

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

PLENDIL[®] ER 2.5 mg extended-release tablets
PLENDIL[®] ER 5 mg extended-release tablets
PLENDIL[®] ER 10 mg extended-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PLENDIL ER 2.5 mg: Each tablet contains 2.5 mg felodipine.
Excipients with known effect: Each tablet contains 28 mg lactose and 2.5 mg macrogolglycerol hydroxystearate.

PLENDIL ER 5 mg: Each tablet contains 5 mg felodipine.
Excipients with known effect: Each tablet contains 28 mg lactose and 5 mg macrogolglycerol hydroxystearate.

PLENDIL ER 10 mg: Each tablet contains 10 mg felodipine.
Excipients with known effect: Each tablet contains 28 mg lactose and 10 mg macrogolglycerol hydroxystearate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged release tablets of felodipine (will be referred to as extended release, ER, tablets in the following text). The extended release is based on the hydrophilic gel matrix principle.

Felodipine 2.5 mg extended release tablets are a yellow, circular, biconvex, film-coated tablet engraved A/FL on one side and 2.5 on the other side. Average mass 0.20 g. Diameter 8.5 mm.

Felodipine 5 mg extended release tablets are pink, circular, biconvex, film-coated tablets, engraved A/Fm on one side, and 5 on the other side. Average mass 0.21 g. Diameter 9 mm.

Felodipine 10 mg extended release tablets are red-brown, circular, biconvex, film-coated tablets, engraved A/FE on one side, and 10 on the other side. Average mass 0.22 g. Diameter 9 mm.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Hypertension

- Chronic, stable angina pectoris. PLENDIL may be used alone or in combination with other anti-anginal medication.

4.2 DOSE 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.

Adults

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 anti-hypertensive 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.

Elderly patients should have their dose adjusted individually taking the patient age into consideration. The lowest effective dose for angina is felodipine 5 mg daily and it is recommended that this dose be employed as the initial dose and alternative treatment considered if this dose is not well tolerated in the individual.

Patients with renal impairment

Dose adjustment is not needed in patients with renal impairment

Patients with hepatic impairment

Patients with impaired hepatic function may have elevated plasma concentrations of felodipine and may respond to lower doses (see section 5.2)

Paediatric patients

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

4.3 CONTRAINDICATIONS

- Pregnancy
- Known hypersensitivity to felodipine or any other component of the product
- 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

Felodipine can like other vasodilators cause hypotension. This may in susceptible patients result in myocardial ischemia.

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

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

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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 increased plasma concentration of felodipine

Enzyme inhibitors of the cytochrome P450 3A4 system have been shown to cause an increase in felodipine plasma concentrations.

Examples:

- Cimetidine
- Erythromycin
- Itraconazole
- Ketoconazole
- Certain flavonoids present in grapefruit juice

Interactions leading to decreased plasma concentration of felodipine

Enzyme inducers of the cytochrome P450 3A4 system may cause a decrease in plasma concentrations of felodipine.

Examples:

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

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

Felodipine does not affect plasma concentrations of cyclosporin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Felodipine should not be given during pregnancy.

Breast-feeding

Felodipine is detected in breast milk. When taken in therapeutic doses by the nursing mother it is, however, not likely to affect the infant.

Fertility

There are no data on the effects of felodipine on patient fertility.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

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.

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.

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

The following adverse events have been reported from clinical trials and from Post Marketing Surveillance.

The following definitions of frequencies are used:

Very common $\geq 1/10$

Common $\geq 1/100$ and $< 1/10$

Uncommon $\geq 1/1\ 000$ and $< 1/100$

Rare $\geq 1/10\ 000$ and $< 1/1\ 000$

Very rare $< 1/10\ 000$

Table 1 Undesirable effects

System Organ class	Frequency	Adverse Drug Reaction
<i>Nervous system disorders</i>	Common	Headache
	Uncommon	Dizziness, paraesthesiae
<i>Cardiac disorders</i>	Uncommon	Tachycardia, palpitations
<i>Vascular disorders</i>	Common	Flush
	Uncommon	Hypotension
	Rare	Syncope
<i>Gastrointestinal disorders</i>	Uncommon	Nausea, abdominal pain
	Rare	Vomiting

