APPROVED PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

APRATE 5 mg (Tablet)

APRATE 10 mg (Tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

APRATE 10 mg

Each tablet contains amlodipine besilate equivalent to amlodipine 5 mg. Sugar free.

APRATE 10 mg:

Each tablet contains amlodipine besilate equivalent to amlodipine 10 mg. Sugar free.

Contains sodium.

APRATE contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

APRATE 5 mg:

White to off white, flat, bevel edged, barrel shaped uncoated tablets, debossed with 'C' on one side and '58' on the other side.

APRATE 10 mg:

White to off white, flat, bevel edged, round shaped uncoated tablets, debossed with 'C' on one side and '59' on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

APRATE is indicated for the:

- Treatment of angina pectoris.

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

4.2. Posology and method of administration

Hypertension and Angina Pectoris:

Adults:

An initial dose of 5 mg **APRATE** 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 **APRATE** to thiazide diuretics, beta-blockers, or angiotensin-converting enzyme inhibitors.

Special populations

In the elderly:

Lower initial doses of **APRATE** may be used in elderly patients, but increase of the dosage should take place with care (see section 4.4)

In patients with renal impairment:

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, **APRATE** is not dialysable.

In patients with hepatic impairment:

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore, dose selection should be cautious and should start at the lower end of the dosing range. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. **APRATE** should be initiated at the lowest dose and titrated slowly in

patients with severe hepatic impairment.

Paediatric population

Safety and efficacy have been established.

Method of administration

Tablet for oral administration.

APRATE can be administered with or without the intake of food. Grapefruit and grapefruit juice should be avoided (see section 4.5).

Missed dose:

If a dose is missed, the tablet should be taken as soon as the missed dose is remembered.

Two tablets should not be taken to make up for the missed dose.

4.3. Contraindications

- hypersensitivity to amlodipine, dihydropyridines or to any of the ingredients of APRATE.
- severe hypotension
- shock, including cardiogenic shock
- haemodynamically unstable heart failure after acute myocardial infarction (during the first 28 days)
- obstruction of the outflow tract of the left ventricle (e.g. high- grade aortic stenosis)
- unstable angina pectoris
- safety in children has not been established
- pregnancy and lactation.

4.4 Special warnings and precautions for use

The substitutability or interchangeability with other amlodipine containing products has not been established.

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

APRATE should not be used to treat angina attack in chronic stable angina, nor should it be used for the acute reduction of blood pressure in adults.

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

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

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

Diabetes mellitus:

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

Interference with diagnostic tests:

Calcium channel blockers, such as **APRATE**, reduce the plasma aldosterone: renin ratio by increasing renin production and reducing plasma aldosterone concentrations, consequently, primary hyperaldosteronism has been misdiagnosed as essential hypertension

Use in the Elderly:

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 **APRATE** therapy at a lower dose (see section 4.4).

Use in Renal Failure:

Although **APRATE** 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 **APRATE** is significantly prolonged in patients with impaired hepatic function.

APRATE should therefore be administered at lower doses in these patients.

Paediatric population

Safety and efficacy has not been established.

Use in Cardiac Failure:

An increased incidence of pulmonary oedema has been reported.

APRATE may have a negative inotropic effect. AUC of **APRATE** may increase in patients with heart failure.

Porphyria:

Safety has not been established

Patients who are taking **APRATE** should inform the anaesthetist accordingly, before receiving anaesthesia.

4.5. Interaction with other medicines and other forms of interaction

Concurrent administration of sublingual nitroglycerin, long-acting nitrates, beta-blockers or other antianginal agents with amlodipine 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 amlodipine therapy for angina prophylaxis.

Amlodipine 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

Enhanced antihypertensive effects may be seen in concomitant use with medicines such as aldesleukin and antipsychotics that cause hypotension. Administration of **APRATE** with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

APRATE may modify insulin and glucose responses and therefore diabetic patients may need to adjust their antidiabetic treatment when receiving **APRATE** (see section 4.4).

APRATE 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.

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

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. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

There is no data available regarding the effect of CYP3A4 inducers on amlodipine.

The concomitant use of CYP3A4 inducers (i.e. rifampicin, hypericum perforatum, St. John's Wort) may give a lower plasma concentration of amlodipine. **APRATE** should be used with caution together with CYP3A4 inducers.

Dantrolene may cause hyperkalaemia when used concomitantly with calcium channel blockers such as **APRATE**. Due to risk of hyperkalaemia, it is recommended that the co-administration of **APRATE** be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

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

Tacrolimus: There is a risk of increased tacrolimus blood levels when coadministered with **APRATE**. In order to avoid toxicity of tacrolimus, administration of **APRATE** in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Co-administration of multiple doses of 10 mg of **APRATE** with 80 mg simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on **APRATE** to 20 mg daily

4.6. Fertility, pregnancy and lactation

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 **APRATE** on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

Pregnancy

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

Breast-feeding

APRATE is excreted in human milk and therefore should not be administered in lactating women

4.7. Effects on ability to drive and use machines

APRATE can cause side effects such as dizziness.

During **APRATE** administration, patients should be cautioned about re-engaging in activities requiring rapid and precise responses such as driving a vehicle or operating machinery.

