

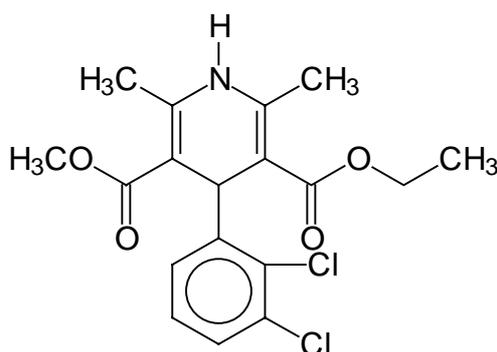
PRODUCT INFORMATION

Name of the Medicine

FELODUR ER tablets contain felodipine, a racemic mixture of ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro 2, 6-dimethyl-3,5 pyridine dicarboxylate.

MW 384.26.

The chemical structure of felodipine is



Description

Felodipine is insoluble in water (0.00012%) at 37°C and is moderately light-sensitive.

Inactive ingredients: polyoxyl 40 hydrogenated castor oil, hydroxypropylcellulose, propyl gallate, hypromellose, aluminium silicate, microcrystalline cellulose, lactose anhydrous, sodium stearyl fumarate, macrogol 6000, titanium dioxide, carnauba wax, iron oxide yellow (CI77492), iron oxide red (CI77491) (5mg and 10mg tablets only).

Pharmacology

Felodipine is a calcium antagonist which lowers arterial blood pressure by decreasing peripheral vascular resistance. Felodipine exhibits a high degree of selectivity for smooth muscle in the arterioles and in therapeutic doses has no direct effect on cardiac contractility or conduction. Because of its lack of effect on venous smooth muscle and on adrenergic vasomotor control, felodipine does not cause orthostatic hypotension.

Felodipine possesses a mild natriuretic/diuretic effect and therefore does not produce any general fluid retention. In various studies in which body weight was monitored, mean values did not generally increase during felodipine therapy.

Felodipine is effective in all grades of hypertension. It can be combined with other antihypertensives, such as beta-receptor blockers, diuretics or ACE-inhibitors, in order to achieve an increased antihypertensive effect.

Felodipine has antianginal and anti-ischæmic effects due to the improved oxygen supply/demand balance of the myocardium. Coronary vascular resistance is decreased and coronary blood flow as well as myocardial oxygen supply are increased by felodipine. 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. It can be used as monotherapy or in combination with β -receptor blockers in these patients.

Site and mechanism of action

The predominant pharmacodynamic feature of felodipine is its pronounced vascular vs. myocardial selectivity. Smooth muscles in arterial resistance vessels which exhibit myogenic activity are particularly sensitive to calcium antagonists such as felodipine. Felodipine inhibits electrical and contractile activity of vascular smooth muscle cells via an action at the cell membrane.

Absorption and Distribution

Felodipine is completely absorbed from the gastrointestinal tract after administration of FELODUR ER tablets.

Peak plasma concentrations following FELODUR ER tablets are usually reached within 3-5 hours.

The systemic availability of felodipine is independent of dose in the therapeutic dose range. Due to pre-systemic metabolism of felodipine the bioavailability of the extended release dosage form (FELODUR ER) is approximately 20%.

FELODUR ER produces a relatively flat plasma concentration vs time curve, minimising the post absorption peak seen with conventional tablets and maintaining therapeutic levels over the 24 hours following dosing. This permits single daily dosing of FELODUR ER.

The plasma protein binding of felodipine in man is approximately 99%. It is bound predominantly to the albumin fraction.

In man, felodipine has a volume of distribution at steady state of approximately 10 L/kg.

Elimination and metabolism

Felodipine is extensively metabolised by the liver. All identified metabolites are inactive. Approximately 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.

The elimination of felodipine from plasma follows a biphasic pattern, with the mean half-life of the α phase approximately 4 hours and that of the β phase approximately 24 hours. There is no significant accumulation during long-term treatment.

Average peak plasma concentrations of felodipine tend to be higher in elderly patients than in young healthy individuals. This can be attributed to reduced systemic clearance of felodipine and a corresponding increase in plasma half-life.

The systemic availability, time to peak plasma concentration and volume of distribution do not appear to be significantly affected by age.

In some patients administered a single dose of 5 mg FELODUR ER there was no detectable blood level of felodipine, indicating a significant inter-individual variation in pharmacokinetic response. Therefore, the dosage of FELODUR ER for all patients should be individually adjusted rather than based solely on patient age.

Haemodynamic effects

The acute haemodynamic effect of felodipine is to reduce total peripheral resistance which leads to a decrease in blood pressure and a slight and transient reflex increase in heart rate and cardiac output. A reduction in blood pressure is usually evident 2 hours after an initial oral dose of FELODUR ER tablets. The effect lasts for at least 24 hours at steady state.

Plasma concentrations of felodipine and change in total peripheral resistance and blood pressure respectively, are correlated.

