CV.000-157-345.3.0

Plendil® 2.5 mg, 5 mg and 10 mg

felodipine

Tablets

Composition

Felodipine 2.5 mg, 5 mg and 10 mg

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 9 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 9 mm.

Therapeutic Indications

Hypertension
Angina pectoris

Posology and method of administration

The extended-release tablet should be given once daily, preferably in the morning. The duration of effect is 24 hours. The tablet should be swallowed with water but must not be chewed or crushed. The extended-release tablet may be taken on an empty stomach or together with a light meal that is low in fat and carbohydrates.

Hypertension

The dose should be adjusted individually. Treatment should be initiated with 5 mg once daily. The normal dosage is 5 mg once daily. If necessary, the dose may be further increased or another antihypertensive agent added to Plendil. For some patients, for example, elderly patients and patients with impaired liver function, 2.5 mg once daily may be sufficient. Doses higher than 10 mg once daily are usually not needed.

Angina pectoris

The dose should be adjusted individually. Treatment should be initiated with 5 mg once daily and, if needed, increased to 10 mg once daily. Plendil may be combined with β-blockers.

Impaired renal function

Impaired renal function does not affect plasma concentrations of felodipine. No dose adjustment is required. Plendil should be used with caution in patients with severely impaired renal function (see Special warnings and precautions for use and Interactions).

Children

Experience from treatment of children with felodipine is limited.

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

Aortic stenosis, liver impairment, severely impaired renal function (GFR<30 ml/min), heart failure after acute myocardial infarction. Hypotension, which may cause myocardial ischaemia in sensitive patients.

Concomitant administration of drugs that induce CYP 3A4 leads to strongly reduced levels of felodipine and the risk of a lack of effect of Plendil (see Interactions). This combination should be avoided.

Concomitant administration of drugs that are potent inhibitors of CYP 3A4 leads to markedly elevated levels of felodipine (see Interactions). This combination should be avoided.

Concomitant intake of grapefruit juice leads to markedly elevated levels of felodipine (see Interactions). This combination should be avoided.

Interactions

Felodipine is a CYP 3A4 substrate. Drugs that inhibit or induce CYP 3A4 have significant effects on the plasma concentration of felodipine.

Cytochrome P450 inducers: Drugs that increase the metabolism of felodipine by induction of P450 are, for example, carbamazepine, phenytoin, phenobarbital and rifampicin, as well as St. John's wort (hypericum perforatum). When Plendil was administered together with carbamazepine, phenytoin and phenobarbital, the AUC of felodipine was reduced by 93% and C_{max} by 82%. Combination with CYP 3A4 inducers should be avoided.

Cytochrome P450 inhibitors: Drugs that are potent CYP 3A4 inhibitors are, for example, azole antimycotics (itraconazole, ketoconazole), macrolide antibiotics (erythromycin) and HIV protease inhibitors. Concomitant administration of itraconazole resulted in eight-fold increases of the C_{max} of felodipine and six-fold increases of the AUC. Concomitant administration of erythromycin led to approximately 2.5-fold increases of the C_{max} and the AUC of felodipine. Combination with potent CYP 3A4 inhibitors should be avoided.

Grapefruit juice inhibits CYP 3A4. Administration of felodipine together with grapefruit juice resulted in approximately two-fold increases of the C_{max} and the AUC of felodipine. Combination with grapefruit juice should be avoided.

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

Cyclosporin: Concomitant treatment with cyclosporin and felodipine increased the plasma concentration of felodipine by 150 % and the AUC by 60 %. The effect of felodipine on the pharmacokinetics of cyclosporin is, however, limited.

Cimetidine: Concomitant treatment with cimetidine and felodipine increased the C_{max} and AUC of felodipine by approx. 55%.

Pregnancy and lactation

Pregnancy

Relevant data from treatment of pregnant women with Plendil is lacking. Plendil should not be used during pregnancy, as teratogenic effects have been seen in animal studies. Calcium antagonists may inhibit premature contractions in the uterus, but there is no definite evidence of delayed delivery in a full-term pregnancy. There is a risk of development of hypoxia in the foetus in hypotensive mothers and of decreased perfusion of the uterus, due to a redistribution of the blood flow through peripheral vasodilatation.

Lactation

Felodipine is excreted in the breast milk. If the mother uses therapeutic doses of felodipine, only a very small dose is transferred via the breast milk to the child. There is insufficient experience of treatment with felodipine during lactation for an assessment of the risks to the child. For this reason, Plendil should not be given during lactation. In cases where the medical benefit of continued treatment is considered to be greater than the risk, stopping lactation should be considered.

