Professional Information

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PENDINE 5 mg tablets

PENDINE 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PENDINE 5: Each tablet contains amlodipine besilate equivalent to 5 mg amlodipine.

PENDINE 10: Each tablet contains amlodipine besilate equivalent to 10 mg amlodipine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

PENDINE 5: White, round, flat, bevel edged uncoated tablets with score on one side and ‘PENDINE’ debossed along the periphery on the other side.

PENDINE 10: White, round, flat, bevel edged uncoated tablets with score on one side and ‘PENDINE’ debossed along the periphery on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

PENDINE is indicated for the treatment of mild to moderate hypertension. PENDINE may be combined with other antihypertensive medicines.

Coronary artery disease (CAD)

Angina pectoris

PENDINE is indicated for the treatment of angina pectoris.

Chronic stable angina

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

Coronary artery disease

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

PENDINE 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

Hypertension and angina pectoris

Adults

The initial dose is 5 mg PENDINE 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 PENDINE 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

PENDINE should be administered with caution in these patients.

Use in renal failure

PENDINE 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 PENDINE 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, dihydropyridines or to any of the excipients 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.
- 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 have not been established.

Patients with cardiac failure

Patients with heart failure should be treated with caution. In a long-term, placebo-controlled study in patients with severe heart failure (New York Heart Association [NYHA] class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Calcium channel blockers, including PENDINE, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

PENDINE may have a negative inotropic effect. The area under the curve (AUC) of PENDINE may increase in patients with heart failure.

Patients with hepatic impairment

The half-life of PENDINE is prolonged and AUC values are higher in patients with impaired hepatic function. PENDINE should therefore be administered at lower initial doses in these patients. 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

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, increase of the dosage should take place with care (see section 5.2).

Patients with renal impairment

PENDINE may be used at normal doses in patients with renal impairment. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

Amlodipine is not dialysable.

Porphyria

Safety has not been established.

Sodium

This medicine 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, such as PENDINE, in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of PENDINE; therefore, administration of PENDINE 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 PENDINE

CYP3A4 inhibitors

Concomitant use of PENDINE 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 PENDINE exposure, resulting in an increased risk of hypotension. The clinical translation of these pharmacokinetic (PK) variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of PENDINE may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant use of PENDINE and a CYP3A4 inducer, particularly a strong CYP3A4 inducer (such as rifampicin, *hypericum perforatum*).

Dantrolene (infusion)

The coadministration of calcium channel blockers, such as PENDINE, 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 PENDINE on other medicines

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

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with PENDINE, but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of PENDINE 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. PENDINE is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, PENDINE may increase exposure of mTOR inhibitors.

Ciclosporin

No medicine interaction studies have been conducted with ciclosporin and PENDINE 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 for monitoring ciclosporin levels in renal transplant patients on PENDINE, and ciclosporin dose reductions should be made as necessary.

Simvastatin

Co-administration of multiple doses of 10 mg PENDINE with 80 mg simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone.

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

Concurrent administration of sublingual nitroglycerin, long-acting nitrates, beta-blockers or other antianginal medicines with PENDINE may produce additive antihypertensive and antianginal effects. Sublingual nitroglycerin may be used as needed to abort acute angina attacks during amlodipine therapy. Nitrate medication may be used during PENDINE therapy for angina prophylaxis. PENDINE 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, a gradual decrease of dosage with medical practitioner supervision is recommended.

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 PENDINE in pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses.

Breastfeeding

PENDINE 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 PENDINE on infants is unknown.

Fertility

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

4.7 Effects on ability to drive and use machines

PENDINE can have minor or moderate influence on the ability to drive and use machines. If patients taking PENDINE suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is advised before driving a vehicle or operating machinery until the effects of PENDINE 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 PENDINE:

Blood and the lymphatic system disorders

Less frequent: Thrombocytopenia, leukopenia.

Immune system disorders

Less frequent: Allergic reactions with 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: Dizziness, headache (especially at the beginning of treatment), somnolence.

Less frequent: Hypertonia, hypoesthesia, paraesthesia, peripheral neuropathy, tremor, dysgeusia, extrapyramidal disorder.

Eye disorders

Frequent: Visual disturbances (including diplopia).

Ear and labyrinth disorders

Less frequent: Tinnitus.

Cardiac disorders

Frequent: Palpitations.

Less frequent: Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation).

Vascular disorders

Frequent: Flushing.

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

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea.

Less frequent: Coughing, rhinitis.

Gastrointestinal disorders

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

Less frequent: Vomiting, gingival hyperplasia, pancreatitis, dry mouth, gastritis.

Hepatobiliary disorders

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

Skin and subcutaneous tissue disorders

Less frequent: Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria, angioedema, erythema multiforme, exfoliative

dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity, toxic epidermal necrolysis.

Frequency unknown: Toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders

Frequent: Ankle swelling, muscle cramps.

Less frequent: Arthralgia, back pain, myalgia.

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: Fatigue, peripheral oedema, asthenia.

Less frequent: Pain, chest pain, malaise.

Investigations

Less frequent: Weight increased, weight decreased.

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 PENDINE. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In humans experience with intentional overdose is limited.

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 PENDINE 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 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. Treatment is symptomatic and supportive.

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.
ATC code: C08CA01.

Mechanism of action

Amlodipine is a dihydropyridine calcium ion influx inhibitor (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 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. Amlodipine has a bioavailability of about 64 %. The volume of distribution is about 20 L/kg. The bioavailability of amlodipine is not affected by food intake.

Biotransformation/elimination

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

Very 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 in AUC of approximately 40 – 60 %.

Elderly population

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 and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Paediatric population

Data reported in children below 6 years is limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate, anhydrous

Magnesium stearate

Microcrystalline cellulose

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.

Store in a dry place.

Keep the blisters strips in the outer carton until required for use. Protect from light.

6.5 Nature and contents of container

PENDINE 5: Aluminium foil blisters containing 10 tablets. 3 blister strips are packed in an outer carton.

PENDINE 10: Aluminium foil blisters containing 10 tablets. 3 blister strips are packed in an outer carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unichem SA (Pty) Ltd

San Domenico

Ground Floor, Unit G4

10 Church Street

Durbanville

7551 Cape Town

8. REGISTRATION NUMBERS

PENDINE 5: A40/7.1/0057

PENDINE 10: A40/7.1/0058

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 11 August 2006

10. DATE OF REVISION OF THE TEXT

04 August 2023

NAMIBIA: NS2

PENDINE 5: 15/7.1/0170

PENDINE 10: 15/7.1/0171