Professional information for AMLODIPINE KIARA

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

AMLODIPINE 5 KIARA tablets

AMLODIPINE 10 KIARA tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMLODIPINE 5 KIARA: Each tablet contains 5 mg amlodipine (as amlodipine besilate).

AMLODIPINE 10 KIARA: Each tablet contains 10 mg amlodipine (as amlodipine besilate).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

AMLODIPINE 5 KIARA: White to off-white, round, flat faced, bevelled edged tablet, debossed with 'U' and 'L' on either side of the break line on one side and break line on the other side.

AMLODIPINE 10 KIARA: White to off-white, round, flat faced, bevelled edged tablet, with 'UH' debossed on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

AMLODIPINE KIARA is indicated for the treatment of mild to moderate hypertension, alone or in combination with other hypertensive medicines.

Coronary artery disease (CAD)

Angina pectoris

AMLODIPINE KIARA is indicated for the treatment of angina pectoris.

Chronic stable angina

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

Coronary artery disease

AMLODIPINE KIARA is indicated to reduce the risk of coronary revascularisation and the need for hospitalisation due to angina in patients with coronary artery disease.
AMLODIPINE KIARA 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 AMLODIPINE KIARA once daily, which may be increased to a maximum dose of 10 mg depending on the individual patient’s response after 10 – 14 days of therapy.
No dose adjustment of AMLODIPINE KIARA 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

AMLODIPINE KIARA should be administered with caution in these patients.

Use in renal failure

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

Method of administration

For oral administration.

AMLODIPINE KIARA can be administered with or without the intake of food.

4.3 Contraindications

- Hypersensitivity to amlodipine, dihydropyridines or to any of the excipients of AMLODIPINE KIARA (listed in section 6.1).
- Severe hypotension.
- Shock, including cardiogenic shock.
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- 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 section 4.6).
- Concomitant use with grapefruit juice (see section 4.5).

4.4 Special warnings and precautions for use

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

Patients with cardiac failure

Patients with heart failure should be treated with caution. Studies in patients with severe heart failure (New York Heart Association (NYHA) class III and IV) have reported a higher incidence of pulmonary oedema in patients treated with amlodipine in comparison to placebo. Calcium channel blockers, including AMLODIPINE KIARA, should be used with caution in patients with congestive heart failure (CHF), as they may increase the risk of future cardiovascular events and mortality.
The area under the curve (AUC) of AMLODIPINE KIARA may increase in patients with heart failure.
AMLODIPINE KIARA may have a negative inotropic effect.
In patients with severe aortic stenosis, AMLODIPINE KIARA may increase the risk of developing heart failure.

Patients with hepatic impairment

The half-life of AMLODIPINE KIARA is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. AMLODIPINE KIARA should therefore be initiated at the lower end of the dosing range (5 mg) and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Elderly patients

The time to reach peak plasma concentrations of AMLODIPINE KIARA is variable and not significantly different between elderly and younger patients. The clearance of AMLODIPINE KIARA is reduced in the elderly, resulting in prolongation of the elimination half-life and higher AUC values (40 – 60 %). AUC and elimination half-life in patients with CHF were increased with age. Therefore, elderly patients should start AMLODIPINE KIARA therapy at a lower dose and increase of the dosage should take place with care (see section 5.2).

Patients with renal impairment

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

Lithium-induced neurotoxicity

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

General

Sudden withdrawal of AMLODIPINE KIARA might be associated with an exacerbation of angina. A gradual decrease of dosage with medical practitioner supervision is recommended.
AMLODIPINE KIARA should be stopped in patients who have ischaemic pain after use.
AMLODIPINE KIARA should be used with caution in patients with hypotension.

Diabetes mellitus

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

Interference with diagnostic tests

Calcium channel blockers such as AMLODIPINE KIARA interfere with plasma aldosterone and renin ratios in laboratory tests.

Porphyria

Safety has not been established.

Concomitant use with potent cytochrome (CYP) 3A4 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).