Effects on ability to drive and use machines

As dizziness and fatigue may occur in connection with Plendil treatment, this should be considered when enhanced attention is required, for example, when driving or operating machines.

Undesirable effects

The most common adverse reaction to Plendil is mild to moderate ankle swelling, which is dose-related and caused by precapillary vasodilatation. Experience from clinical trials has shown that 2 % of patients interrupted treatment due to ankle swelling.

Flushing, headache, palpitations, dizziness and fatigue may occur at the start of treatment or after a dose increase. These reactions are normally transient.

Occasional cases of confusion and sleep disturbances have been reported, but a connection with felodipine has not been established with certainty.

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

Hyperglycaemia is a class-related undesirable effect, but has only been reported in individual cases for felodipine.

Frequency/ Organ	**Common (≥ 1/100)**	**Less common (≥1/1000, <1/100)**	**Rare (≥1/10 000, <1/1000)**	**Very rare (<1/10 000)**
General		fatigue		fever
Circulation	flushing with hot feeling, ankle swelling	palpitations, tachycardia		extrasystole, hypotension with tachycardia that may aggravate angina pectoris in sensitive individuals, leucocytoclastic vasculitis
Endochrine				hyperglycaemia
Gastrointestinal		nausea, stomach pain	vomiting	gingival hyperplasia, gingivitis
Skin		exanthema, pruritus	urticaria	photosensitivity, angio-oedema with swollen lips or tongue
Immunological reactions				hypersensitivity reactions
Liver				elevated liver enzymes
Musculoskeletal			arthralgia, myalgia	
Neurological	headache	paraesthesia, dizziness	syncope secondary to	

			hypotension	
Psychiatric			impotence/sexual dysfunction	
Urogenital				pollakisuria

Overdose

Toxicity: 10 mg to a two-year-old child caused mild intoxication. 150-200 mg to a 17-year-old and 250 mg to an adult caused mild to moderate intoxication. Felodipine probably has a more pronounced effect on the peripheral circulation than on the heart, compared with other drugs in the same group.

Symptoms: The symptoms of intoxication with extended-release tablets may be delayed 12-16 hours and severe symptoms may set in after several days. Circulatory effects constitute the greatest risk: bradycardia (sometimes tachycardia), AV block I-III, AV dissociation, VES, ventricular fibrillation, asystole. Dizziness, headache, impaired consciousness, coma, spasms. Dyspnoea, lung oedema (non-cardiac) and apnoea. Possibly ARDS (Adult Respiratory Distress Syndrome). Acidosis, hypokalaemia, hyperglycaemia, potentially hypocalcaemia. Flush, hypothermia. Nausea and vomiting.

Management: Charcoal, gastric lavage if indicated, in certain cases also late after exposure. Note: Atropine (0.25-0.5 mg intravenously to adults, 10-20 mcg/kg to children) should be given *before* gastric lavage (due to the risk of vagal stimulation). ECG monitoring. Respirator treatment on broad indication. Correction of acid-base and electrolyte status. In bradycardia and AV block: Atropine 0.5-1.0 mg intravenously to adults (20-50 mcg/kg to children), which may be repeated, or isoprenaline initially, 0.05-0.1 mcg/kg/minute. Use pacemaker early in severe cases. In hypotension: fluid i.v., calcium glubionate (9 mg Ca/ml), 20 (-30 ml) i.v. for 5 minutes to adults (3-5 mg Ca/kg to children) initially and repeated, if needed, or as infusion. Adrenalin or dopamine if needed. Glucagone may be used in severe cases. In circulatory arrest, resuscitation attempts may be required during several hours. In the case of spasms, diazepam should be given. Otherwise symptomatic therapy.

Pharmacodynamic properties

Pharmacotherapeutic group: Calcium antagonist ATC code: C08C A02

Felodipine (Plendil) is a vasoselective calcium antagonist for the treatment of hypertension and stable angina pectoris.

The active substance in Plendil, felodipine, is a dihydropyridine derivate. Felodipine is a racemate.

Felodipine exerts its effect by reducing peripheral vascular resistance, particularly in arterial resistance vessels. The electrical and contractile activity of vascular smooth muscle cells is inhibited via an effect on the calcium channels in the cell membranes.

Due to the selective effect on smooth muscle in arterial resistance vessels, felodipine in therapeutic doses has no negative inotropic effects on the heart, nor any clinically significant electrophysiological cardiac effects.

Felodipine relaxes smooth muscle in the airways. Clinical experience has shown that felodipine has little effect on gastrointestinal muscle motor function. No clinically significant effect of felodipine on blood lipids has been observed during long-term treatment, nor have any clinically significant effects on metabolic control (HbA1c) been observed in patients with type II diabetes during six months of treatment.

