

AUSTRALIAN PRODUCT INFORMATION

FELODUR[®] ER (felodipine) extended release tablets

1 NAME OF THE MEDICINE

Felodipine.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FELODUR ER tablets contain 2.5mg, 5mg or 10mg felodipine.

Excipient with known effect

Lactose.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

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.

FELODUR ER TABLETS 5MG

Pink, circular, biconvex, film-coated, engraved A/Fm on one side and 5 on the other. Diameter 9 mm.

FELODUR ER TABLETS 10MG:

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension.

4.2 DOSE AND METHOD OF 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.

Special patient populations

Renal impairment

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

Hepatic impairment

The dose of felodipine should be reduced in patients with severely impaired liver function. Patients with impaired hepatic function may have elevated plasma concentrations of felodipine and may respond to lower doses.

Use in the Elderly

The dose should be adjusted individually, taking patient age into consideration (see Section 4.4 Special warnings and precautions for use). An initial dose of 2.5mg once daily should be considered.

Paediatric use

Due to limited clinical trial experience, felodipine should not be used in paediatric patients.

Method of Administration

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

4.3 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 Section 6.1 List of excipients).
- Uncompensated heart failure.
- Acute myocardial infarction.
- Unstable angina pectoris.
- Haemodynamically significant cardiac valvular obstruction.
- Dynamic cardiac outflow obstruction.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 other vasodilators, can cause significant hypotension, which, in susceptible individuals, may result in myocardial ischaemia.

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.

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.

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.

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.

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.

Gingival enlargement

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

Lactose

FELODUR ER contains lactose and should not be given to patients with hereditary galactose intolerance or glucose-galactose malabsorption.

Use in the 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.

Paediatric use

Due to limited clinical trial experience, felodipine should not be used in paediatric patients.

Effects on 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 of the cytochrome P450 3A4 system (eg. phenytoin, carbamazepine, rifampicin, barbiturates, hypericum perforatum [St John's wort]) will cause a decrease in plasma levels of felodipine.

Enzyme inhibitors of the cytochrome P450 3A4 system (eg. cimetidine, erythromycin, itraconazole, ketoconazole and certain flavonoids present in grapefruit juice) have been shown to cause an increase in felodipine plasma levels.

Digoxin

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

Food

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

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.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Data on male and female fertility in patients are missing.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

Very common ($\geq 10\%$)

Cardiovascular: peripheral oedema

More common ($>1\%$)

Cardiovascular: flushing (feeling of warmth)

Gastrointestinal: nausea, vomiting, gum hyperplasia

CNS: headache, dizziness/vertigo

Less common ($\leq 1\%$)

Cardiovascular: hypotension, palpitations, tachycardia, syncope, chest pain. In isolated cases, 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 rare cases, impotence/sexual dysfunction, pollakisuria (urinary frequency) and leucocytoclastic vasculitis.

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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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-ischaemic 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.

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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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.

Distribution

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.

Metabolism

Felodipine is extensively metabolised in the liver by cytochrome P450 3A4 (CYP3A4). 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.

Excretion

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Stored below 25°C. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Packs of 7 and 30 tablets. PVC/PVDC/Al blisters.

*Not all pack sizes may be available in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

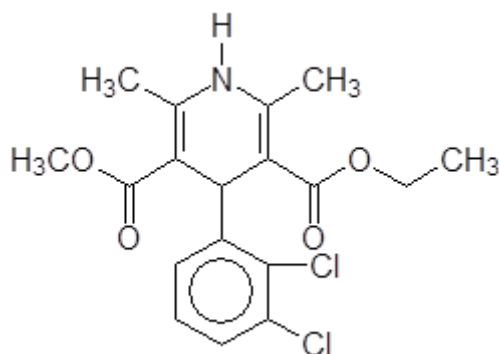
6.7 PHYSICOCHEMICAL PROPERTIES

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

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.

Chemical structure

Figure 1 Chemical structure of felodipine



MW 384.26

CAS number

CAS number: 72509-76-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4).

8 SPONSOR

Clinect Pty Ltd.
120 - 132 Atlantic Drive
Keysborough VIC 3173
Australia

Free Call Australia: 1800 899 005

9 DATE OF FIRST APPROVAL

10 November 1997

10 DATE OF REVISION.

26 September 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Change of sponsor