APRATE
P1536515

APRATE
P1536515

PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE
SCHEDULING STATUS

S3

AUROGEN

1. NAME OF THE MEDICINE

APRATE 5 mg (tablet)
APRATE 10 mg (tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

APRATE 5 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 has not 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).

Breastfeeding
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)

DETACH BEFORE DISPENSING

PATIENT INFORMATION LEAFLET
SCHEDULING STATUS

S3

APRATE 5 mg (tablet)
APRATE 10 mg (tablet)
Amlodipine besilate
Sugar free

Read all of this leaflet carefully before you start taking APRATE.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist, nurse or other healthcare provider.
- **APRATE** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet:

1. What **APRATE** is and what it is used for.
2. What you need to know before you use **APRATE**.
3. How to use **APRATE**.
4. Possible side effects.
5. How to store **APRATE**.
6. Contents of the pack and other information.

1. What APRATE is and what it is used for

APRATE belongs to a group of medicines called calcium channel blocking medicines (dihydropyridine calcium antagonists).

APRATE is used for the treatment of:
- Treatment of angina pectoris.
- Treatment of mild to moderate hypertension, alone or in combination with other antihypertensives.

2. What you need to know before you take APRATE

Do not take APRATE:
- If you are hypersensitive (allergic) to amlodipine besilate or any of the other ingredients of **APRATE**.
- If you are hypersensitive (allergic) to dihydropyridines.
- If you suffer from severe hypotension (severe low blood pressure, symptoms include light-headedness or dizziness).
- If you have previously experienced shock which could include cardiogenic shock (this is the term used when blood pressure becomes so low that your heart stops working properly and medical treatment is required).
- If you recently (within the past 28 days) suffered a heart attack.
- If the blood flow from the left side of your heart is obstructed (e.g. aortic valve narrowing).
- If you have unstable angina (chest pain which may occur when you are resting).
- If you are pregnant or breastfeeding your baby.
- If you are younger than 18 years of age.

Warnings and precautions
Take special care with APRATE:
- If your doctor diagnosed you with severe high blood pressure.
- If you suffer from aortic stenosis with symptoms such as fatigue, feeling faint or fainting when exercising and shortness of breath.
- If you experience chest pain when taking **APRATE**.
- If you suffer from diabetes.
- If you need to undergo blood tests, as the use of **APRATE** may interfere with the results.
- If you have low blood pressure or other heart conditions.
- If you are about to have a procedure where you would need general anaesthesia.
- Elderly patients should start **APRATE** therapy at a lower dose.
- Dosage adjustments may be necessary in patients with kidney and liver disease.
- Safety and efficacy in children have not been established.
- Safety in porphyria has not been established.

Other medicines and APRATE:

Always tell your healthcare professional if you are taking any other medicine (this includes complementary or traditional medicines). See "Do not take **APRATE**".

Medicine that may influence **APRATE**:
- **APRATE** interacts with nitroglycerin, long-acting nitrates, beta-blockers or other antianginal agents
- aldesleukin used in the treatment of kidney cancer and skin melanoma or medicines used to treat mental conditions (antipsychotics), as this may increase the levels of **APRATE** in the blood
- grapefruit or grapefruit juice may increase the blood pressure-lowering effects of **APRATE**
- medicines used to treat diabetes, as the doses of these medicines may need to be adjusted
- medicines that alter the heart rate, such as quinidine or procainamide
- certain medicines used to treat fits (carbamazepine, phenobarbital, phenytoin), as these may reduce the effect of **APRATE**
- sodium valproate (used for epilepsy), as this may increase **APRATE** blood levels (discuss with your doctor if you are unsure)
- medicines used to treat viral, fungal and bacterial infections (such as clarithromycin, erythromycin, ketoconazole, itraconazole or rifampicin), or St John's wort (a herbal medicine used to treat anxiety), as these may lead to either increased or decreased levels of **APRATE** in the blood
- ritonavir used in the treatment of HIV infections, as this may lead to increased levels of **APRATE** in the blood
- dantrolene (a muscle relaxant) may affect potassium levels in the blood
- lithium, as this may result in toxic blood concentrations if used in combination with **APRATE**
- simvastatin (used to lower cholesterol), as this may result in increased levels of simvastatin in the blood. The simvastatin dose may need to be reduced.

Tell your doctor before you receive anaesthesia that you are taking **APRATE.**

APRATE with food and drink
APRATE can be taken with or without food.