4.8. Undesirable effects

a. Summary of the safety profile

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

b. Tabulated list of adverse reactions

System Organ Class	Frequency	Side effects

Blood and lymphatic system disorders	Less frequent	Purpura, leukopenia, thrombocytopenia, haemorrhagic complications in surgical patients, 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	Insomnia, mood changes (including anxiety), depression
Nervous system disorders	Frequent	Dizziness, headache, somnolence
	Less frequent	Mood changes, peripheral neuropathy increased sweating, hypertonia, hypoaesthesia/paraesthesia, tremor, taste perversion (dysgeusia)
Eye disorders	Less frequent	Visual disturbances
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Frequent	Palpitations
	Less frequent	Myocardial infarction,

		dysrhythmia (including ventricular tachycardia and atrial fibrillation), chest pain, bradycardia
Vascular disorders	Frequent	Flushing, peripheral oedema
	Less frequent	Hypotension (including orthostatic hypotension), syncope, vasculitis
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, coughing, rhinitis
Gastrointestinal disorders	Frequent	Nausea, abdominal pain, altered bowel habits
	Less frequent	Vomiting, dyspepsia, gingival hyperplasia, pancreatitis, dry mouth, constipation, diarrhoea
Hepato-biliary 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, erythema multiforme, exfoliative dermatitis, Stevens Johnson syndrome, photosensitivity

Musculoskeletal, connective tissue and bone disorders	Frequent	Ankle swelling
	Less frequent	Arthralgia, asthenia, back pain, muscle cramps, myalgia
Renal and urinary disorders	Less frequent	Increased urinary frequency, micturition disorder, nocturia
Reproductive system and breast disorders	Less frequent	Impotence, gynaecomastia
General disorders and administrative site conditions	Less frequent	Fatigue, Facial oedema, upper extremity oedema
Investigations	Less frequent	Weight increase/decrease

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 "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications https://www.sahpra.org.za/Publications/Index/8.

4.9. Overdose

Signs and symptoms:

Overdosage could result in excessive peripheral vasodilatation, resulting in marked and probably prolonged systemic hypotension.

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.

Management of overdose:

Clinically significant hypotension due to **APRATE** 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.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

There is no documented experience with APRATE over- dosage. Gross over-dosage could result in excessive peripheral vasodilation, resulting in marked and probably prolonged systemic hypotension.

TREATMENT IS SYMPTOMATIC AND SUPPORTIVE

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: A 7.1 Vasodilators, hypotensive medicine

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

ATC CODE: C 08 CA 01

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).

Dilatation of the main coronary arteries and the coronary arterioles also probably plays a role in its action.

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

Patients with hypertension:

Once-daily dosing provides clinically significant reductions of blood pressure (in both supine and standing positions) that persist for 24 hours. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

Patients with angina:

Once-daily administration of amlodipine increases total exercise time, the delay of occurrence of anginal attack and the delay of the occurrence of a 1-mm ST interval.

Amlodipine decreases both attack frequency and glyceryl trinitrate tablet

consumption. Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with coronary artery disease (CAD):

Amlodipine treatment was associated with fewer hospitalisations for angina and revascularisation procedures in patients with CAD.

Use in patients with cardiac failure:

Haemodynamic studies and exercise based controlled clinical trials in NYHA class IIIV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A study designed to evaluate patients with NYHA class III-IV heart failure receiving digoxin, diuretics and angiotensin-converting enzyme (ACE) inhibitors has shown that amlodipine did not lead to an increase in the risk of mortality or combined mortality and morbidity in patients with heart failure.

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 – 80 %.

Peak plasma levels are attained 6 to 12 hours after administration. The volume of distribution is about 21 L/kg. Plasma protein binding in vitro is approximately 97.5 %.

Biotransformation:

Amlodipine has a 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.

Elimination:

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:

Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increased AUC, and a lower initial dose may be required.

Renal impairment:

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

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 and elimination half-life in elderly patients, and a lower initial dose may be required. A similar increase in AUC may be observed in patients with moderate to severe heart failure

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Cellulose Microcrystalline

Calcium Hydrogen Phosphate, Anhydrous

Magnesium Stearate

Sodium starch glycolate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at or below 30 °C.

KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN

6.5. Nature and contents of container

APRATE 5 mg:

1. PVC/PE/Aclar – Alu Blister Pack

   Tablets are packed in 250 micron white opaque PVC film laminated with 25 micron PE coated with 23 micron Aclar and 25 microns printed aluminium foil.Each blister contains 10 tablets.

   Pack size: 30's— Each carton contains 3 blisters of 10 tablets each.

2. PVC/PVdC – Alu Blister Pack

   Tablets are packed in white opaque 250 micron PVC film laminated with 90 gsm PVdC and 25 microns printed aluminium foil. Each blister contains 10 tablets.

   Pack size: 30's — Each carton contains 3 blisters of 10 tablets each.

3. HDPE Container:

Tablets are packed in a HDPE container with a stock ribbed closure andinduction sealing wad, in the following pack sizes:

Pack size: 30's

PRODUCT NAME] 10 mg:

15. PVC/PE/Aclar -. Alu Blister Pack

Tablets are packed in 250 micron white opaque PVC film laminated with 25 micron PE coated with 23 micron Aclar and 25 microns printed aluminium foil.Each blister contains 10 tablets.

Pack size: 30's — Each carton contains 3 blisters of 10 tablets each.

2. PVC/PVdC – Alu Blister Pack

Tablets are packed in white opaque 250 micron PVC film laminated with 90 gsmPVdC and 25 microns printed aluminium foil. Each blister contains 10 tablets.

Pack size: 30's — Each carton contains 3 blisters of 10 tablets each.

3. HDPE Container:

Tablets are packed in a HDPE container with a stock ribbed closure andinduction sealing wad, in the following pack sizes:

Pack size: 30's

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SOUTH AFRICA (PTY) LTD

WOODHILL OFFICE PARK, BUILDING 1

53 PHILLIP ENGELBRECHT AVENUE

MEYERSDAL, EXT. 12,

1448, JOHANNESBURG

8. REGISTRATION NUMBER

APRATE 5 mg: 41/7.1/0754

APRATE 10 mg: 41/7.1/0755

9. DATE OF FIRST AUTHORISATION

18 April 2008

10. DATE OF REVISION OF TEXT

30 December 2023