PLENDIL®
(felodipine)

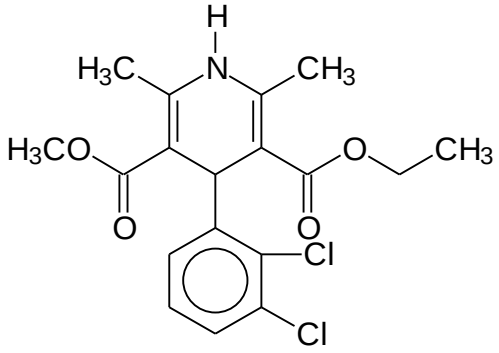
1. NAME OF THE MEDICINAL PRODUCT

Plendil®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Plendil 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.

Felodipine is insoluble in water (0.00012%) at 37°C and is moderately light-sensitive.
The chemical structure of felodipine is



Inactive ingredients: polyoxyl 40 hydrogenated castor oil, hydroxypropylcellulose, propyl gallate, hypromellose, aluminium silicate, microcrystalline cellulose, lactose anhydrous, sodium stearyfumarate, macrogol 6000, titanium dioxide, carnauba wax, iron oxide yellow (CI77492), iron oxide red (CI7491) (5 mg and 10 mg tablets only).

3. PHARMACEUTICAL FORM

PLENDIL Tablets 2.5 mg:

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.

PLENDIL Tablets 5 mg:

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

PLENDIL Tablets 10 mg:

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension. Stable angina pectoris.

4.2 Posology and method of administration

Adults

Hypertension

The dose should be adjusted individually.

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

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

Stable angina pectoris

Treatment should be started with 5 mg once daily and if needed be increased to 10 mg once daily.

Administration

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

Paediatric patients

Felodipine should, due to limited clinical trial experience, not be used in paediatric patients.

Elderly patients

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

Patients with hepatic impairment

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

Patients with 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.

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 “Description” section).
- Uncompensated heart failure.
- Acute myocardial infarction.
- Unstable angina pectoris.
- Haemodynamically significant cardiac valvular obstruction.
- Dynamic cardiac outflow obstruction.

4.4 Special warnings and special 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 may cause significant hypotension with subsequent tachycardia. This may lead to myocardial ischaemia in susceptible patients.

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.

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.

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 2.5 mg once daily in the elderly may be appropriate.

Use in children

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

Gingival enlargement and dental care

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

Lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

Enzyme P450 3A4 (CYP3A4) substrates, inducers and inhibitors

Felodipine is metabolised in the liver by cytochrome P450 3A4 (CYP3A4). Concomitant administration of substances which interfere with the CYP3A4 enzyme system may affect plasma concentrations of felodipine.

Interactions leading to decreased plasma concentration of felodipine.
Enzyme inducers of the cytochrome P450 3A4 system will cause a decrease in plasma levels of felodipine.

Examples:

- Phenytoin
- Carbamazepine
- Rifampicin
- Barbiturates
- Hypericum perforatum (Saint John's wort)

Interactions leading to increased plasma concentration of felodipine.
Enzyme inhibitors of the cytochrome P450 3A4 system have been shown to cause an increase in felodipine plasma levels.

Examples:
- Cimetidine
- Erythromycin
- Itraconazole
- Ketaconazole
- Certain flavonoids present in grapefruit juice

Digoxin

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

Food

No significant effect on absorption of felodipine was observed when Plendil 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 concentration of tacrolimus. When used together, the tacrolimus serum concentration should be monitored and the tacrolimus dose may need to be adjusted.

4.6 Pregnancy and lactation

Fertility

Data on male and female fertility in patients are missing.

Pregnancy

PLENDIL 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.

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 Effect on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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

Felodipine can 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.

Dose-dependent ankle swelling, resulting from precapillary vasodilation can occur in patients treated with felodipine.

Mild gingival enlargement has been reported in patients with pronounced gingivitis or peridontitis. 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.

System Organ Class	**Adverse Drug Reaction**
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.

4.9 Overdose

Symptoms

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

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 0.5-1.0 mg 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 Plendil 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.

5.2 Pharmacokinetic properties

Absorption and Distribution

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

Peak plasma concentrations following Plendil 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 (Plendil) is approximately 20%.

Plendil 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 Plendil.

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 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.

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 ß 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 Plendil there was no detectable blood level of felodipine, indicating a significant inter-individual variation in pharmacokinetic response. Therefore, the dosage of Plendil for all patients should be individually adjusted rather than based solely on patient age.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf life

Please refer to expiry date on outer carton.

6.2 Special precautions for storage

Store below 25°C.

Product Owner

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Date of revision of text

July 2022
07/BB/SG/Doc ID-001687904 V8.0
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