (e.g. cimetidine, erythromycin, itraconazole, ketoconazole and certain flavonoids present in grapefruit juice) have been shown to cause an increase in felodipine plasma concentrations. Enzyme inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates, hypericum perforatum (Saint John's wort) may cause a decrease in plasma concentrations of felodipine.

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

Felodipine does not affect plasma concentrations of cyclosporin. The high degree of plasma protein binding of felodipine does not appear to affect the unbound fraction of other extensively bound drugs such as warfarin.

Statement on Usage During Pregnancy and Lactation
Felodipine should not be given during pregnancy. Felodipine is detected in breast milk. When taken in therapeutic doses by the nursing mother it is, however, not likely to affect the infant.

Adverse Effects / Undesirable Effects
Felodipine can cause flushing, headache, palpitations, dizziness and fatigue. Most of these reactions are dose-dependent and appear at the start of treatment or after a dose increase. Should such reactions occur, they are usually transient and diminish with time.

Dose-dependent ankle swelling can occur in patients treated with felodipine. This results from precapillary vasodilatation and is not related to any generalised fluid retention.

Mild gingival enlargement has been reported in patients with pronounced gingivitis/periodontitis. The enlargement can be avoided or reversed by careful dental hygiene.

The adverse drug reactions listed below have been identified from clinical trials and from Post Marketing Surveillance.

Nervous system disorders
Common : Headache
Uncommon : Dizziness, paraesthesiae

Cardiac disorders
Uncommon : Tachycardia, palpitations

Vascular disorders
Common : Flush
Uncommon : Hypotension
Rare: Syncope

Gastrointestinal disorders
Uncommon : Nausea, abdominal pain

Rare: Vomiting
Very rare: Gingival hyperplasia, gingivitis

Hepatobiliary disorders
Very rare: Increased liver enzymes

Skin and subcutaneous tissue disorders
Uncommon : Rash, pruritus
Rare: Urticaria
Very rare: Photosensitivity reactions, leucocytoclastic vasculitis

Musculoskeletal and connective tissue disorders
Rare: Arthralgia, myalgia

Renal and urinary disorders
Very rare: Pollakisuria

Reproductive system and breast disorders
Rare: Impotence/sexual dysfunction

General disorders and administration site conditions
Very common : Peripheral oedema
Common : Fatigue
Very rare: Hypersensitivity reactions, e.g. angio-oedema, fever

Overdose and Treatment
Symptoms
Overdosage may cause excessive peripheral vasodilatation with marked hypotension and sometimes bradycardia.

Management
Activated charcoal, if necessary gastric lavage. If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. In case of accompanying bradycardia, atropine 0.5-1 mg should be administered intravenously. If this is not sufficient, plasma volume should be increased by infusion of e.g. glucose, saline, or dextran. Sympathomimetic drugs with predominant effect on the a_1-adrenoceptor may be given if the above-mentioned measures are insufficient.

Storage Conditions
Store below ….°C

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]