Felodipine can generally also be given to patients with concomitant impairment of left ventricular function who receive conventional therapy, or with asthma, diabetes mellitus, gout or hyperlipidaemia.

Anti-hypertensive effect: Felodipine lowers arterial blood pressure by decreasing peripheral vascular resistance. Treatment of hypertensive patients with Plendil reduces the blood pressure, both in the sitting and standing position and at rest and during exercise. Felodipine does not give rise to orthostatic hypotension, as the substance has no effect of venous smooth muscle or adrenergic control mechanisms.

The lowered blood pressure may initially cause a temporary reflex increase in heart rate and cardiac output. The increased heart rate is counteracted when felodipine is given together with beta-blockers. Plasma concentrations of felodipine are positively correlated to the decrease in total peripheral resistance and blood pressure. At steady state the effect remains over the entire dose range and gives a 24-hour reduction in blood pressure.
Treatment with felodipine is associated with regression of left ventricular hypertrophy.
Felodipine has a natriuretic and diuretic effect but no potassiuretic effect. The tubular reabsorption of sodium and water is reduced, which may explain the absence of salt and fluid retention in the patient. Felodipine reduces renal vascular resistance and increases renal perfusion. The glomerular filtration rate is unchanged. Felodipine does not influence urinary albumin excretion.

In the so-called HOT (Hypertension Optimal Treatment) study, including 18,790 patients with mild to moderate hypertension, treatment with Plendil, in combination with an ACE inhibitor, a β-blocker and/or a diuretic, if needed, resulted in a diastolic blood pressure (DBP) of ≤ 90 mm Hg in 93 % of the patients.
In the same study, the incidence of cardiovascular events in patients with type II diabetes (n=1501) was significantly lower (50%) in the group where the target DBP was ≤ 80 mm Hg (11.9/1000 patient years), compared with the group where the target DBP was below 90 mmHg (24.4/1000 patient years).

Plendil was included as one of two calcium antagonists in the Swedish STOP-2 study, performed in 6,614 patients aged 70-84 years. The study indicates that hypertensive treatment initiated with dihydropyridine calcium antagonists and with the addition of β-blockers, if needed, has no effect of cardiovascular mortality compared with conventional treatment with β-blockers and/or diuretics.

For the treatment of hypertensive patients, Plendil can be used as monotherapy or in combination with other antihypertensive drugs, such as β-blockers, diuretics or ACE inhibitors.

Anti-anginal effect: Felodipine exerts its effect through dilatation of coronary vessels, which also improves perfusion and the oxygen supply to the heart. Cardiac work load is decreased through a reduction of the peripheral arterial resistance (reduced afterload), which results in reduced oxygen demand in the myocardium. Coronary vasospasm is counteracted by felodipine.

Felodipine improves exercise capacity and reduces anginal attacks in patients with stable effort-induced angina pectoris.
Initially during treatment there is a transient reflex increase in heart rate, which is counteracted if Plendil is given in combination with a β-blocker. The time to onset of effect is two hours and the effect duration is 24 hours.
Felodipine can be used in combination with β-adrenoceptor blockers or as monotherapy for the treatment of patients with angina pectoris.

Pharmacokinetic properties

The active substance in Plendil extended-release tablets, felodipine, is imbedded in a polymer that forms a gel layer in contact with water, from which felodipine is released continuously, which leads to a slow onset of effect.

The bioavailability of felodipine is approximately 15% and is independent of concomitant food intake. However, the rate of absorption – although not the degree of absorption – is affected by concomitant intake of food, and the maximum plasma concentration is thereby increased by approx. 65%. The maximum plasma concentration is reached after 3-5 hours. The degree of binding to plasma proteins is approximately 99%. The distribution volume at steady state is 10 L/kg. The half-life of felodipine in the elimination phase is approximately 25 hours and steady state is reached after 5 days. There is no risk of accumulation during long-term treatment.
Average clearance is 1200 ml/min. Reduced clearance in elderly patients and patients with impaired liver function leads to higher plasma concentrations of felodipine. However, age can only partly explain the interindividual variations in plasma concentrations. Felodipine is metabolised in the liver and none of the identified metabolites has a vasodilating effect. About 70% of a given dose is excreted as metabolites in the urine and the rest is excreted in the faeces. Less than 0.5% of a given dose is recovered unchanged in the urine.
Impaired renal function does not affect plasma concentrations of felodipine, although there is accumulation of inactive metabolites. Felodipine is not eliminated by haemodialysis.

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.

Pack size

Please refer to outer carton for pack size.

Date of revision of text

August 2004

AstraZeneca AB, Södertälje, Sweden