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SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

AMLODIPINE 5 mg PD tablets

AMLODIPINE 10 mg PD tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each AMLODIPINE 5 mg PD tablet contains amlodipine maleate equivalent to 5 mg amlodipine.

Each AMLODIPINE 10 mg PD tablet contains amlodipine maleate equivalent to 10 mg amlodipine.

AMLODIPINE 5/10 mg PD tablets are sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

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

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

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AMLODIPINE 5/10 mg PD is indicated:

Hypertension

- for treatment of mild to moderate hypertension, alone or in combination with other antihypertensives.

Coronorary artery disease

- *Angina pectoris*

  for treatment of angina pectoris.

- *Chronic stable angina*

  AMLODIPINE 5/10 MG PD is indicated for 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 5/10 MG PD may be used alone, as monotherapy, or in combination with other antianginal medicines.

- *Coronary artery disease*

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

Hypertension and Angina pectoris

Adults:

An initial dose of 5 mg AMLODIPINE 5/10 mg PD 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.

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No dose reduction is required when adding AMLODIPINE 5/10 mg PD to thiazide diuretics, beta-blockers, or angiotensin-converting enzyme inhibitors.

Coronary artery disease

Adults:

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

Special populations

In the elderly:

The usual dosage regimens are recommended.

In patients with renal impairment:

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. AMLODIPINE 5/10 mg PD is not dialysable.

In patients with hepatic impairment:

AMLODIPINE 5/10 mg PD should be administered with caution in patients with impaired hepatic function.

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.
Safety and efficacy of AMLODIPINE 5/10 MG PD in children less than 6 years of age has not been established.

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Method of administration

Tablet for oral use.

AMLODIPINE 5/10 MG PD can be administered with or without the intake of food.

Missed dose

Doctors should advise patients who forget to take AMLODIPINE 5/10 MG PD to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 CONTRAINDICATIONS:

AMLODIPINE 5/10 mg PD is contraindicated in patients with:

- Hypersensitivity to amlodipine, dihydropyridines or to any of the ingredients of AMLODIPINE.5/10 mg PD
- 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
- concomitant use with grapefruit juice (see section 4.5)
- severe hypotension
- obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).

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4.4 Special warnings and precautions for use

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

Concomitant therapy with potent cytochrome CYP3A4 medicines

Potent CYP3A4 inhibitors such as ketoconazole, itraconazole or ritonavir, may enhance the blood pressure lowering effect of AMLODIPINE 5/10 mg PD when taken together (see section 4.5).

Use in the elderly

The time to reach peak plasma concentrations of AMLODIPINE 5/10 MG PD is variable and not significantly different between elderly and younger subjects. 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 AMLODIPINE 5/10 mg PD therapy at a lower dose.

Use in renal failure

Although AMLODIPINE 5/10 mg PD 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 AMLODIPINE 5/10 mg PD is significantly prolonged in patients with impaired hepatic function. AMLODIPINE 5/10 mg PD should therefore be administered at lower initial doses (5 mg) in these patients.

Use in cardiac failure

An increased incidence of pulmonary oedema has been reported. AMLODIPINE 5/10 mg PD may have a negative inotropic effect. AUC of AMLODIPINE 5/10 mg PD may increase in patients with heart failure.

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In patients with severe aortic stenosis, AMLODIPINE 5/10 mg PD may increase the risk of developing 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.

Porphyria

Safety has not been established.

Hypotension

AMLODIPINE 5/10 mg PD should be used with caution in patients with hypotension.

Withdrawal

Sudden withdrawal of AMLODIPINE 5/10 mg PD might be associated with an exacerbation of angina. A gradual decrease of dosage with medical practitioner supervision is recommended.

Diabetes mellitus

AMLODIPINE 5/10 mg PD's effect on insulin and glucose responses may require antidiabetic therapy to be adjusted.

