PACKAGE INSERT

SCHEDULING STATUS: **S 3**

PROPRIETARY NAME AND DOSAGE FORM:

Plendil® 2,5 mg (Tablet)

Plendil® 5 mg (Tablet)

Plendil® 10 mg (Tablet)

COMPOSITION:

Each 2,5 mg tablet contains felodipine 2,5 mg in an extended release formulation.

Each 5 mg tablet contains felodipine 5 mg in an extended release formulation.

Each 10 mg tablet contains felodipine 10 mg in an extended release formulation.

List of excipients:

Carnauba wax, hydroxypropyl cellulose, hypromellose, iron oxide, lactose anhydrous, microcrystalline cellulose, polyethylene glycol, polyoxyl 40 hydrogenated castor oil, propyl gallate, sodium aluminium silicate, sodium stearyl fumarate, titanium dioxide.

Contains sugar.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1 Vasodilators, hypotensive medicines

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Felodipine is a dihydropyridine Class A calcium antagonist, which lowers arterial blood pressure by decreasing vascular resistance. Felodipine exhibits *in-vitro* selectivity for smooth muscle in

the arterioles and, in therapeutic doses, has no direct effect on cardiac contractility. Felodipine does not affect venous smooth muscle or adrenergic vasomotor control.

Electro-physiological studies have shown that felodipine has no direct effect on conduction in the specialised conducting system of the heart and no effect on the AV nodal refractoriness.

Felodipine produces an increase in heart rate, which is counteracted when concurrent beta-receptor blockers are administered.

Felodipine has a mild natriuretic, diuretic and kaliuretic effect during the first few weeks of therapy.

Felodipine reduces both systolic and diastolic blood pressure.

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.

The reduction in systemic blood pressure caused by felodipine leads to decreased left ventricular afterload and myocardial oxygen demand.

These effects are dose-dependent.

Generally, a reduction in blood pressure is evident 2 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:

Antihypertensive treatment with felodipine is associated with regression of pre-existing left ventricular hypertrophy.

Renal effects:
Felodipine has a natriuretic and diuretic effect due to reduced tubular re-absorption of filtered sodium. 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.

Mortality/morbidity data:
Lowering of elevated arterial pressure results in a reduction in hypertension-induced morbidity and mortality.

In the Hypertension Optimal Treatment (HOT) Study, felodipine was given as monotherapy or in combination with a beta-blocker, and/or an ACE inhibitor and/or a diuretic. The HOT study showed that lowering DBP to 80 mmHg compared to DBP 90 mmHg was particularly beneficial in the subgroup of patients with diabetes mellitus. In these patients major cardiovascular events (myocardial infarction, stroke and cardiovascular death) were reduced. Increasing blood pressure control was often obtained by increasing the dose of felodipine or by combining it with the above mentioned drug classes.

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 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 1 200 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.

INDICATIONS:
PLENDIL tablets are indicated in the management of hypertension.

CONTRAINDICATIONS:

PLENDIL should not be given during pregnancy (see "Pregnancy and lactation").

Known hypersensitivity to PLENDIL or any other component of the product. Patients with cardiogenic shock, acute myocardial infarction, uncompensated heart failure and unstable angina pectoris.

WARNINGS AND SPECIAL PRECAUTIONS:
PLENDIL may precipitate significant hypotension with tachycardia which, in susceptible individuals, may result in myocardial ischaemia.

Effects on ability to drive and use machines:

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

INTERACTIONS:

Concomitant administration of substances which interfere with the cytochrome P450 3A4 enzyme system affect plasma concentrations of felodipine, as contained in PLENDIL.

Enzyme inhibitors, such as cimetidine, erythromycin, itraconazole, ketoconazole and certain flavonoids present in grapefruit juice, have been shown to cause an increase in PLENDIL plasma concentration.

Enzyme inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates) may cause a decrease in plasma concentrations of PLENDIL.

PLENDIL 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.

PLENDIL does not affect plasma concentrations of cyclosporin.
PLENDIL maintains its antihypertensive effect during concomitant therapy with non-steroidal anti-inflammatory drugs (NSAID).

No dosage adjustment is required when PLENDIL is given concomitantly with digoxin. The high degree of plasma protein binding of PLENDIL does not appear to affect the unbound fraction of other extensively bound medicines such as warfarin.

PREGNANCY AND LACTATION:

PLENDIL should not be given during pregnancy.