Grapefruit and grapefruit juice should be avoided (see "Other medicines and **APRATE**").

Pregnancy, breastfeeding and fertility
Safety of **APRATE** in pregnant and lactating women has not been established.

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before taking **APRATE**.

Driving and using machines
APRATE can cause dizziness.

It is not always possible to predict to what extent **APRATE** may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which **APRATE** affects them.

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

3. How to take APRATE

Do not share medicines prescribed for you with any other person.

Always take **APRATE** exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are unsure.

The usual dose is:
Hypertension and angina pectoris:
Adults:
An initial dose of 5 mg **APRATE** orally 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.

Your doctor will tell you how long your treatment with **APRATE** will last. Do not stop treatment early because your condition may worsen. If you have the impression that the effect of **APRATE** is too strong or too weak, tell your doctor or pharmacist.

If you take more APRATE than you should
Taking too many tablets may cause your blood pressure to become low or even dangerously low. You may feel dizzy, lightheaded, faint or weak. If blood pressure drop is severe enough shock can occur. Your skin could feel cool and clammy and you could lose consciousness. Excess fluid may accumulate in your lungs (pulmonary oedema) causing shortness of breath that may develop up to 24 - 48 hours after intake.

There is no documented experience with **APRATE** over-dosage. 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.

TREATMENT IS SYMPTOMATIC AND SUPPORTIVE.

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

If you forget to take APRATE
Do not take a double dose to make up for forgotten individual doses.

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. Possible side effects

APRATE can have side effects.

Not all side effects reported for this **APRATE** are included in this leaflet. Should your general health worsen while taking **APRATE**, or if you experience any untoward effects while using **APRATE**, please consult your healthcare provider for advice.

If any of the following happens, stop using **APRATE** and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing
- rash or itching
- fainting
- jaundice (yellow discolouration of the skin and eyes).

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to **APRATE**. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
- slow heartbeat (bradycardia) or rapid heartbeat (tachycardia), palpitations
- low blood pressure (hypotension) with symptoms such as fainting or light-headedness
- high blood sugar levels (hyperglycaemia)
- hepatitis, a liver condition, with symptoms such as stomach pain, fever, nausea, vomiting or loss of appetite
- weakness, fatigue, weight loss, headache (symptoms of a condition called vasculitis)
- kidney problems (passing less urine than is normal for you)
- pancreatitis (inflammation of the pancreas with symptoms such as stomach pain, increased heart rate and fever).

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:
Frequent side effects:
- headache, dizziness and fatigue
- flushing
- nausea, stomach pain, change in bowel habits
- ankle swelling, swelling in any part of the body.

Less frequent side effects:
- joint pain, back pain, muscle cramps or weakness
- mood and/or sleep disorders, depression, anxiety
- reduced sense of touch or sensation (numbness)
- tingling sensation in hands, feet or lips (feeling of "pins and needles")
- involuntary trembling (tremors), increased sweating
- blurred vision, worsening eyesight
- ringing in the ears (tinnitus)
- cough
- inflammation of the mucous membrane in the nose (rhinitis).

Reporting of side effects
If you get side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects via the "6.04 Adverse Drug reaction Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store APRATE

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

Store at or below 30 °C.

Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What APRATE contains
- The active substance is amlodipine besilate.

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

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

The other ingredients are microcrystalline cellulose, calcium hydrogen phosphate, anhydrous magnesium stearate and sodium starch glycolate.

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 and induction sealing wad, in the following pack sizes:
   Pack size: 30's.

APRATE 10 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 and induction sealing wad, in the following pack sizes:
   Pack size: 30's.

What APRATE looks like and contents of the pack
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.

Holder of Certificate of Registration
AUROGEN SOUTH AFRICA (PTY) LTD.
Woodhill Office Park, Building 1,
53 Phillip Engelbrecht Avenue,
Meyersdal, Ext. 12,
1448, Johannesburg.

Date of registration
18 April 2008

This leaflet was last revised in
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Registration numbers
SOUTH AFRICA:
APRATE 5 mg: 41/7.1/0754
APRATE 10 mg: 41/7.1/0755

NAMIBIA NS2:
APRATE 5 mg: 10/7.1/0248
APRATE 10 mg: 10/7.1/0249

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. Healthcare 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: C08CA01

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 and induction sealing wad, in the following pack sizes:
   Pack size: 30's.