System Organ class	Frequency	Adverse Drug Reaction
	Very rare	Gingival hyperplasia, gingivitis
<i>Hepatobiliary disorders</i>	Very rare	Increased liver enzymes
<i>Skin and subcutaneous tissue disorders</i>	Uncommon Rare Very rare	Rash, pruritus Urticaria Photosensitivity reactions, leucocytoclastic vasculitis
<i>Musculoskeletal and connective tissue disorders</i>	Rare	Arthralgia, myalgia
<i>Renal and urinary disorders</i>	Very rare	Pollakisuria
<i>Reproductive system and breast disorders</i>	Rare	Impotence/sexual dysfunction
<i>General disorders and administration site conditions</i>	Very common Uncommon Very rare	Peripheral oedema Fatigue Hypersensitivity reactions, e.g. angio-oedema, fever

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://pophealth.my.site.com/carmreportnz/s/>.

4.9 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 agents with predominant effect on the α_1 -adrenoceptor may be given if the above mentioned measures are insufficient.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: C08C A02.

Felodipine is a 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 agents, 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 agents (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. Therefore felodipine can be used in patients with hypertension or angina pectoris who also have 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.

Clinical efficacy and safety

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 PLENDIL as baseline therapy. A total of 18 790 hypertensive patients (DBP 100 -115 mmHg), aged 50 to 80 years were followed for a mean period of 3.8 years (range 3.3 to 4.9).

PLENDIL was given as monotherapy or in combination with a betablocker and/or ACE-inhibitor and/or diuretic. The study showed benefits of lowering the 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 1 000 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-2 (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.

5.2 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 time to maximum plasma concentration (t_{max}) is between 2.5 and 5 hours.

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.

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

Metabolism and elimination

Felodipine is extensively metabolised in the liver by cytochrome P450 3A4 (CYP3A4) and all identified metabolites are inactive. Felodipine is a high clearance agent with an average blood clearance of 1200 mL/min. The average half-life of felodipine in the terminal phase is 24 hours. 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.

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

Since there is often significant inter-individual variation in pharmacokinetic characteristics, dosage of felodipine should be individually adjusted rather than based only on patient's age.

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.

Felodipine 2.5 mg is not proven to be effective in treating angina.

5.3 PRECLINICAL SAFETY DATA

Reproduction toxicity

In a study on fertility and general reproductive performance in rats treated with felodipine, a prolongation of parturition resulting in difficult labour/increased foetal deaths and early postnatal deaths was observed in the medium and high dose groups. These effects were attributed to the inhibitory effect of felodipine in high doses on uterine contractility. No disturbances of fertility were observed when doses within the therapeutic range were given to rats.

Reproduction studies in rabbits have shown a dose-related reversible enlargement of the mammary glands of the parent animals and dose-related digital anomalies in the foetuses. The anomalies in the foetuses were induced when felodipine was administered during early foetal development (before day 15 of pregnancy).

Carcinogenicity

Studies have been performed in mice and rats. In the rat, interstitial cell tumours in the testes were observed. This species-specific effect is caused by an endocrinological effect of felodipine in the rat.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Carnauba wax, hydroxypropyl methylcellulose, hydroxypropyl cellulose, 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.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF-LIFE

2.5 mg: 24 months
5 and 10 mg: 36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C

6.5 NATURE AND CONTENTS OF CONTAINER

PLENDIL ER 2.5 mg: PVC/PVDC-aluminium memory pack of 30 extended-release tablets.

PLENDIL ER 5 mg: PVC/PVDC-aluminium memory pack of 30 extended-release tablets.

PLENDIL ER 10 mg: PVC/PVDC-aluminium memory pack of 30 extended-release tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Clinect NZ Pty Limited
C/- Ebos Group Limited
108 Wrights Road
Christchurch 8024
New Zealand
Free Call New Zealand: 0800 138 803

9. DATE OF FIRST APPROVAL

2.5 mg: 23 September 1992
5 mg & 10 mg: 17 December 1987

10. DATE OF REVISION OF THE TEXT

06 March 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Sponsor Change