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

DOSAGE AND DIRECTIONS FOR USE:

Adults, including the elderly :

The dose should be adjusted according to the individual requirements of the patient. The recommended starting dose is 5 mg once daily. The maintenance dose is 5 mg to 10 mg once daily. For dose titration purposes a 2,5 mg tablet is available. In elderly patients initial treatment with 2,5 mg daily should be considered.

In the elderly and in patients with impaired liver function the dose of PLENDIL should in general, not exceed 10 mg daily. The pharmacokinetics of PLENDIL is not significantly affected in patients with impaired renal function.

The tablets should be taken in the morning, swallowed with water, and must not be divided, crushed or chewed. Should not be administered after a meal rich in fat or carbohydrates.

Children:

The safety and efficacy of PLENDIL in children have not been established.

PLENDIL may be used in combination with beta-blockers, ACE-inhibitors or diuretics. The effects on blood pressure are likely to be additive and combination therapy will usually enhance the antihypertensive effect. Care should be taken to avoid hypotension.

SIDE EFFECTS:

Most of the undesirable effects due to vasodilation such as flushing and headache 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 PLENDIL. This results from precapillary vasodilatation and is not related to any generalised fluid retention. A paradoxical increase in ischaemic chest pain may occur at the start of treatment and in a few patients excessive fall in blood pressure has led to cerebral or myocardial ischaemia or transient blindness. Gingival hyperplasia has been reported in patients with pronounced gingivitis/periodontitis. The enlargement can be avoided or reversed by careful dental hygiene. Rare cases of gynaecomastia have been reported.

Frequency	**System Organ Class**	**Adverse Drug Reaction**
Common > 1/100	Central and peripheral nervous system:	Headache
	Skin:	Flush
	Vascular (extra cardiac):	Peripheral oedema
Uncommon > 1/1 000 and < 1/100	Cardiovascular system:	Tachycardia, palpitations, hypotension
	Central and peripheral nervous system:	Dizziness, paraesthesiae
	Gastrointestinal:	Nausea, abdominal pain, gastrointestinal disturbances
	Skin:	Rash, pruritus
	General:	Fatigue
Rare < 1/1 000 and > 1/10 000	Cardiovascular system:	Syncope
	Gastrointestinal:	Vomiting
	Musculo-skeletal:	Arthralgia, myalgia

	Psychiatric:	Impotence/sexual dysfunction
	Skin:	Urticaria
Very rare < 1/10 000	Gastrointestinal:	Gingival hyperplasia, gingivitis
	Hepatic:	Increased liver enzymes
	Skin:	Photosensitivity reactions, leucocytoclastic vasculitis
	Urinary system:	Increased micturition frequency
	General:	Hypersensitivity reactions e.g. angio-oedema, fever

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage may cause excessive peripheral vasodilation with marked hypotension, which may be accompanied by bradycardia. Severe hypotension should be treated symptomatically, with the patient placed supine and the legs elevated. Bradycardia, if present, should be treated with atropine 0,5 mg to 1 mg intravenously. If this is not sufficient, plasma volume should be increased by infusion with e.g. glucose, normal saline or dextran solutions. Sympathomimetic drugs with a predominant effect on the alpha-1-adrenoceptor may be given e.g. metaraminol or phenylephrine. Activated charcoal, induction of vomiting or gastric lavage, if appropriate or indicated.

IDENTIFICATION:

PLENDIL 2,5 mg:

Yellow, circular, biconvex, film-coated tablets, engraved F[A]L on one side and 2,5 on the other side.

PLENDIL 5 mg:

Pink, circular, biconvex, film-coated tablets, engraved F^{A}M on one side and 5 on the other side.

PLENDIL 10 mg:

Red-brown, circular, biconvex, film-coated tablets, engraved F^{A}E on one side and 10 on the other side.

PRESENTATION:

Plastic bottles of 30 and 100 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 ºC in well-closed containers. Protect from light.

Keep out of reach of children.

REGISTRATION NUMBER:

PLENDIL 2,5 mg: 29/7.1/0662

PLENDIL 5 mg: Y/7.1/294

PLENDIL 10 mg: Y/7.1/295

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

AstraZeneca Pharmaceuticals (Pty) Limited

Building 2, Northdowns Office Park

17 Georgian Crescent West, Bryanston

Johannesburg, 2191

DATE OF PUBLICATION OF THE PACKAGE INSERT:

10 August 2007

Inclusion of Namibia + Botswana registration details (15-11-2010)

Plendil 5 mg	Plendil 10 mg
BOTSWANA: S2	BOTSWANA: S2
Reg. No.: BOT 0500787	Reg. No.: BOT 0500786

Plendil 5 mg
NAMIBIA: NS2
Reg. No.: 04/7.1/1770