Interference with diagnostic tests

Calcium channel blockers like AMLODIPINE 5/10 mg PD interfere with plasma aldosterone and renin ratios in laboratory tests.

General

AMLODIPINE 5/10 mg PD should be stopped in patients who have ischaemic pain after use.

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4.5 Interaction with other medicines and other forms of interaction

AMLODIPINE 5/10 mg PD 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 5/10 mg PD has no effect on protein binding of the medicines tested (digoxin, phenytoin, warfarin, or indomethacin).

Effects of other medicines on AMLODIPINE 5/10 MG PD

CYP3A4 inhibitors

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 resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers

The concomitant use of CYP3A4 inducers, i.e., rifampicin, St John's Wort (Hypericum perforatum), may give a lower plasma concentration of amlodipine.

AMLODIPINE 5/10 MG PD should be used with caution together with CYP3A4 inducers, blood pressure should be monitored, and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers.

Grapefruit

Administration of AMLODIPINE 5/10 MG PD with grapefruit or grapefruit juice is not recommended

as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium-channel blockers, such as AMLODIPINE 5/10 MG PD, be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Antidysrhythmics

AMLODIPINE 5/10 MG PD 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.

Antihypertensive medicines

AMLODIPINE 5/10 MG PD may enhance the antihypertensive effects of other antihypertensive medicines such as beta blockers, although the combination is generally well tolerated.
AMLODIPINE 5/10 MG PD will not protect against the consequences of abrupt beta-blocker withdrawal; gradual beta-blocker dose reduction is therefore recommended.
Enhanced antihypertensive effects may also be seen in concomitant use with medicines such as aldesleukin and antipsychotics that cause hypotension.

Effects of AMLODIPINE 5/10 MG PD on other medicines

Anti-epileptic medicines

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The effects of AMLODIPINE 5/10 MG PD 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.

Clarithromycin

Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with AMLODIPINE 5/10 MG PD, close observation of patients is therefore recommended when these two are co-administered. There is no information on the effect of the combination on the QT interval.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone (see Simvastatin professional information). Limit the dose of simvastatin in patients taking AMLODIPINE 5/10 MG PD to 20 mg daily.

Mechanistic Target of Rapamycin (mTOR) inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak inhibitor. With concomitant use of mTOR inhibitors, AMLODIPINE 5/10 MG PD may increase exposure of mTOR inhibitors.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with AMLODIPINE 5/10 MG PD, but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of AMLODIPINE 5/10 MG PD in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

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Cyclosporin

No interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations, with the exception of renal transplant patients, where variable trough concentration increases (average 0 - 40 %) of ciclosporin were observed. Consideration should be given to monitoring ciclosporin levels in renal transplant patients on AMLODIPINE 5/10 MG PD, and ciclosporin dose reductions should be made as necessary.

Lithium

The use of lithium with AMLODIPINE 5/10 MG PD may cause lithium induced neurotoxicity in the form of nausea, vomiting, diarrhoea, ataxia, tremors and/or tinnitus, caution is recommended.

Cimetidine

Co-administration of cimetidine did not alter the pharmacokinetics of AMLODIPINE 5/10 MG PD.

Aluminium/magnesium (antacid)

A single dose of AMLODIPINE 5/10 MG PD co-administered with an aluminium/magnesium antacid had no significant effect on the pharmacokinetics of AMLODIPINE 5/10 MG PD.

Sildenafil

A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of AMLODIPINE 5/10 MG PD. When AMLODIPINE 5/10 MG PD and sildenafil were used in combination, each medicine independently exerted its own blood pressure lowering effect.

Digoxin

In healthy volunteers, neither serum digoxin levels nor renal clearance were changed when digoxin was co-administered with AMLODIPINE 5/10 MG PD.

Ethanol (alcohol)

Single and multiple 10 mg doses of AMLODIPINE 5/10 MG PD had no significant effect on the

pharmacokinetics of ethanol.