APRATE 10 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 and induction 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.

AUROGEN

8. REGISTRATION NUMBER

SOUTH AFRICA:
APRATE 5 mg: 41/7.1/0754
APRATE 10 mg: 41/7.1/0755

NAMIBIA NS2:
APRATE 5 mg: 10/7.1/0248
APRATE 10 mg: 10/7.1/0249

9. DATE OF FIRST AUTHORISATION

18 April 2008

10. DATE OF REVISION OF TEXT

30 December 2023

P1536515

DETACH BEFORE DISPENSING

PASIËNTINLIGTINGSBLAD
SKEDULERINGSTATUS

S3

APRATE 5 mg (tablet)
APRATE 10 mg (tablet)
Amlodipienbesilaat
Suikervry

Lees hierdie inligtingsblad noukeurig deur voordat jy begin om APRATE te neem.
- Hou hierdie inligtingsblad. Dit mag nodig wees om dit later weer te lees.
- Indien jy enige verdere vrae het, vra asseblief jou dokter, apteker, verpleegkundige of ander gesondheidsorgverskaffer.
- **APRATE** is vir jou persoonlik voorgeskryf en jy moenie jou medisyne met ander persone deel nie. Dit kan skadelik wees vir hulle, al is hulle simptome dieselfde as joune.

Wat is in hierdie inligtingsblad:

1. Wat is **APRATE** en waarvoor word dit gebruik.
2. Wat jy moet weet voordat jy **APRATE** neem.
3. Hoe om **APRATE** te neem.
4. Moontlike newe-effekte.
5. Hoe om **APRATE** te berg.
6. Inhoud van die verpakking en ander inligting.

1. Wat is APRATE en waarvoor word dit gebruik

APRATE behoort aan 'n groep medisynes bekend as kalsiumkanaalblokkers (dihidropiridien-kalsiumantagoniste).

APRATE word gebruik vir die behandeling van:
- **Behandeling van angina pectoris.**

Behandeling van geringe tot matige hipertensie, alleen of in kombinasie met ander antihipertensiewe middels.

2. Wat jy moet weet voordat jy APRATE neem

Moenie APRATE neem nie:
- Indien jy hipersensitief (allergies) vir amlodipienbesilaat of vir enige van die ander bestanddele van **APRATE** is.
- Indien jy hipersensitief (allergies) vir dihidropiridiene is.
- Indien jy aan erge hipotensie ly (erg lae bloeddruk, simptome sluit in lighoofdigheid of duiseligheid).
- Indien jy voorheen skok ervaar het, wat kardiogene skok kan insluit (dit is die term wat gebruik word wanneer die bloeddruk so laag raak dat jou hart ophou om behoorlik te werk en mediese behandeling noodsaaklik is).
- Indien jy onlangs (binne die afgelope 28 dae) 'n hartaanval gehad het.
- Indien die bloedvloei van die linkerkant van jou hart af versper word (bv. aortaklepvernouing).
- Indien jy onstabiele angina het (borspyn wat kan voorkom terwyl jy rustend is).
- Indien jy swanger is of jou baba borsvoed.
- Indien jy jonger as 18 jaar is.

Waarskuwings en voorsorgmaatreëls
Neem spesiale sorg met APRATE:
- Indien jou dokter jou met erge hoë bloeddruk gediagnoseer het.
- Indien jy aan aortastenose ly, met simptome soos matheid, lighoofdigheid of floute wanneer jy oefen, en kortasemheid.
- Indien jy pyn in jou borskas ondervind wanneer jy **APRATE** neem.
- Indien jy aan diabetes ly.
- Indien jy bloedtoetse moet ondergaan, want die gebruik van **APRATE** kan inmeng met die resultate.
- Indien jy aan lae bloeddruk of ander harttoestande ly.
- Indien jy op die punt staan om 'n prosedure te ondergaan waar algemene narkose gebruik gaan word.
- Bejaarde pasiënte behoort **APRATE**-terapie teen 'n laer dosis te begin.
- Dit mag nodig wees om die dosis aan te pas by pasiënte met nier- en lewersiekte.
- Dit is nie bepaal of dit veilig en doeltreffend by kinders is nie.
- Dit is nie bepaal of dit veilig is vir pasiënte wat porfirie het nie.

