

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Felodipine extended release tablets USP

Plendil® 2.5mg, 5mg & 10mg

COMPOSITION:

Each extended release film coated tablet contains:

Felodipine USP 2.5 mg

Colour : Yellow Oxide of Iron

Felodipine USP 5 mg

Colour : Red Oxide of Iron
Yellow Oxide of Iron

Felodipine USP 10 mg

Colour : Red Oxide of Iron
Yellow Oxide of Iron

PHARMACEUTICAL FORM

Film-coated extended-release tablets based on the hydrophilic gel matrix principle.

The Plendil 2.5 mg tablet is yellow, circular, biconvex, engraved A/FL on one side and 2.5 on the other side, with a diameter of 8.5 mm.

The Plendil 5 mg tablet is pink, circular, biconvex, engraved A/Fm on one side and 5 on the other side, with a diameter of 11 mm.

The Plendil 10 mg tablet is reddish-brown, circular, biconvex, engraved A/FE on one side and 10 on the other side, with a diameter of 11 mm.

THERAPEUTIC INDICATIONS

Hypertension
Angina pectoris

POSODOGY AND METHOD OF ADMINISTRATION

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.

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.

There is limited experience of felodipine treatment in children.

CONTRAINDICATIONS

Pregnancy
Known hypersensitivity to felodipine or any other component of the product
Uncompensated heart failure
Acute myocardial infarction
Unstable angina pectoris

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

INTERACTIONS

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) may cause a decrease in plasma concentrations of felodipine. 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.

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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

UNDESIRABLE EFFECTS

Like other arteriolar dilators, 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.

As with other dihydropyridines, 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.

As with other calcium antagonists, 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.

The following definitions of frequencies are used:

Common	≥ 1/100
Uncommon	≥ 1/1000 and < 1/100
Rare	< 1/1000 and ≥ 1/10000
Very rare	< 1/10000

COMMON

Central and peripheral nervous system: Headache

Skin: Flush

Vascular (extra cardiac): Peripheral oedema

UNCOMMON

Cardiovascular system: Tachycardia, palpitations

Central and peripheral nervous system: Dizziness, paraesthesiae

Gastrointestinal: Nausea, abdominal pain

Skin: Rash, pruritus

General: Fatigue

RARE

Cardiovascular system: Syncope

Gastrointestinal: Vomiting

Musculo-skeletal system: Arthralgia, myalgia

Psychiatric: Impotence/sexual dysfunction

Skin: Urticaria

VERY RARE

Gastrointestinal: Gingival hyperplasia, gingivitis

Hepatic: Increased liver enzymes

Skin: Photosensitivity reactions, leucocytoclastic vasculitis

Urinary system: Pollakisuria

General: Hypersensitivity reactions e.g. angio-oedema, fever

OVERDOSE

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 α_1 -adrenoceptor may be given if the above-mentioned measures are insufficient.

PHARMACODYNAMIC PROPERTIES

ATC code: C08C A02

Felodipine is a highly 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. β -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 β -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, Plendil 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.

Mortality/morbidity data

In the HOT (Hypertension Optimal Treatment) study, the effect on major cardiovascular events (i.e. acute myocardial infarction, stroke and cardiovascular death) was studied in relation to diastolic blood pressure targets ≤ 90 mmHg, ≤ 85 mmHg and ≤ 80 mmHg and achieved blood pressure, with felodipine as baseline therapy.

A total of 18790 hypertensive patients (DBP 100-115 mmHg), aged 50-80 years were followed for a mean period of 3.8 years (range 3.3-4.9). Felodipine was given as monotherapy or in combination with a betablocker, and/or an ACE-inhibitor and/or a diuretic. The study showed benefits of lowering SBP and DBP down to 139 and 83 mmHg, respectively. When the baseline DBP was lowered from 105 mmHg to 83 mmHg, it suggests that from five to ten major cardiovascular events can be prevented in every 1000 patients treated for 1 year. This implies a 30% risk reduction. Active lowering of blood pressure was particularly beneficial in the subgroup of patients with diabetes mellitus.

According to the STOP (Swedish Trial in Old Patients) with Hypertension -2 study, performed in 6614 patients, aged 70-84 years, dihydropyridine calcium antagonists (felodipine and isradipine) have shown the same preventive effect on cardiovascular mortality and morbidity as other commonly used classes of antihypertensive drugs – ACE inhibitors, beta-blockers and diuretics.

PHARMACOKINETIC PROPERTIES

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.

LIST OF EXCIPIENTS

Carnauba wax, hydroxypropylcellulose, hydroxypropyl methylcellulose, iron oxides E 172, lactose anhydrous, microcrystalline cellulose, polyethylene glycol 6000, polyoxyl 40 hydrogenated castor oil, propyl gallate, sodium aluminium silicate, sodium stearyl fumarate, titanium dioxide E 171, water purified.

SHELF LIFE

Please refer to expiry date on the label and outer carton.

SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C.

PRESENTATION

Plendil 2.5 mg, 5 mg, 10mg

Please refer to outer carton for pack size.

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For further information:

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