SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

AMLOC 5 mg tablets

AMLOC 10 mg tablets

COMPOSITION

Each **AMLOC 5 mg** contains amlodipine maleate equivalent to 5 mg amlodipine.

Each **AMLOC 10 mg** contains amlodipine maleate equivalent to 10 mg amlodipine.

Inactive ingredients:

Colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose, pregelatinised starch, sodium starch glycolate.

AMLOC tablets are sugar free.

PHARMACOLOGICAL CLASSIFICATION

A 7.1 Vasodilators, hypotensive medicines.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Amlodipine is a dihydropyridine calcium channel blocker. It inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle without affecting serum calcium concentrations. Direct relaxation of vascular smooth muscle forms the basis of the antihypertensive action.

In angina pectoris, amlodipine acts as a peripheral arteriolar vasodilator resulting in a reduction in total peripheral resistance (afterload). Myocardial energy and oxygen

requirements are reduced. Amlodipine exerts its activity by binding to the dihydropyridine binding sites. It exerts minimal action on cardiac conduction, contraction and heart rate.

Pharmacokinetic properties:

Absorption:

Complete absorption of amlodipine is slow following oral administration with peak plasma levels being attained after 6 to 12 hours.

The absorption of amlodipine is unaffected by the concomitant intake of food.

Distribution:

Amlodipine has a bioavailability of about 64 % and peak plasma levels are attained after 6 to 12 hours. The volume of distribution is about 20 l/kg.

Metabolism:

The plasma elimination half-life of 35 to 50 hours, allowing for once-daily oral dosing. Steady state plasma concentrations are achieved after 7 to 8 days of consecutive dosing. Metabolism is via the liver and is extensive with less than 10 % of amlodipine appearing unchanged in the urine. Metabolites are inactive and primarily (up to 60 %) excreted via the kidney.

Characteristics in Patients:

Hepatic impairment:

Limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase AUC of approximately 40-60 % and a lower initial dose may be required.

Renal impairment:

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly:

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC of approximately 40-60 % and elimination half-life in elderly patients, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Children:

Data reported in children below 6 years is limited.

INDICATIONS

AMLOC is indicated for the:

- Treatment of angina pectoris.
- Treatment of mild to moderate hypertension, alone or in combination with other antihypertensives.

CONTRAINDICATIONS

AMLOC is contraindicated in patients with:

- Hypersensitivity to amlodipine, dihydropyridines or to any of the ingredients of **AMLOC**.
- Shock, including cardiogenic shock.
- Haemodynamically unstable heart failure after acute myocardial infarction (during the first 28 days).
- Unstable angina pectoris.
- Should not be used for acute reduction of blood pressure.
- Pregnancy and lactation (see **HUMAN REPRODUCTION**).
- Safety in children has not been established.

WARNINGS AND SPECIAL PRECAUTIONS

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

In patients with severe aortic stenosis, **AMLOC** may increase the risk of developing heart failure.

Sudden withdrawal of **AMLOC** might be associated with an exacerbation of angina. A gradual decrease of dosage with medical practitioner supervision is recommended.

AMLOC should be stopped in patients who have ischaemic pain after use.

AMLOC should be used with caution in patients with hypotension.

The use of lithium with **AMLOC** may cause lithium induced neurotoxicity in the form of nausea, vomiting, diarrhoea, ataxia, tremors and/or tinnitus, caution is recommended.

Diabetes mellitus:

AMLOC's effect on insulin and glucose responses may require antidiabetic therapy to be adjusted.

Interference with diagnostic tests:

Calcium channel blockers like **AMLOC** interfere with plasma aldosterone and renin ratios in laboratory tests.

Use in the elderly:

Amlodipine clearance is decreased (40 - 60 %) in the elderly, which results in increases of amlodipine concentration in the area under the concentration-time curve (AUC) and elimination half-life. Therefore, elderly patients should start **AMLOC** therapy at a lower dose.

Use in renal failure:

Although **AMLOC** is excreted primarily via the kidney, mild renal impairment does not appear to have an effect on the plasma concentrations. Severe renal impairment may however require a dosage reduction. Amlodipine is not dialysable.

Use in impaired hepatic function:

The half-life of **AMLOC** is significantly prolonged in patients with impaired hepatic function. **AMLOC** should therefore be administered at lower doses in these patients.

Use in cardiac failure*:*

An increased incidence of pulmonary oedema has been reported. **AMLOC** may have a negative inotropic effect. AUC of **AMLOC** may increase in patients with heart failure.

Use in children:

Safety and efficacy have not been established.

Porphyria:

Safety has not been established.

Effects on ability to drive and use machines:

AMLOC can cause side effects such as dizziness. During **AMLOC** administration, patients should be cautioned about driving a vehicle or operating machinery.

INTERACTIONS

- Concurrent administration of sublingual nitro-glycerine, long acting nitrates, or other antianginal medicines with **AMLOC** may produce additive antihypertensive and antianginal effects. Sublingual nitro-glycerine may be used as needed to abort acute angina attacks during **AMLOC** therapy. Nitrate medication may be used during **AMLOC** therapy for angina prophylaxis.
- **AMLOC** may enhance the antihypertensive effects of other antihypertensive medicines such as beta blockers, although the combination is generally well

tolerated. **AMLOC** will not protect against the consequences of abrupt beta-blocker withdrawal; gradual beta-blocker dose reduction is recommended.

