PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PRESNO TABLETS 5 mg

PRESNO TABLETS 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRESNO TABLETS 5 mg: Each tablet contains 5 mg amlodipine (as amlodipine besilate).

PRESNO TABLETS 10 mg: Each tablet contains 10 mg amlodipine (as amlodipine besilate).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PRESNO TABLETS 5 mg

White to off white, capsule shaped, biconvex, uncoated tablets, debossed, “ML22” on one side and plain on other side.

PRESNO TABLETS 10 mg

White to off white, round, biconvex, uncoated tablets, debossed, “ML23” on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

PRESNO TABLETS is indicated for the:

- Treatment of angina pectoris.

- Treatment of mild to moderate hypertension, alone or in combination with other antihypertensive medicines.

4.2 Posology and method of administration

Hypertension and angina pectoris

Adults

An initial dose of 5 mg **PRESNO TABLETS** 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.

No dose reduction is required when adding **PRESNO TABLETS** to thiazide diuretics, beta-blockers, or angiotensin-converting enzyme inhibitors.

Special populations

Elderly

Lower initial doses of **PRESNO TABLETS** may be used in elderly patients (see section 4.4).

Patients with renal impairment

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. **PRESNO TABLETS** is not dialysable.

Patients with hepatic impairment

The pharmacokinetics of amlodipine have not been studied in hepatic impairment. **PRESNO TABLETS** should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Paediatric population

The safety and efficacy of **PRESNO TABLETS** in children have not been established (see section 4.3).

Method of administration

For oral administration

PRESNO TABLETS can be administered with or without the intake of food

4.3 Contraindications

- Hypersensitivity to amlodipine, dihydropyridines or to any of the ingredients of **PRESNO TABLETS**.
- 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).
- Safety in children has not been established.

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 **PRESNO TABLETS**, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality. The area under the curve (AUC) of **PRESNO TABLETS** may increase in patients with heart failure.

PRESNO TABLETS may have a negative inotropic effect.

In patients with severe aortic stenosis, **PRESNO TABLETS** may increase the risk of developing heart failure.

Patients with hepatic impairment

The half-life of **PRESNO TABLETS** is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. **PRESNO TABLETS** should therefore be initiated 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 may be required in patients with severe hepatic impairment.

Elderly patients

The clearance of **PRESNO TABLETS** is reduced (40 – 60 %) in the elderly, resulting in prolongation of the elimination half-life and higher AUC values. Therefore, elderly patients should start **PRESNO TABLETS** therapy at a lower dose and increase of the dosage should take place with care (see sections 4.2 and 5.2).

Patients with renal impairment

PRESNO TABLETS may be used in patients with renal impairment at normal doses. Changes in **PRESNO TABLETS** plasma concentrations are not associated with the degree of renal impairment. **PRESNO TABLETS** is not dialysable.

Lithium-induced neurotoxicity

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

General

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

PRESNO TABLETS should be stopped in patients who have ischaemic pain after use.

PRESNO TABLETS should be used with caution in patients with hypotension.

Diabetes Mellitus

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

Interference with diagnostic tests

Calcium channel blockers such as **PRESNO TABLETS** interfere with plasma aldosterone and renin ratios in laboratory tests.

Porphyria

Safety has not been established

Paediatric population

Safety and efficacy have not been established

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on PRESNO TABLETS

Cytochrome (CYP) 3A4 inhibitors

The concomitant use of **PRESNO TABLETS** with strong or moderate CYP3A4 inhibitors may result in an significant increase in **PRESNO TABLETS** 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 **PRESNO TABLETS** with one of the following:

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

CYP3A4 inducers

The concomitant use of **PRESNO TABLETS** with CYP3A4 inducers may result in varying plasma

concentration of **PRESNO TABLETS**. The monitoring of blood pressure and dose regulation is advised during and after the concomitant use of **PRESNO TABLETS** and a CYP3A4 inducing medicine, particularly a strong CYP3A4 inducing medicine (such as rifampicin and St. John's wort).

The effects of **PRESNO TABLETS** may be reduced in combination with enzyme-inducing anti-epileptic medicines, such as carbamazepine, phenobarbitone and phenytoin. In contrast, sodium valproate has been reported to increase plasma concentrations.

Grapefruit juice

Administration of **PRESNO TABLETS** 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

The co-administration of calcium channel blocking medicine (such as **PRESNO TABLETS**) and 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.

