Applicant: Oethmaan Biosims (Pty) Ltd	**SAHPRA approved date:** 22 December 2023
Product: AMLODIPINE 5 OETHMAAN AMLODIPINE 10 OETHMAAN	**Dosage form and strength:** Each tablet contains amlodipine maleate equivalent to 5 mg or 10 mg amlodipine

PROPOSED PROFESSIONAL INFORMATION - CLEAN

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE:

AMLODIPINE 5 OETHMAAN (Tablets)

AMLODIPINE 10 OETHMAAN (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each Amlodipine 5 Oethmaan tablet contains: Amlodipine maleate equivalent to 5 mg Amlodipine.

Each Amlodipine 10 Oethmaan tablet contains: Amlodipine maleate equivalent to 10 mg Amlodipine.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

AMLODIPINE 5 OETHMAAN: White to off-white, uncoated, oblong tablet.

AMLODIPINE 10 OETHMAAN: White to off-white, uncoated, oblong tablet, scored on one side.

Initial:	22/12/2023

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

AMLODIPINE OETHMAAN is indicated for the:

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

  AMLODIPINE OETHMAAN 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. AMLODIPINE OETHMAAN may be used alone, as monotherapy, or in combination with other antianginal medicines.
- Coronary artery disease

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

<u>Posology</u>

Hypertension and angina pectoris:

Adults:

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

No dose reduction is required when adding AMLODIPINE OETHMAAN to 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

AMLODIPINE OETHMAAN should be administered with caution in these patients.

Use in renal failure

AMLODIPINE OETHMAAN 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 AMLODIPINE OETHMAAN on blood pressure in patients less than 6 years of age is not known.

Method of administration

For oral use

4.3 Contraindications

- Hypersensitivity amlodipine, dihydropyridines or to any of the ingredients of AMLODIPINE OETHMAAN.
- Severe hypotension.
- Shock, including cardiogenic shock.
- Haemodynamically unstable heart failure after acute myocardial infarction (during the first 28 days).
- Obstruction of the outflow tract of the left ventricle (e.g. high- grade aortic stenosis).
- Unstable angina pectoris.
- Safety in children less than 6 years of age has not been established
- Pregnancy and lactation.
- Concomitant use with grapefruit juice (see section 4.5).

4.4 Special warnings and precautions for use

The safety and efficacy of AMLODIPINE OETHMAAN in hypertensive crisis has not been established.

AMLODIPINE OETHMAAN should not be used to treat angina attack in chronic stable angina, nor should it be used for the acute reduction of blood pressure in adults.

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

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

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

Diabetes mellitus:

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

Interference with diagnostic tests:

Calcium channel blockers, such as AMLODIPINE OETHMAAN, reduce the plasma aldosterone: renin ratio by increasing renin production and reducing plasma aldosterone concentrations, consequently, primary hyperaldosteronism has been misdiagnosed as essential hypertension.

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:

Amlodipine clearance is decreased (40 to 60 %) in the elderly, which results in increases of amlodipine exposure and elimination half-life. Therefore, elderly patients should start AMLODIPINE OETHMAAN therapy at a lower dose.

Use in renal failure/impairment:

Although AMLODIPINE OETHMAAN 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. AMLODIPINE OETHMAAN should be administered with particular caution to patients undergoing dialysis.

Use in impaired hepatic function:

The half-life of AMLODIPINE OETHMAAN are significantly prolonged in patients with impaired hepatic function. AMLODIPINE OETHMAAN should therefore be administered at lower doses in these patients.

Use in children:

Safety and efficacy have not been established in children less than 6 years of age.

Use in heart failure:

Calcium channel blockers, including amlodipine, should be used with caution in patients with hypotension, patients whose cardiac reserve is poor and those with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

AMLODIPINE OETHMAAN should not be used in cardiogenic shock or in patients who have suffered myocardial infarction in the previous 2 to 4 weeks, or in acute unstable angina (see section 4.3).

An increased incidence of pulmonary oedema has been reported.

AMLODIPINE OETHMAAN may have a negative inotropic effect. AUC of AMLODIPINE OETHMAAN may increase in patients with heart failure.

Porphyria:

Safety has not been established.

Patients who are taking AMLODIPINE OETHMAAN should inform the anaesthetist accordingly, before receiving anaesthesia.

4.5 Interaction with other medicines and other forms of interaction

Amlodipine, as in AMLODIPINE OETHMAAN, 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 amlodipine, as in AMLODIPINE OETHMAAN, has no effect on protein binding of the medicines tested (digoxin, phenytoin, warfarin, or indomethacin).