- Enhanced antihypertensive effects may also be seen in concomitant use with medicines such as aldesleukin and antipsychotics that cause hypotension.
- **AMLOC** is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 and interactions may occur with other medicines, such as quinidine or procainamide, sharing the same metabolic pathway, since both groups possess negative inotropic properties.
- The effects of **AMLOC** may be reduced in combination with enzyme-inducing anti-epileptic medicines such as carbamazepine, phenobarbital and phenytoin. In contrast, sodium valproate has been reported to increase plasma concentrations.
- Concomitant use with strong or moderate CYP3A4 inhibitors, protease inhibitors, azole antifungals, macrolide antibacterials (such as clarithromycin, erythromycin), verapamil or diltiazem, ketoconazole, itraconazole and ritonavir may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.
- The concomitant use of CYP3A4 inducers, i.e. rifampicin, St John's Wort (*Hypericum perforatum*), may give a lower plasma concentration of amlodipine. **AMLOC** should be used with caution together with CYP3A4 inducers.

HUMAN REPRODUCTION

Safety in pregnancy and lactation has not been established (see **CONTRAINDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

AMLOC can be administered with or without the intake of food.

Hypertension and Angina pectoris:

Adults:

An initial dose of 5 mg **AMLOC** once daily is recommended which may be increased to 10 mg once a day after 10 -14 days of therapy if there is no improvement.

No dose reduction is required when adding **AMLOC** to thiazide diuretics, beta-blockers, or angiotensin-converting enzyme inhibitors.

In the elderly:

Lower initial doses of **AMLOC** may be used in elderly patients (see **WARNINGS AND SPECIAL PRECAUTIONS**).

In patients with renal impairment:

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. **AMLOC** is not dialysable.

In patients with hepatic impairment:

The pharmacokinetics of amlodipine have not been studied in hepatic impairment. **AMLOC** should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

SIDE EFFECTS

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	*Less frequent*	Purpura, thrombocytopenia, leucocytopenia, haemorrhage, blood dyscrasias
Immune system disorders	*Less frequent*	Hypersensitivity reactions: pruritus, rash, angioedema and erythema multiforme
Endocrine disorders	*Less frequent*	Gynaecomastia

Metabolism and nutrition disorders	*Less frequent*	Hyperglycaemia
Nervous system disorders	*Frequent* *Less frequent*	Headache, somnolence, dizziness Hypertonia, hypoaesthesia/paraesthesia, peripheral neuropathy, tremor, insomnia, mood changes, increased sweating
Eye disorders	*Less frequent*	Visual disturbances
Ear and labyrinth disorders	*Less frequent*	Tinnitus
Cardiac disorders	*Frequent* *Less frequent*	Palpitations Myocardial infarction, dysrhythmia (including ventricular tachycardia and atrial fibrillation), chest pain, bradycardia
Vascular disorders	*Frequent* *Less frequent*	Flushing, peripheral oedema Hypotension (including orthostatic hypotension), syncope, vasculitis
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Coughing, dyspnoea, rhinitis
Gastrointestinal disorders	*Frequent* *Less frequent*	Nausea, abdominal pain Altered bowel habits, constipation, diarrhoea, vomiting, dyspepsia, pancreatitis, dry mouth, gingival hyperplasia
Hepato-biliary disorders	*Less frequent*	Hepatitis, jaundice, raised liver enzymes (mostly consistent with cholestasis)

Skin and subcutaneous tissue disorders	*Less frequent*	Alopecia exanthema, pruritus, purpura, skin discolouration, hyperhidrosis, rash
Musculoskeletal, connective tissue and bone disorders	*Frequent* *Less frequent*	Ankle swelling Arthralgia, asthenia, back pain, muscle cramps, myalgia
Renal and urinary disorders	*Less frequent*	Increased urinary frequency, micturition disorder, nocturia
Reproductive system and breast disorders	*Less frequent*	Sexual dysfunction
General disorders and administrative site conditions	*Frequent* *Less frequent*	Facial oedema, upper extremity oedema Taste perversion
Investigations	*Less frequent*	Weight increase/decrease

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In overdose side effects may be exaggerated and exarcebated.

Gastric lavage may be of benefit. Gross overdosage could result in excessive peripheral vasodilatation, resulting in marked and probably prolonged systemic hypotension. Clinically significant hypotension due to **AMLOC** overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevating of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided there is no contraindication to its use. Intravenous calcium gluconate may be of benefit in

reversing the effects of calcium channel blockade. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

Treatment is symptomatic and supportive.

IDENTIFICATION

AMLOC 5 mg: A white, round, slightly biconvex, bevelled edge tablet, scored on one side. Diameter: 8,0 mm.

AMLOC 10 mg: A white, round, slightly biconvex, bevelled edge tablet, scored on one side. Diameter: 10,0 mm.

PRESENTATION

AMLOC 5 mg: Opaque PVC / Aluminium foil blisters of 30 tablets, contained in a printed outer carton.

AMLOC 10 mg: Opaque PVC / Aluminium foil blisters of 30 tablets, contained in a printed outer carton.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep the blister in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

AMLOC 5 mg : RSA: A38/7.1/0183

AMLOC 10 mg : RSA: A38/7.1/0147

NAMIBIA:

AMLOC 5 mg: NS2 06/7.1/0011

AMLOC 10 mg: NS2 06/7.1/0012

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

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