Warfarin

Co-administration of AMLODIPINE 5/10 MG PD with warfarin did not change the warfarin prothrombin response time.

Antianginal medicines

Concurrent administration of sublingual nitro-glycerine, long-acting nitrates, or other antianginal medicines with AMLODIPINE 5/10 MG PD may produce additive antihypertensive and antianginal effects. Sublingual nitro-glycerine may be used as needed to abort acute angina attacks during AMLODIPINE 5/10 MG PD therapy. Nitrate medication may be used during AMLODIPINE 5/10 MG PD therapy for angina prophylaxis.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see section 4.3).

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.

4.7 Effects on ability to drive and use machines

AMLODIPINE 5/10 mg PD can have minor or moderate influence on the ability to drive and use machines.

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AMLODIPINE 5/10 mg PD can cause side effects such as dizziness, headache, fatigue, or nausea and their ability to react may be impaired. During AMLODIPINE 5/10 mg PD administration, patients should be cautioned about driving a vehicle or operating machinery.

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 summary of adverse reactions

System Organ Class	Frequency	Adverse Event
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, leucocytopenia, haemorrhage, blood dyscrasias
Immune system disorders	Less frequent	Hypersensitivity reactions: pruritus, rash, angioedema and erythema multiforme
Metabolism and nutrition disorders	Less frequent	Hyperglycaemia
Psychiatric disorders	Less frequent	Depression, mood changes (including anxiety), insomnia confusion
Nervous system disorders	Frequent Less frequent	Headache, somnolence, dizziness Hypertonia, hypoaesthesia/paraesthesia, peripheral neuropathy, tremor, increased sweating, taste perversion, hypertonia, extrapyramidal disorder

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Eye disorders	Less frequent	Visual disturbances (including diplopia)
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
Hepatobiliary 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, angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity, Quincke oedema

	Frequency unknown	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Frequent Less frequent	Ankle swelling, muscle cramps Arthralgia, asthenia, back pain, myalgia
Renal and urinary disorders	Less frequent	Increased urinary frequency, micturition disorder, nocturia
Reproductive system and breast disorders	Less frequent	Sexual dysfunction, gynaecomastia
General disorders and administration site conditions	Frequent Less frequent	Facial oedema, upper extremity oedema, fatigue Chest pain, pain, malaise
Investigations	Less frequent	Weight increase/decrease

c) Paediatric population

Adverse events were similar to those seen in adults. In a study of 268 children, the most frequently reported adverse events were headaches, dizziness, vasodilation, epistaxis, abdominal pain, 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

requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

In overdose side effects may be exaggerated and exacerbated.

Gross overdosage resulting in excessive peripheral vasodilatation, and possibly reflex tachycardia resulting in marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

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 ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

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Management of overdose:

Clinically significant hypotension due to AMLODIPINE 5/10 mg PD 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 in no contraindication to its use. Intravenous calcium gluconate may be of benefit in reversing the effects of calcium channel blockade. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects.

ATC code: C08C A01

Pharmacological classification: A 7.1 Vasodilators, hypotensive medicines.

Mechanism of action

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

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.

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

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 21 l/kg

Biotransformation/elimination:

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.

Pharmacokinetics in special patient groups

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 increased 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 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.

Paediatric population

Data reported in children below 6 years is limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch

Sodium starch glycolate.

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6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store at or below 25 °C.

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

6.5 Nature and contents of container

AMLODIPINE 5 MG PD: Opaque PVC / Aluminium foil blisters of 30 tablets, contained in a printed outer carton.

AMLODIPINE 10 MG PD: Opaque PVC / Aluminium foil blisters of 30 tablets, contained in a printed outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

AMLODIPINE 5 mg PD: RSA: 38/7.1/0146

AMLODIPINE 10 mg PD: RSA: 38/7.1/0184

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 17 September 2004

10. DATE OF REVISION OF THE TEXT

19 February 2026