Simvastatin

Co-administration of multiple doses of 10 mg amlodipine, as in AMLODIPINE OETHMAAN, 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 amlodipine, as in AMLODIPINE OETHMAAN 10 mg, in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine, as in AMLODIPINE OETHMAAN. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of amlodipine, as in AMLODIPINE OETHMAAN; therefore, administration of AMLODIPINE OETHMAAN 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).

Effects of other medicines on AMLODIPINE OETHMAAN

CYP3A4 inhibitors

Concomitant use with diltiazem inhibits metabolism of amlodipine and plasma concentration increases by 50 %. Co-administration with other strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration to a greater extent than diltiazem.

Caution should be exercised when AMLODIPINE OETHMAAN is given concomitantly with CYP3A4 inhibitors.

Clarithromycin

Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine, as in AMLODIPINE OETHMAAN. Close observation of patients is recommended when AMLODIPINE OETHMAAN is co- administered with clarithromycin.

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

CYP3A4 inducers

Co-administration with CYP3A4 inducers (e.g. rifampicin, St. John's wort) may lead to reduced plasma concentration of amlodipine.

Caution should be exercised in combination use of AMLODIPINE OETHMAAN and CYP3A4 inducers.

In clinical interaction studies grapefruit juice, cimetidine, aluminium/magnesium (antacid) and sildenafil did not affect the pharmacokinetics of amlodipine.

Effects of AMLODIPINE OETHMAAN on other medicines

Concurrent administration of sublingual nitroglycerin, long acting nitrates, beta-blockers or other antianginal agents with AMLODIPINE OETHMAAN may produce additive antihypertensive and antianginal effects. Sublingual nitroglycerin may be used as needed to abort acute angina attacks during AMLODIPINE OETHMAAN therapy. Nitrate medication may be used during amlodipine therapy for angina prophylaxis.

AMLODIPINE OETHMAAN will not protect against the consequences of abrupt beta-blocker withdrawal; gradual beta-blocker dose reduction is recommended.

Although no “rebound effect” has been reported upon discontinuation of AMLODIPINE OETHMAAN, a gradual decrease of dosage with medical practitioner supervision is recommended.

In clinical interaction studies with amlodipine, as in AMLODIPINE OETHMAAN did not affect the pharmacokinetics of atorvastatin, digoxin warfarin or ciclosporin.

Ethanol (alcohol)

Single and multiple 10 mg doses of amlodipine, as in AMLODIPINE OETHMAAN, had no significant effect on the pharmacokinetics of ethanol.

Ciclosporin

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

Tacrolimus

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

Mechanistic target of rapamycin (mTOR) inhibitors

mTOR inhibitors such as sirolimus, temsirolimus and everolimus are CYP3A substrates. AMLODIPINE OETHMAAN is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, AMLODIPINE OETHMAAN may increase exposure of mTOR inhibitors.

Enhanced antihypertensive effects may be seen in concomitant use with medicines such as aldesleukin and antipsychotics that cause hypotension.

AMLODIPINE OETHMAAN may modify insulin and glucose responses and therefore diabetic patients may need to adjust their antidiabetic treatment when receiving AMLODIPINE OETHMAAN (see section 4.4).

AMLODIPINE OETHMAAN 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 AMLODIPINE OETHMAAN may be reduced in combination with enzyme-inducing antiepileptics such as carbamazepine, phenobarbitone and phenytoin. In contrast, sodium valproate has been reported to increase plasma concentrations.

Dantrolene may cause hyperkalaemia when used concomitantly with calcium channel blockers such as AMLODIPINE OETHMAAN. Due to risk of hyperkalaemia, it is recommended that the co-administration of AMLODIPINE OETHMAAN be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

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

There is no effect of amlodipine on laboratory parameters.

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation has not been established.

Women of childbearing potential/ Contraception in males and females

Women of childbearing potential and their partners should be advised to ensure adequate contraceptive cover.

Pregnancy

The safety of AMLODIPINE OETHMAAN in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses.

Breastfeeding

AMLODIPINE OETHMAAN is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 - 7 %, with a maximum of 15 %. The effect of AMLODIPINE OETHMAAN on infants is unknown.

4.7 Effects on ability to drive and use machines

In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired. Patients are advised to be careful when engaging with activities that require attention,

such as driving or using dangerous machines, until they know how they react to AMLODIPINE OETHMAAN treatment.