Electrophysiological and other cardiac effects

Felodipine in therapeutic doses has no effect on conduction in the specialised conducting system of the heart and no effect on the A-V nodal refractoriness. In therapeutic doses felodipine has no negative effect on cardiac contractility. Antihypertensive treatment with felodipine is associated with significant regression of pre-existing left ventricular hypertrophy.

Renal effects

Felodipine has a natriuretic and diuretic effect. Studies in rats have shown that the reabsorption of filtered sodium is reduced in the distal tubules and collecting ducts in the kidney. The salt and water retention observed with other vasodilators is not observed with felodipine. Felodipine does not affect daily potassium excretion.

Renal vascular resistance is decreased by felodipine. In normal renal function, glomerular filtration rate is unchanged.

In patients with impaired renal function, the glomerular filtration rate may increase.

Indications

Hypertension.

Contraindications

- Pregnancy, including the early stages. Women who are likely to become pregnant should not be treated with felodipine.
- Known hypersensitivity to felodipine. or any other component of the product (see “Description” section).
- Uncompensated heart failure.
- Acute myocardial infarction.
- Unstable angina pectoris.

Precautions

1. Excessive hypotension

Because felodipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of felodipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure.

Felodipine, like any hypertensives, may in rare cases precipitate significant hypotension, which, in susceptible individuals, may result in myocardial ischaemia.

2. Exacerbation of angina

Rarely, too great a reduction in blood pressure with an initial reflexogenic increase in heart rate may lead to increased frequency, duration and/or severity of angina, particularly in patients who have severe obstructive coronary artery disease. Therefore, the possibility of precipitation of myocardial ischaemia exists. This may occur in the initial stages of felodipine treatment or following a dosage increase.

3. Combination with beta-blockers in patients with congestive heart failure

Beta-blockers are contraindicated in patients with uncompensated heart failure. Although felodipine may appear safe in these patients, combination with a beta-blocker is not recommended.

4. Leydig cell tumours in rats

An increased incidence of benign interstitial cell testicular tumours has been observed in rats but not in mice following dosing with felodipine. The relevance of this finding in man is not known, although clinical studies have demonstrated that felodipine has no influence on testosterone formation or on luteinising hormone secretion.

5. Outflow obstruction

Calcium antagonists should be used with caution in the presence of fixed left ventricular outflow obstruction. In animal and *in-vitro* studies, felodipine was 6 times more potent than nifedipine in inhibiting vascular, relative to myocardial, contractility. Therefore, in patients with raised left ventricular end diastolic pressure, felodipine is less likely to precipitate pulmonary oedema.

6. Peripheral oedema

Mild to moderate peripheral oedema resulting from precapillary vasodilation may occur in about 20% of patients treated with felodipine. This oedema appears to be dose-related. The effect of a diuretic on this oedema has not been investigated.

7. Use in elderly

Felodipine plasma levels are higher on average in elderly patients than in young and middle-aged patients due to reduced first-pass effect, reduced clearance capacity or both. It appears, however, that age *per se* has relatively little impact on the pharmacokinetics of felodipine. However, an initiation dose of 2.5mg once daily in the elderly may be appropriate.

8. Use in children

Clinical data on the use of felodipine in children is unavailable and its use in this age group is not recommended.

Use in Pregnancy: Category C

FELODUR ER should not be given to pregnant women or those likely to become pregnant. Calcium channel blockers carry the potential to produce foetal hypoxia associated with maternal hypotension.

Following administration of felodipine to pregnant dams during the period of organogenesis, morphological abnormalities of the phalanges were observed in the rabbit foetus.

In rats, oral doses of felodipine 3.8 mg/kg or higher, caused prolongation of labour.

Use in Lactation

Felodipine is detected in breast milk. When taken in therapeutic doses by the nursing mother however, it is unlikely to affect the infant.

Interactions with Other Medicines

1. Enzyme P450 inducers and inhibitors

Concomitant administration of substances which interfere with the cytochrome P450 3A4 system may affect plasma concentrations of felodipine.

Enzyme inducers (eg. phenytoin, carbamazepine, rifampicin, barbiturates) will cause a decrease in plasma levels of felodipine.

Enzyme inhibitors (eg. cimetidine, erythromycin, itraconazole, ketaconazole and certain flavonoids present in grapefruit juice) have been shown to cause an increase in felodipine plasma levels.

2. Digoxin

No increase in digoxin levels was observed during concomitant treatment with felodipine extended release (FELODUR ER) tablets.

3. Food

No significant effect on absorption of felodipine was observed when FELODUR ER was given with food.

4. Grapefruit juice

An increase in the bioavailability of dihydropyridines has been shown when they have been taken with grapefruit juice. The interaction is thought to be due to a bioflavonoid present in grapefruit juice which is not found in other citrus fruits. The interaction is more pronounced with immediate release formulations.

5. Tacrolimus

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

Adverse Effects

FELODUR ER has been extensively studied in Australia and overseas, both as monotherapy and in combination with other hypotensives such as beta-blockers and/or diuretics.

FELODUR ER can, like other vasodilators, cause flushing, peripheral oedema, 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 in intensity with time.

