SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

LOMANOR® 5 mg

LOMANOR® 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LOMANOR 5 mg tablet contains amlodipine besylate equivalent to 5 mg active amlodipine base.

Each LOMANOR 10 mg tablet contains amlodipine besylate equivalent to 10 mg active amlodipine base.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

LOMANOR 5 mg: White, emerald shaped tablets marked PFIZER on one side and AML-5 on the other.

LOMANOR 10 mg: White, emerald shaped tablets marked PFIZER on one side and AML-10 on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

LOMANOR is indicated for the treatment of mild to moderate hypertension. LOMANOR may be combined with other antihypertensive medicines.

Coronary artery disease (CAD)

Angina pectoris

LOMANOR is indicated for the treatment of angina pectoris.

Chronic stable angina

LOMANOR is indicated for the first line treatment of myocardial ischaemia, whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. LOMANOR may be used alone, as monotherapy, or in combination with other antianginal medicines.

Coronary artery disease

LOMANOR is indicated to reduce the risk of coronary revascularisation and the need for hospitalisation due to angina in patients with coronary artery disease.

LOMANOR is also indicated to reduce the risk of fatal coronary heart disease and non-fatal myocardial infarction, and to reduce the risk of stroke.

4.2 Posology and method of administration

Posology

Hypertension and angina pectoris

The initial dose is 5 mg LOMANOR once daily, which may be increased to a maximum dose of 10 mg depending on the individual patient's response after 10 – 14 days therapy.

No dose adjustment of LOMANOR is required during combined administration of thiazide diuretics, beta blockers, or angiotensin converting enzyme inhibitors.

Coronary artery disease

The recommended dosage range is 5 – 10 mg once daily. In clinical studies the majority of patients required 10 mg.

Special populations

Use in the elderly

The usual dosage regimens are recommended.

Use in patients with impaired hepatic function

LOMANOR should be administered with caution in these patients.

Use in renal failure

LOMANOR may be used in such patients at normal doses. Changes in plasma concentrations are not correlated with degree of renal impairment.

Paediatric population

The recommended antihypertensive oral dose in paediatric patients ages 6 – 17 years is 2,5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in paediatric patients.

The effect of LOMANOR on blood pressure in patients less than 6 years of age is not known.

Method of administration

For oral use.

4.3 Contraindications

- LOMANOR is contraindicated in patients with a known hypersensitivity to dihydropyridines, amlodipine, or to any of the excipients.
- Concomitant use with grapefruit juice (see section 4.5).

4.4 Special warnings and precautions for use

Concomitant use with potent cytochrome CYP3A4 medicines

The blood pressure lowering effect may be enhanced when potent CYP3A4 inhibitors such as ketoconazole, itraconazole or ritonavir are co-administered (see section 4.5).

Use in the elderly

The time to reach peak plasma concentrations of LOMANOR is variable and not significantly different between elderly and younger subjects. LOMANOR clearance is decreased with resulting increases in AUC (40 – 60 %) and elimination half-life in elderly patients. AUC and elimination half-life in patients with congestive heart failure (CHF) were increased with age. Elderly patients should start LOMANOR therapy at a lower dose.

Use in patients with renal failure

LOMANOR may be used at normal doses in patients with renal impairment. Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment. In patients with severe renal impairment, LOMANOR doses may need to be reduced. LOMANOR is not dialysable.

Use in patients with impaired hepatic function

The half-life of LOMANOR is prolonged in patients with impaired liver function. LOMANOR should therefore be administered at lower (5 mg) initial dose in these patients.

Use in patients with heart failure

In a long-term, placebo-controlled study (PRAISE-2) of LOMANOR in patients with New York Heart Association (NYHA) class III and IV heart failure of non-ischaemic etiology, LOMANOR was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

4.5 Interaction with other medicines and other forms of interaction

LOMANOR has been administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and oral hypoglycaemic medicines.

In vitro data from studies with human plasma indicate that LOMANOR has no effect on protein binding of the medicines tested (digoxin, phenytoin, warfarin, or indomethacin).

Simvastatin

Co-administration of multiple doses of 10 mg LOMANOR with simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone (see simvastatin professional information).