Effects of PRESNO TABLETS on other medicines

Antihypertensive medicine

The blood pressure lowering effects of **PRESNO TABLETS** adds to the blood pressure-lowering effects of other medicines with antihypertensive properties.

PRESNO TABLETS will not protect against the consequences of abrupt beta-blocker withdrawal. Gradual beta-blocker dose reduction is recommended.

Tacrolimus

Although the pharmacokinetic mechanism remains uncertain, there is a risk of increased tacrolimus blood levels when tacrolimus is used concomitantly with **PRESNO TABLETS**. In order to avoid toxicity of tacrolimus, monitoring of blood levels and appropriate dose adjustments of tacrolimus is advised when co-administered with **PRESNO TABLETS**.

Mechanistic target of Rapamycin (mTOR) inhibitors

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

Ciclosporin

In renal transplant patients, the co-administration of ciclosporin and amlodipine resulted on variable trough concentrations increases of ciclosporin (0 % – 40 %). Monitoring and appropriate dose adjustments of ciclosporin is advised in renal transplant patients with concomitant administration of **PRESNO TABLETS**. No drug interaction studies have been conducted with ciclosporin and **PRESNO TABLETS** in healthy volunteers or any other populations.

Simvastatin

When compared to the administration of simvastatin alone, studies have shown that the concomitant use of 80 mg simvastatin and 10 mg **PRESNO TABLETS** in multiple doses resulted in a 77 % increase of simvastatin exposure. It is advised to limit the dose of simvastatin to 20 mg per day when co-administered with **PRESNO TABLETS**.

Clinical interaction studies have shown that **PRESNO TABLETS** does not affect the pharmacokinetics of atorvastatin, digoxin and warfarin.

CYP3A4 substrates

PRESNO TABLETS 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 nitro-glycerine, long acting nitrates, or other antianginal

medicines with **PRESNO TABLETS** may produce additive antihypertensive and antianginal effects. Sublingual nitro-glycerine may be used as needed to abort acute angina attacks during **PRESNO TABLETS** therapy. Nitrate medicine may be used during **PRESNO TABLETS** therapy for angina prophylaxis.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of **PRESNO TABLETS** during pregnancy has not been established. **PRESNO TABLETS** is contraindicated during pregnancy (see section 4.3).

Animal studies have reported reproductive toxicity at high doses of **PRESNO TABLETS**.

Breastfeeding

PRESNO TABLETS is excreted in human milk. The use of **PRESNO TABLETS** 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 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 **PRESNO TABLETS**. Clinical data regarding the potential effect of **PRESNO TABLETS** on human fertility are insufficient.

4.7 Effects on ability to drive and use machines

PRESNO TABLETS 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 **PRESNO TABLETS** 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 PRESNO TABLETS:

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

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 administrative site conditions

Frequent: oedema, fatigue, asthenia, peripheral oedema

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

Investigations

Less frequent: increased weight, decreased weight

Exceptional cases of extrapyramidal syndrome have been reported.

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 **PRESNO TABLETS**. 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 exarcebated.

Available data suggest that large 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.

Management of overdose

Clinically significant hypotension due to PRESNO TABLETS 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 PRESNO TABLETS 10 mg has been shown to reduce the absorption rate of amlodipine.

Since PRESNO TABLETS 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:

1. 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
2. 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 increase 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 4.2).

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

Contains: Anhydrous dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Keep the blister in the carton until required for use.

Keep the containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister pack:

Amber coloured 250 µ PVC/ 90 gsm PVdC as the forming material and silver coloured plain 25 µ aluminium foil/ 6-8 gsm HSL as the lidding material, packed in a pre-printed unit carton. Pack sizes 28’s, 30’s and 100’s.

HDPE container pack:

Round, white, HDPE container (40 ml for **PRESNO TABLETS 5 mg** and 60 ml for **PRESNO TABLETS 10 mg**) with 33 mm neck finish, containing 90's tablets, closed with white a polypropylene child resistant closure, 33 mm with white printed pulp and heat seal liner and packed in a pre-printed unit carton. Pack size 90’s.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

Office Block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBERS

PRESNO TABLETS 5 mg: 51/7.1/0028.026

PRESNO TABLETS 10 mg: 51/7.1/0029.027

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 December 2021.

10. DATE OF REVISION OF THE TEXT