Ander medisynes en APRATE:

Sê altyd vir jou gesondheidsorgdeskundige indien jy enige ander medisyne neem (dit sluit komplementêre of tradisionele medisynes in). Sien "Moenie **APRATE** neem nie".

Medisyne wat **APRATE** kan beïnvloed:
- **APRATE** het wisselwerking met nitrogliserien, langwerkende nitrate, betablokkers of ander middels teen angina
- aldesleukien, gebruik in die behandeling van nierkanker en velmelanoom, of medisynes wat gebruik word om geestestoestande te behandel (antipsigotiese middels), want dit kan die bloedvlakke van **APRATE** verhoog
- pomelovrug of pomelosap kan die bloeddrukverlagende effekte van **APRATE** versterk
- medisynes wat gebruik word om diabetes te behandel, want dit mag nodig wees om hierdie medisynes se dosisse aan te pas
- medisynes wat die hartspoed wysig, soos kinidien of prokaïenamied
- sekere medisynes gebruik om toevalle te behandel (karbamasepien, fenobarbitaal, fenitoïen), aangesien dit die uitwerking van **APRATE** kan verswak
- natriumvalproaat (gebruik vir epilepsie), aangesien dit die bloedvlakke van **APRATE** kan verhoog (bespreek dit met jou dokter indien jy onseker is)
- medisynes gebruik om virus-, swam- en bakteriese infeksies te behandel (soos klaritromisien, eritromisien, ketokonasool, itrakonasool of rifampisien), of sint janskruid ('n kruiemedisyne wat gebruik word om angstigheid te behandel), want hierdie medisynes kan tot óf verhoogde óf verlaagde vlakke van **APRATE** in die bloed lei
- ritonavir, wat gebruik word in die behandeling van MIV-infeksies, want dit kan tot verhoogde vlakke van **APRATE** in die bloed lei
- dantroleen ('n spierverslapper) kan kaliumvlakke in die bloed affekteer
- litium, want dit kan toksiese bloedkonsentrasies veroorsaak indien dit in kombinasie met **APRATE** gebruik word
- simvastatien (gebruik om cholesterol te verlaag), want dit kan tot verhoogde bloedvlakke van simvastatien lei. Dit mag nodig wees om die dosis van simvastatien te verlaag.

Voordat jy narkose kry, sê vir jou dokter dat jy **APRATE** neem.

APRATE met kos en drinkgoed
APRATE kan met of sonder kos geneem word.

Vermy pomelo en pomelosap (sien "Ander medisynes en **APRATE**").

Swangerskap, borsvoeding en vrugbaarheid
Dit is nie bepaal of dit veilig is vir swanger en borsvoedende vrouens om **APRATE** te gebruik nie.

Indien jy swanger is of jou baba borsvoed, vermoed dat jy swanger mag wees of beplan om swanger te raak, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgverskaffer voordat jy **APRATE**.

Bestuur en gebruik van masjiene
APRATE kan duiseligheid veroorsaak.

Dit is nie altyd moontlik om te voorspel tot watter mate **APRATE** met jou daaglikse aktiwiteite mag inmeng nie. Verseker asseblief dat jy nie bogenoemde aktiwiteite uitvoer nie, totdat jy weet tot watter mate **APRATE** jou affekteer.

APRATE bevat natrium.
APRATE bevat minder as 1 mmol (23 mg) natrium per dosis, dit is dus wesenlik natriumvry.

3. Hoe om APRATE te neem

Moenie medisynes wat vir jou voorgeskryf is, met enigiemand anders deel nie.

Neem **APRATE** altyd presies soos wat jou dokter of apteker vir jou gesê het. Vra gerus jou dokter of apteker indien jy onseker is.

Die gebruiklike dosis is:
Hipertensie en angina pectoris:
Volwassenes:
'n Aanvanklike dosis van 5 mg **APRATE** een keer daagliks mondeliks geneem word aanbeveel, wat ná 10 – 14 dae se terapie verhoog mag word tot 10 mg een keer daagliks indien daar geen verbetering is nie.

Dit is nie nodig om die dosis te verlaag wanneer APRATE by tiasieddiuretika, betablokkers of angiotensien-omsettingsensiem-inhibeerders gevoeg word nie.

Jou dokter gaan vir jou sê hoe lank jou behandeling met **APRATE** gaan duur. Moenie behandeling vroeg staak nie, want jou toestand kan vererger. Indien jy die indruk kry dat die uitwerking van **APRATE** te sterk of te swak is, bespreek dit met jou dokter of apteker.