Grapefruit juice

Co-administration of 240 mL of grapefruit juice with a single oral dose of LOMANOR 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of LOMANOR. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of LOMANOR; therefore, administration of LOMANOR with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects (see section 4.3).

CYP3A4 inhibitors

Co-administration of a 180 mg daily dose of diltiazem with 5 mg LOMANOR in elderly hypertensive patients (69 to 87 years of age) resulted in a 57 % increase in LOMANOR systemic exposure and a significant further decrease in systolic blood pressure than with LOMANOR alone.

Strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of LOMANOR. LOMANOR should be used with caution when administered with CYP3A4 inhibitors (see section 4.4).

Clarithromycin

Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with LOMANOR. Close observation of patients is recommended when LOMANOR is co-administered with clarithromycin.

There is no information on the effect of the combination on the QT interval.

CYP3A4 inducers

There is no data available regarding the effect of CYP3A4 inducers on LOMANOR. Concomitant use of CYP3A4 inducers (e.g. rifampicin, *hypericum perforatum*) may decrease the plasma concentrations of LOMANOR. LOMANOR should be used with caution when administered with CYP3A4 inducers.

In the following studies, there were no significant changes in the pharmacokinetics of either LOMANOR or another medicine within the study, when co-administered.

Special studies: Effect of other medicines on LOMANOR

Cimetidine

Co-administration with cimetidine did not alter the pharmacokinetics of LOMANOR.

Aluminium/magnesium (antacid)

Co-administration of an aluminium/magnesium antacid with a single dose of LOMANOR had no significant effect on the pharmacokinetics of LOMANOR.

Sildenafil

A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of LOMANOR. When LOMANOR and sildenafil were used in combination, each medicine independently exerted its own blood pressure lowering effect.

Special studies: Effect of LOMANOR on other medicines

Digoxin

Co-administration of LOMANOR with digoxin did not change serum digoxin levels or digoxin renal clearance in healthy volunteers.

Ethanol (alcohol)

Single and multiple 10 mg doses of LOMANOR had no significant effect on the pharmacokinetics of ethanol.

Warfarin

Co-administration of LOMANOR with warfarin did not change the warfarin prothrombin response time.

Ciclosporin

No medicine interaction studies have been conducted with ciclosporin and LOMANOR in healthy volunteers or other populations, with the exception of renal transplant patients. Various studies in renal transplant patients report that co-administration of LOMANOR with ciclosporin increased the trough

concentrations of ciclosporin and increased ciclosporin toxicity, from no change up to an average increase of 40 %. Consideration should be given for monitoring ciclosporin levels in renal transplant patients on LOMANOR.

Tacrolimus

There is a risk of increased tacrolimus blood levels and toxicity when co-administered with LOMANOR. In order to avoid toxicity of tacrolimus, administration of LOMANOR in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Medicine/laboratory test interactions

None known.

4.6 Fertility, pregnancy and lactation

Safety of LOMANOR in pregnancy or lactation has not been established.

4.7 Effects on ability to drive and use machines

LOMANOR can cause dizziness. The patient's ability to drive or use machinery should be individually assessed.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following adverse events, listed according to the system organ class have been categorised as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Blood and lymphatic system disorders	Uncommon	Leukopenia, thrombocytopenia
Immune system disorders	Rare	Allergic reaction including pruritus, rash, angioedema and erythema multiforme
Metabolism and nutrition disorders	Uncommon	Hyperglycaemia
Psychiatric disorders	Uncommon	Insomnia, mood changes

Nervous system disorders	Common	Somnolence, dizziness, headache
	Uncommon	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia, hypertonia, peripheral neuropathy, extrapyramidal disorder
Eye disorders	Uncommon	Visual impairment
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations
	Very rare	Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), chest pain
Vascular disorders	Common	Flushing
	Uncommon	Hypotension, vasculitis
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea, rhinitis, cough
Gastrointestinal disorders	Common	Abdominal pain, nausea
	Uncommon	Vomiting, dyspepsia (including gastritis), altered bowel habits, dry mouth, pancreatitis, gingival hyperplasia
Hepatobiliary disorders	Very rare	Hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash
	Very rare	Angioedema, erythema multiforme, urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia, myalgia, muscle spasms, back pain
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, pollakiuria
Reproductive system and breast disorders	Uncommon	Erectile dysfunction, gynaecomastia
General disorders and	Common	Oedema, fatigue

administration site conditions	Uncommon	Asthenia, pain, malaise
Investigations	Uncommon	Weight increase, weight decrease

