Approved Professional Information (PI)

for Medicines for Human Use

AMLODIPINE 5 UNIMED (Tablets)

AMLODIPINE 10 UNIMED (Tablets)

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

AMLODIPINE 5 UNIMED (Tablets)

AMLODIPINE 10 UNIMED (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each AMLODIPINE 5 UNIMED mg tablet contains amlodipine besilate equivalent to 5 mg active amlodipine base.

Each AMLODIPINE 10 UNIMED mg tablet contains amlodipine besilate equivalent to 10 mg active amlodipine base.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

AMLODIPINE 5 UNIMED: White to off-white round tablets with a score line on one side and “5” on the other side.

AMLODIPINE 10 UNIMED: White to off-white round tablets with “AB” over score line over “10” on one side and “G” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

AMLODIPINE UNIMED is indicated for the treatment of mild-to-moderate hypertension, alone or in combination with other antihypertensives.

Coronary artery disease (CAD)

Angina pectoris

AMLODIPINE UNIMED is indicated for the treatment of angina pectoris.

Chronic stable angina

AMLODIPINE UNIMED 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 UNIMED may be used alone, as monotherapy, or in combination with other antianginal medicines.

Coronary artery disease

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

Adults:

An initial dose of 5 mg AMLODIPINE UNIMED once daily is recommended, which may be increased to a maximum dose of 10 mg once a day depending on the individual patient's response after 10 -14 days of therapy.
No dose reduction is required when adding AMLODIPINE UNIMED 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 elderly

The usual dosage regimens are recommended.

Use in patients with impaired hepatic function

AMLODIPINE UNIMED should be administered with caution in these patients. The pharmacokinetics of amlodipine have not been studied in hepatic impairment. AMLODIPINE UNIMED should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Use is renal failure

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

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to amlodipine or any of the ingredients in section 6.1.
- Hypersensitivity to dihydropyridines.
- Severe hypotension.

- Shock (including cardiogenic shock).
- Heart failure after acute myocardial infarction.
- Obstruction of the outflow-tract of the left ventricle (e.g. aortic stenosis).
- Unstable angina pectoris.
- Safety in pregnancy and lactation has not been established.
- 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 AMLODIPINE UNIMED 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 UNIMED therapy at a lower dose.

Use in patients with renal failure:

AMLODIPINE UNIMED may be used at normal doses in patients with renal impairment. Although AMLODIPINE UNIMED is excreted primarily via the kidneys, mild renal impairment does not appear to have an effect on the plasma concentrations. Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment.

AMLODIPINE UNIMED should be administered with particular caution to patients undergoing dialysis. Severe renal impairment may, however, require a dosage reduction. AMLODIPINE UNIMED is not dialysable.

Use in patients with impaired hepatic function:

The half-life of AMLODIPINE UNIMED is significantly prolonged and AUC values are higher in patients with impaired hepatic function. AMLODIPINE UNIMED should, therefore, be administered at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring maybe required in patients with severe hepatic impairment.

Use in Children:

The effect of AMLODIPINE UNIMED on blood pressure in patients less than 6 years of age is not known (see section 4.2).

Use in patients with heart failure:

An increased incidence of pulmonary oedema has been reported.

AMLODIPINE UNIMED may have a negative inotropic effect. The AUC of AMLODIPINE UNIMED may increase in patients with heart failure. AMLODIPINE UNIMED should be used with caution in patients with a low cardiac reserve. The safety and efficacy of AMLODIPINE UNIMED in hypertensive crisis have not been established.

Porphyria:

Safety has not been established.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on AMLODIPINE UNIMED

CYP3A4 inhibitors

Concomitant use of AMLODIPINE UNIMED with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in AMLODIPINE UNIMED 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.

Clarithromycin

Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with AMLODIPINE UNIMED. Close observation of patients is recommended when AMLODIPINE UNIMED 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 AMLODIPINE UNIMED. Concomitant use of CYP3A4 inducers (e.g. rifampicin, hypericum perforatum) may decrease the plasma concentrations of AMLODIPINE UNIMED. AMLODIPINE UNIMED should be used with caution when administered with CYP3A4 inducers.