As with other dihydropyridines, dose-dependent ankle swelling, resulting from precapillary vasodilation can occur in patients treated with felodipine.

As with other calcium antagonists, gingival enlargement has been reported in patients with pronounced gingivitis or periodontitis. The enlargement can be avoided or reversed by attention to dental hygiene.

The following adverse events have been reported from clinical trials and from Post Marketing Surveillance. In the great majority of the less common reactions, a causal relationship and treatment with felodipine has not been established.

More common (>1%)

Cardiovascular: peripheral oedema, flushing (feeling of warmth)

Gastrointestinal: nausea, vomiting, gum hyperplasia

CNS: headache, dizziness/vertigo

Less common (≤1%)

Cardiovascular: palpitations, tachycardia, syncope, chest pain. In isolated cases, hypotension, sensation of cold.

Respiratory: dyspnoea, respiratory infection

Gastrointestinal: dyspepsia, flatulence, abdominal pain, gingivitis, constipation

CNS: paraesthesia. In isolated cases, depression.

Hepatic: increased liver enzymes eg. alkaline phosphatase, ASAT and ALAT.

General: hypersensitivity reactions eg. skin rashes, (including on rare occasions photosensitivity reactions), pruritis, urticaria, angio-oedema, fever, arthralgia, myalgia, fatigue. In isolated cases, impotence/sexual dysfunction, pollakisuria (urinary frequency) and leucocytoclastic vasculitis.

Laboratory tests

Slight increases in thrombocyte count, and rare, usually transient, elevations of enzymes such as alkaline phosphatase, ASAT and ALAT have occasionally been noted during felodipine treatment. These laboratory abnormalities have not been associated with clinical symptoms and their relationship to felodipine is uncertain.

Serious Adverse Events

The following serious adverse events were reported rarely in patients receiving felodipine in placebo-controlled studies: myocardial infarction (non-fatal), second degree atrio-ventricular block, stroke and chest pain. However, a causal relationship with drug therapy has not been established.

Dosage and Administration

Adults

Hypertension

The dose should be adjusted individually.

Treatment should be started with 5mg once daily. In elderly patients a starting dose of 2.5mg once daily should be considered.

If necessary, the dose can be increased in 2.5 or 5mg/day increments. The usual maintenance dose is 5mg to 10mg daily. Doses higher than 20mg daily of FELODUR ER are not recommended.

Administration

FELODUR ER tablets should be swallowed whole and taken with water and must not be divided, crushed or chewed.

Paediatric

Clinical data on the use of felodipine in children is unavailable and its use in this age group is not recommended.

Elderly

The dose should be adjusted individually, taking patient age into consideration (see PRECAUTIONS). An initial dose of 2.5mg once daily should be considered.

Impaired hepatic function

The dose of felodipine should be reduced in patients with severely impaired liver function.

Impaired renal function

Impaired renal function does not influence felodipine peak plasma concentrations or AUC, and a dosage reduction is not necessary for patients with renal impairment.

Overdosage

Symptoms

Overdosage may cause excessive peripheral vasodilation with marked hypotension and sometimes bradycardia.

Symptoms and signs of overdose may be delayed due to the controlled release properties of Felodur ER, so patients should be kept under observation for at least 24 hours.

Management

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. In cases of accompanying bradycardia, atropine 0.5-1.0mg should be administered intravenously. If this is not sufficient, plasma volume should be increased by electrolyte

infusion (e.g. glucose, saline, or dextran). Sympathomimetic drugs with predominant effect on the α_1 -adrenoreceptor may be given if the above-mentioned measures are insufficient.

The physician should consider contacting the Poisons Information Centre on 131126 for advice on the management of overdose.

Presentation and Storage Conditions

FELODUR ER Tablets 2.5mg:

Yellow, circular, biconvex, film-coated, engraved A/FL on one side and 2.5 on the other. Diameter 8.5 mm. Packs of 30 tablets.

FELODUR ER Tablets 5mg:

Pink, circular, biconvex, film-coated, engraved A/FM on one side and 5 on the other. Diameter 9 mm. Packs of 30 tablets.

FELODUR ER Tablets 10mg:

Red-brown, circular, biconvex, film-coated, engraved A/FE on one side and 10 on the other. Diameter 9 mm. Packs of 30 tablets.

FELODUR ER tablets 2.5 mg: 18 months stored below 25°C in PVC/PVDC/Al blisters. Protect from moisture.

FELODUR ER tablets 5 mg and FELODUR ER tablets 10 mg: 24 months stored below 25°C in PVC/PVDC/Al blisters. Protect from moisture.

Poison Schedule of the Medicine

S4 (Prescription Only Medicine)

Name and Address of the Sponsor

Alphapharm Pty Limited

Chase Building 2

Wentworth Park Road

Glebe NSW 2037

ABN 93 002 359 739

www.alphapharm.com.au

Date of Approval

Approved by the Therapeutic Goods Administration on 6 May 1997.

Date of most recent amendment: 18 October 2006.

Felodur[®] ER is a registered trademark.