Paediatric population

Paediatric patients (ages 6 – 17 years)

Adverse events were similar to those seen in adults. In a study of 268 children, the most frequently reported adverse events were:

MedDRA System Organ Class	**Undesirable effects**
Nervous system disorders	Headaches, dizziness
Vascular disorders	Vasodilation
Respiratory, thoracic, and mediastinal disorders	Epistaxis
Gastrointestinal disorders	Abdominal pain
General disorders and administration site conditions	Asthenia

Severe adverse events (predominantly headache) were experienced by 7,2 % with LOMANOR 2,5 mg, 4,5 % with LOMANOR 5 mg, and 4,6 % with placebo. The most common cause of discontinuation from the study was uncontrolled hypertension. There were no discontinuations due to laboratory abnormalities. There was no significant change in heart rate.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Available data suggest that overdosage could result in excessive peripheral vasodilation and possibly reflex tachycardia, with subsequent marked and prolonged systemic hypotension. Shock with fatal outcome has been reported. Administration of activated charcoal to healthy volunteers immediately after or up to 2 hours after LOMANOR 10 mg ingestion has been shown to significantly decrease LOMANOR

absorption. Activated charcoal given 6 hours after LOMANOR had no effect. Clinically significant hypotension due to LOMANOR overdosage may need active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. Treatment is symptomatic and supportive. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Since LOMANOR is highly protein-bound, dialysis is not likely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1 Vasodilators, hypotensive, antihypertensive medicines include other antihypertensive medicines e.g. ACE-inhibitors, ARBs, RAAS, etc

Mechanism of action

Amlodipine is a dihydropyridine, calcium ion influx inhibitor (calcium channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined, but in experimental animals, amlodipine reduces total ischaemic burden by the following action:

Amlodipine dilates peripheral arterioles and thus reduces the total peripheral resistance (afterload) against which the heart works. Unloading of the heart reduces myocardial energy consumption and oxygen requirements.

5.2 Pharmacokinetic properties

Absorption

After oral administration of therapeutic doses, amlodipine is absorbed with peak blood levels between 6 and 12 hours post dose. Absolute bioavailability has been estimated to be approximately 64 %. The volume of distribution is approximately 21 L/kg. Absorption of amlodipine is unaffected by consumption of a low-fat breakfast.

In vitro studies have shown that approximately 97,5 % of circulating amlodipine is bound to plasma

proteins.

Biotransformation/elimination

The terminal plasma elimination half-life is about 35 – 50 hours. Steady state plasma levels are reached after 7 – 8 days of consecutive dosing.

Amlodipine is extensively metabolised by the liver to inactive metabolites. 10 % of the parent compound and 60 % of the metabolites are excreted in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dibasic calcium phosphate anhydrous

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycollate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light.

6.5 Nature and contents of container

LOMANOR 5 mg and 10 mg are available strip packed in blister packs in outer cardboard cartons each containing 30, 60 and 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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2196

South Africa

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8. REGISTRATION NUMBERS

LOMANOR 5 mg: 38/7.1/0271

LOMANOR 10 mg: 38/7.1/0272

9. DATE OF FIRST AUTHORISATION

LOMANOR 5 mg and 10 mg: 23 September 2005

10. DATE OF REVISION OF THE TEXT

22 January 2022

BOTSWANA: S2

LOMANOR 5 mg – Reg. no.: BOT1101949

LOMANOR 10 mg – Reg. no.: BOT1101948

NAMIBIA: NS2

LOMANOR 5 mg – Reg. no.: 07/7.1/0126

LOMANOR 10 mg – Reg. no.: 07/7.1/0127

ZAMBIA: POM

LOMANOR 5 mg – Reg. no.: 357/004

LOMANOR 10 mg – Reg. no.: 357/005

ZIMBABWE: PP10

LOMANOR 5 mg – Reg. no.: 2012/12.6/4716

LOMANOR 10 mg – Reg. no.: 2012/12.6/4717