Dantrolene (Infusion)

Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as AMLODIPINE UNIMED and dantrolene (infusion) be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Grapefruit juice

Administration of AMLODIPINE UNIMED 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).

Effect of AMLODIPINE UNIMED on other medicines

Ciclosporin

No medicine interaction studies have been conducted with ciclosporin and AMLODIPINE UNIMED 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 UNIMED 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 UNIMED.

Tacrolimus

There is a risk of increased tacrolimus blood levels and toxicity when co-administered with AMLODIPINE UNIMED. In order to avoid toxicity of tacrolimus, administration of AMLODIPINE UNIMED 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 UNIMED is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, AMLODIPINE UNIMED may increase exposure of mTOR inhibitors.

Simvastatin

Co-administration of multiple doses of 10 mg AMLODIPINE UNIMED with simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone.

Clinical interaction studies have shown that AMLODIPINE UNIMED does not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

Concurrent administration of sublingual nitroglycerine, long-acting nitrates, beta-blockers or other antianginal agents with AMLODIPINE UNIMED may produce additive antihypertensive and antianginal effects.

Sublingual nitroglycerine may be used as needed to abort acute angina attacks during amlodipine therapy. Nitrate medication may be used during AMLODIPINE UNIMED therapy for angina prophylaxis.

AMLODIPINE UNIMED 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 UNIMED, a gradual decrease of dosage with medical practitioner supervision is recommended.

In patients with an increased risk (for example after myocardial infarction) the combination of AMLODIPINE UNIMED with beta- blockers may lead to heart failure, hypotension or another myocardial infarction.

Medicine/laboratory test interactions

None known.

4.6 Fertility, pregnancy and lactation

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

Safety of AMLODIPINE UNIMED in human pregnancy has not been established (see section 4.3).

Breastfeeding

AMLODIPINE UNIMED 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 UNIMED on infants is unknown.

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients receiving calcium channel blockers, such as AMLODIPINE UNIMED. Clinical data are insufficient regarding the potential effect of AMLODIPINE UNIMED on fertility.

4.7 Effect on the ability to drive and use machines:

AMLODIPINE UNIMED can cause dizziness. Patients suffering from dizziness, headache, fatigue or nausea 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 UNIMED treatment.

4.8 Undesirable effects

The frequency of adverse reactions reported with AMLODIPINE UNIMED are summarised in Table 1 as per the MedDRA system organ classification (SOC).

Table 1: Tabulated list of adverse reactions		
System Organ Class	**Adverse reactions**	**Frequency**

Blood and lymphatic system disorders	Leukopenia, thrombocytopenia	*Less frequent*
Immune system disorders	Allergic reaction including pruritis, rash, angioedema, anaphylaxis	*Less frequent*
Metabolism and nutritional disorders	Hyperglycaemia.	*Less frequent*
Psychiatric disorders	Insomnia, mood changes (including anxiety), depression, confusion	*Less frequent*
Nervous system disorders	Dizziness, headache, somnolence	*Frequent*
	Peripheral neuropathy, increased sweating, irritability, hypertonia, hypoesthesia /paraesthesia, tremor, dysgeusia, extrapyramidal disorder, syncope	*Less frequent*
Eye disorders	Visual disturbances.	*Less frequent*
Ear and labyrinth disorders	Tinnitus.	*Less frequent*