4.8 Undesirable effects

a) Summary of the safety profile

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

b) Tabulated list of adverse effects

System Organ Class	Frequency	Side effect
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, leukocytopenia, haemorrhagic complications in surgical patients, blood dyscrasias
Immune system disorders	Less frequent	Allergic reactions including pruritus, rash, angioedema and erythema multiforme
Metabolism and nutrition disorders	Less frequent	Hyperglycaemia
Psychiatric disorders	Less frequent	Sleep disorder, irritability, depression, confusion

		mood changes including anxiety
Nervous system disorders	Frequent	Headache (especially at the beginning of the treatment), fatigue, dizziness, asthenia
	Less frequent	Malaise, dry mouth, paraesthesia, increased sweating, tremor, hypoaesthesia, taste disorders, peripheral neuropathy
Eye disorders	Less frequent	Visual disturbances
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Frequent	Palpitations
	Less frequent	Syncope, tachycardia, chest pain, at the beginning of treatment aggravation of angina pectoris may happen, cases of myocardial infarction and dysrhythmias (including extrasystole, ventricular tachycardia, bradycardia and atrial dysrhythmias) and chest pain have been reported in

		patients with coronary artery disease.
Vascular disorders	Less frequent	Hypotension, vasculitis, peripheral oedema
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, rhinitis, cough
Gastro-intestinal disorders:	Frequent	Nausea, dyspepsia, abdominal pain, altered bowel habits
	Less frequent	Vomiting, diarrhoea, constipation, gingival hyperplasia gastritis and pancreatitis
Hepato-biliary disorders	Less frequent	Elevated liver enzymes, jaundice, and hepatitis.
Skin and subcutaneous tissue disorder	Frequent	Ankle swelling, facial flushing with heat sensation, especially at the beginning of the treatment.
	Less frequent	Exanthema, pruritus, urticaria, alopecia, skin discolouration, purpura, angioedema, cases of

		allergic reactions, rash, angioedema and erythema exsudativum multiforme, exfoliative dermatitis and Steven Johnson syndrome, Quincke's oedema have been reported, photosensitivity.
Musculoskeletal and connective tissue disorders	Less frequent	Muscle cramps, back pain, myalgias and arthralgia
Renal and urinary disorders	Less frequent	Increased micturition frequency, micturition disorder, nocturia
Reproductive system and breast disorders	Less frequent	Impotence, sexual dysfunction, gynaecomastia
General disorders and administrative site conditions	Frequent	Peripheral oedema, facial oedema
	Less frequent	Increase or decrease of weight

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:

System Organ Class	Frequency	Side effect
Nervous system disorders	Frequent	Headache, dizziness
Vascular disorders	Frequent	Vasodilation
Respiratory, thoracic and mediastinal disorders	Frequent	Epistaxis
Gastro-intestinal disorders:	Frequent	Abdominal pain
General disorders and administration site conditions	Frequent	Asthenia

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 to SAHPRA via the **"6.04 Adverse Medicine Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Available data for amlodipine suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilator support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Administration of activated charcoal to healthy volunteers immediately after or up to 2 hours after amlodipine ingestion has been shown to significantly decrease amlodipine absorption. Activated charcoal given 6 hours after amlodipine had no effect.

Clinically significant hypotension due to AMLODIPINE OETHMAAN overdosage requires active cardiovascular support. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 7.1 Vasodilators, hypotensive medicines

ATC Code: C08CA01

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.

5.2 Pharmacokinetic properties

Complete absorption of amlodipine is slow following oral administration with peak plasma levels being attained after 6 to 12 hours. Amlodipine has a bioavailability of about 64 % and a 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. The volume of distribution is about 20 l/kg.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Calcium hydrogen phosphate anhydrous

Magnesium stearate

Sodium starch glycollate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25 °C and protect from moisture.

6.5 Nature and contents of container

White opaque blisters and white opaque plastic securitainers of 30 and 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

207A Sherwood House

Greenacres Office Park

c/o Victory and Rustenburg Roads

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Johannesburg

2195

8 REGISTRATION NUMBER(S):

AMLODIPINE 5 OETHMAAN: 37/7.1/0376

AMLODIPINE10 OETHMAAN: 37/7.1/0377

9 DATE OF FIRST AUTHORISATION

16 May 2011

10 DATE OF REVISION OF THE TEXT

22 December 2023