Excipient warning

AMLODIPINE KIARA contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

Grapefruit juice

Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg, as in AMLODIPINE KIARA, had no significant effect on the pharmacokinetics of amlodipine in 20 healthy volunteers. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of amlodipine. Therefore, administration of AMLODIPINE KIARA 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 KIARA

CYP3A4 inhibitors

The concomitant use of AMLODIPINE KIARA with strong or moderate CYP3A4 inhibitors may

result in a significant increase in AMLODIPINE KIARA exposure, increasing the risk of hypotension. The clinical translation of these pharmacokinetic (PK) variations may be more pronounced in the elderly. Clinical monitoring and dose adjustments may be required in the co-administration of AMLODIPINE KIARA with one of the following:

- protease inhibitors (such as ritonavir),
- azole antifungals (such as ketoconazole and itraconzole),
- macrolide antibacterials (such as erythromycin or clarithromycin),
- verapamil,
- diltiazem.

CYP3A4 inducers

The concomitant use of AMLODIPINE KIARA with CYP3A4 inducers may decrease the plasma concentration of AMLODIPINE KIARA. AMLODIPINE KIARA should be used with caution when administered with CYP3A4 inducers. The monitoring of blood pressure and dose regulation is advised during and after the concomitant use of AMLODIPINE KIARA and a CYP3A4 inducing medicine, particularly a strong CYP3A4 inducing medicine (such as rifampicin and *Hypericum perforatum* [St John's wort]).

Dantrolene infusion

The co-administration of a calcium channel blocking medicine (such as AMLODIPINE KIARA) and a dantrolene infusion may result in hyperkalaemia and should be avoided in patients susceptible to malignant hyperthermia, as well as in the management of malignant hyperthermia.

The effects of AMLODIPINE KIARA 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.

Effects of AMLODIPINE KIARA on other medicines

Antihypertensive medicine

The blood pressure lowering effects of AMLODIPINE KIARA adds to the blood pressure-lowering effects of other medicines with antihypertensive properties. AMLODIPINE KIARA will not protect against the consequences of abrupt beta-blocker withdrawal. Gradual beta-blocker dose reduction is recommended.

Tacrolimus

There is a risk of increased tacrolimus blood levels and toxicity when tacrolimus is used concomitantly with AMLODIPINE KIARA. In order to avoid toxicity of tacrolimus, monitoring of tacrolimus blood levels and dose adjustments of tacrolimus, when appropriate, is advised when co-administered wth AMLODIPINE KIARA.

Mechanistic target of rapamycin (mTOR) inhibitors

Caution is advised with the concomitant use of AMLODIPINE KIARA and mTOR inhibitors (such as temsirolimus, everolimus and sirolimus). AMLODIPINE KIARA is a weak CYP3A inhibitor and as mTOR inhibitors are CYP3A substrates, the concomitant use with AMLODIPINE KIARA may increase the exposure of mTOR inhibitors.

Ciclosporin

No medicine interaction studies have been conducted with ciclosporin and AMLODIPINE KIARA in healthy volunteers or any other populations, with the exception of renal transplant patients. In renal transplant patients, the co-administration of ciclosporin and amlodipine, as in AMLODIPINE KIARA, resulted in increased trough concentrations of ciclosporin and increased ciclosporin toxicity, from no change up to an average increase of 40 %. Monitoring and appropriate dose adjustments of ciclosporin is advised in renal transplant patients with concomitant administration of AMLODIPINE KIARA.

Simvastatin

Co-administration of multiple doses of 10 mg amlodipine, as in AMLODIPINE KIARA, with simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone. It is advised to limit the dose of simvastatin to 20 mg per day when co-administered with AMLODIPINE KIARA.

CYP3A4 substrates

AMLODIPINE KIARA 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.

Antianginal medicines

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

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

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

The safety of AMLODIPINE KIARA during pregnancy has not been established. AMLODIPINE

KIARA is contraindicated during pregnancy (see section 4.3). Animal studies have reported reproductive toxicity at high doses of AMLODIPINE KIARA.

Breastfeeding

AMLODIPINE KIARA is excreted in human milk. The use of AMLODIPINE KIARA during breastfeeding is contraindicated (see section 4.3).

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 KIARA on infants is unknown.

Fertility

There have been reports of reversible biochemical changes in the head of spermatozoa in patients receiving calcium channel blocker medicines, such as AMLODIPINE KIARA. Clinical data regarding the potential effect of AMLODIPINE KIARA on human fertility are insufficient.