Cardiac disorders	Palpitations	*Frequent*
	Aggravation of angina pectoris at the beginning of treatment, myocardial infarction, dysrhythmias, (including extrasystole, bradycardia, ventricular tachycardia and atrial fibrillation), chest pain	*Less frequent*
Vascular disorders	Flushing	*Frequent*
	Hypotension (including orthostatic hypotension), vasculitis	*Less frequent*
Respiratory, thoracic and mediastinal disorders	Dyspnoea	*Frequent*
	Rhinitis, coughing.	*Less frequent*
Gastrointestinal disorders	Nausea, abdominal pain.	*Frequent*
	Vomiting, altered bowel habits, dyspepsia, gingival	*Less frequent*

	hyperplasia, pancreatitis, gastritis, dry mouth.	
Hepato-biliary disorders	Hepatitis, jaundice, raised liver enzymes (mostly consistent with cholestasis).	*Less frequent*
Skin and subcutaneous tissue disorders	Alopecia, photosensitivity, allergic reactions with pruritus, rash and exfolliative dermatitis, Stevens Johnson syndrome, purpura, skin discolouration, hyperhidrosis, urticaria, erythema multiforme	*Less frequent*
	toxic epidermal necrolysis	*Frequency unknown*
Musculoskeletal and connective tissue disorders	Ankle swelling, muscle cramps	*Frequent*
	Arthralgia, back pain, myalgia.	*Less frequent*
Renal and urinary disorders	Increased urinary frequency,	*Less frequent*

	micturition disorder, nocturia	
Reproductive system and breast disorders	Impotence, erectile dysfunction, gynaecomastia	*Less frequent*
General disorders and administration site conditions	Fatigue, peripheral oedema	*Frequent*
	Asthenia, pain, malaise	*Less frequent*
Investigations	Weight increase, weight decrease	*Less frequent*

Paediatric population

Paediatric patients (ages 6 – 17 years)

Adverse events were similar to those seen in adults. In studies, the most frequently reported adverse events were:

System Organ Class (SOC)	**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

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no well documented experience with AMLODIPINE UNIMED overdose.

Symptoms

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.

Treatment

Clinically significant hypotension due to AMLODIPINE UNIMED overdose requires active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is 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 activated charcoal up to 2 hours after AMLODIPINE 10 UNIMED (10 mg) has been shown to significantly decrease AMLODIPINE UNIMED absorption. Activated charcoal given 6 hours after AMLODIPINE UNIMED

ingestion had no effect. 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 / Category and Class: A 7.1 Vasodilators, hypotensive medicines.

ATC code: C08 CA01

AMLODIPINE UNIMED (amlodipine besilate) is a dihydropyridine derivative, and has the following chemical name: 3-ethyl5-methyl 2-(2-aminoethoxy-methyl).4-(2-chlorophenyl)-1,4:-dihydro-6 -methyl-3,5- pyridine dicarboxylate benzene sulphonate. Amlodipine besilate is slightly soluble in water and sparingly soluble in ethanol, and has a molecular weight of 567.1 (free base 408.9).

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. Amlodipine has a bioavailability of about 64 %.

Biotransformation/elimination

The plasma elimination half-life is about 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 kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

AMLODIPINE UNIMED tablets include the following inert ingredients:

Pregelatinised starch, microcrystalline cellulose, sodium starch glycollate and magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf-life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep the tablets in their original container and keep blister strips in cartons until tablets are required.

6.5 Nature and contents of container

AMLODIPINE 5 UNIMED tablets are available in:

- Aluminium/aluminium foil blister packs in outer cardboard cartons each containing 28 tablets or

- Aclar/aluminium foil blister packs in outer cardboard cartons each containing 14, 28 or 30 tablets or
- White HDPP bottles containing 60 tablets.

AMLODIPINE 10 UNIMED tablets are available in:

- Aclar/aluminium foil blister packs in outer cardboard cartons each containing 14, 28 or 30 tablets or
- White HDPP bottles containing 60 tablets.

6.6 Special precautions for disposal

- Not applicable

7. HOLDER OF CERTIFICATE OF REGISTRATION

UNIMED HEALTHCARE (PTY) LTD

Corner Birch Road & Bluegum Avenue, Anchorville,

Lenasia, 1827

South Africa

Tel: +27 11 056 6999

8. REGISTRATION NUMBERS:

AMLODIPINE 5 UNIMED: 41/7.1/0782

AMLODIPINE 10 UNIMED: 41/7.1/0783

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORIZATION

04 March 2011

10. DATE OF REVISION OF TEXT

09 May 2025