4.7 Effects on ability to drive and use machines

AMLODIPINE KIARA can have a minor or moderate influence on the ability to drive and use machines. Side effects, such as dizziness, headaches, fatigue or nausea may impair the ability to react. Caution is advised before driving a vehicle or operating machinery until the effects of AMLODIPINE KIARA are known, especially at the start of treatment.

4.8 Undesirable effects

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

The following adverse reactions have been reported during treatment with AMLODIPINE KIARA:

Blood and lymphatic system disorders

Less frequent: leukocytopenia, thrombocytopenia, purpura, haemorrhage, blood dyscrasias

Immune system disorders

Less frequent: hypersensitivity reactions (pruritus, rash, angioedema, erythema multiforme)

Metabolism and nutrition disorders

Less frequent: hyperglycaemia

Psychiatric disorders

Less frequent: depression, mood changes (including anxiety), insomnia, confusion

Nervous system disorders

Frequent: somnolence, dizziness, headache (especially at the beginning of treatment)

Less frequent: tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia, hypertonia, peripheral neuropathy, extrapyramidal disorder

Eye disorders

Frequent: visual disturbance (including diplopia)

Ear and labyrinth disorders

Less frequent: tinnitus

Cardiac disorders

Frequent: palpitations

Less frequent: dysrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), myocardial infarction

Vascular disorders

Frequent: flushing

Less frequent: hypotension (including orthostatic hypotension), syncope, vasculitis

Respiratory, thoracic and mediastinal disorders

Frequent: dyspnoea

Less frequent: cough, rhinitis

Gastrointestinal disorders

Frequent: abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)

Less frequent: vomiting, dry mouth, pancreatitis, gastritis, gingival hyperplasia

Hepatobiliary disorders

Less frequent: hepatitis, jaundice, hepatic enzyme increased (mostly consistent with cholestasis)

Skin and subcutaneous tissue disorders

Less frequent: alopecia, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria, angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity

Frequency unknown: toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders

Frequent: ankle swelling, muscle cramps

Less frequent: arthralgia, myalgia, back pain

Renal and urinary disorders

Less frequent: micturition disorder, nocturia, increased urinary frequency

Reproductive system and breast disorders

Less frequent: impotence, gynaecomastia

General disorders and administration site conditions

Frequent: oedema, fatigue, asthenia, peripheral oedema

Less frequent: chest pain, pain, malaise, taste perversion

Investigations

Less frequent: increased weight, decreased weight

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:

Nervous system disorders

Headache, 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 AMLODIPINE KIARA. Healthcare 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: www.sahpra.org.za

4.9 Overdose

Symptoms of overdose

In overdose side effects may be exaggerated and exacerbated.

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 conseguence 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.

Management of overdose

Clinically significant hypotension due to AMLODIPINE KIARA overdosage requires active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

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 beneficial in reversing the effects of calcium channel blockade. In healthy volunteers the use of charcoal up to 2 hours after administration of AMLODIPINE 10 KIARA has been shown to reduce the absorption rate of

amlodipine. Since AMLODIPINE KIARA 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 medicines.

Pharmacotherapeutic group: Selective calcium channel blockers with mainly vascular effects. Dihydropyridine derivatives.

ATC code: C08CA01

Mechanism of action

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist). 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 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. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

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.

Distribution

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

Biotransformation

The plasma elimination half-life is 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.

Special populations

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 is similar in elderly and younger patients (see section 4.4).

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.

Paediatric population

Data reported in children below 6 years is limited.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium phosphate, dibasic, anhydrous

Magnesium stearate (E572)

Microcrystalline cellulose (E460[i])

Sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

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

6.5 Nature and contents of container

AMLODIPINE KIARA is packed in clear PVC/PVdC and aluminium blister strips, placed in an outer carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unichem SA (Pty) Ltd

San Domenico

Ground Floor, Unit G4

10 Church Street

Durbanville

Cape Town 7551

8. REGISTRATION NUMBERS

AMLODIPINE 5 KIARA: 49/7.1/0028

AMLODIPINE 10 KIARA: 49/7.1/0029

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 October 2021

10. DATE OF REVISION OF THE TEXT

07 November 2023