Indien jy meer APRATE neem as wat jy behoort te neem
Indien jy te veel tablette neem, kan jou bloeddruk laag of self gevaarlik laag raak. Jy kan duiselig, lighoofdig, flou of swak voel. Indien die val in bloeddruk erg genoeg is, kan skok voorkom. Jou vel kan koud en klam voel, en jy kan jou bewussyn verloor. Oormaat vloeistof kan in jou longe ophoop (pulmonale edeem) en kortasemheid veroorsaak, wat tot soveel as 24 – 48 uur ná inname kan ontwikkel.

Geen voorvalle van oordosering met **APRATE** is gedokumenteer nie. Binneaarse kalsiumglukonaat kan van nut wees om die effekte van kalsiumkanaalblokkade om te keer. Dit is onwaarskynlik dat dialise gaan help, aangesien amlodipien hoogs proteïengebonde is.

BEHANDELING IS SIMPTOMATIES EN ONDERSTEUNEND.

In geval van oordosering, raadpleeg jou dokter of apteker. Indien nie een van hulle beskikbaar is nie, kontak die naaste hospitaal of gifsentrum.

Indien jy vergeet om APRATE te neem
Moenie 'n dubbele dosis neem om te vergoed vir die individuele dosisse wat oorgeslaan is nie.

Indien 'n dosis oorgeslaan is, moet die tablet geneem word sodra jy onthou. Moenie twee tablette neem om te vergoed vir die dosis wat oorgeslaan is nie.

4. Moontlike newe-effekte

APRATE kan newe-effekte hê.

Nie alle newe-effekte wat vir **APRATE** gerapporteer is, word in hierdie inligtingsblad ingesluit nie. Indien jou algemene gesondheid sou verswak terwyl jy hierdie medisyne neem, of indien jy enige ongunstige effekte ondervind terwyl jy **APRATE** neem, moet jy asseblief jou gesondheidsorgverskaffer raadpleeg.

Indien enige van die volgende voorkom, hou op om **APRATE** te neem en sê onmiddellik vir jou dokter of gaan na die ongevalle-afdeling by jou naaste hospitaal:
- swelling van jou hande, voete, enkels, gesig, lippe, mond of keel, wat probleme met sluk en asemhaling kan veroorsaak
- uitslag of gejeuk
- floute
- geelsug (geel verkleuring van die vel en oë).

Al hierdie newe-effekte is baie ernstig. Indien jy enige daarvan ondervind, mag jy 'n ernstige allergiese reaksie op **APRATE** gehad het. Jy mag dringend mediese bystand of hospitalisasie benodig.

Indien jy enige van die volgende opmerk, sê onmiddellik vir jou dokter of gaan na die ongevalle-afdeling by jou naaste hospitaal:
- stadige hartklop (bradikardie) of vinnige hartklop (tagikardie), palpitasies
- lae bloeddruk (hipotensie), met simptome soos floutes of lighoofdigheid
- hoë bloedsuikervlakke (hiperglukemie)
- hepatitis, 'n lewertoestand, met simptome soos maagpyn, koors, naarheid, braking of verlies van eetlus
- swakheid, moegheid, gewigsverlies, hoofpyn (simptome van 'n toestand genaamd vaskulitis)
- nierprobleme (produseer minder urine as normaalweg)
- pankreatitis (inflammasie van die pankreas met simptome soos buikpyn, versnelde hartklop en koors).

Hierdie is ernstige newe-effekte. Jy mag dringend mediese sorg benodig.

Sê vir jou dokter indien jy enige van die volgende opmerk:
Newe-effekte wat dikwels voorkom:
- hoofpyn, duiseligheid en moegheid
- blosing
- naarheid, maagpyn, verandering in ontlastingspatroon
- swelling van jou enkels, swelling in enige deel van die liggaam.

Newe-effekte wat minder dikwels voorkom:
- gewrigspyn, rugpyn, spierkrampe of -swakheid
- gemoed- en/of slaapversteurings, depressie, angstigheid
- verminderde gevoeligheid vir aanraking (gevoelloosheid)
- tintelende sensasie in jou hande, voete of lippe (naalde-en-speldegevoel)
- onwillekeurige bewing (tremore), toename in sweetafskeiding
- dowwe visie, visie verswak
- gesuis in die ore (tinnitus)
- hoes
- inflammasie van die slymvlies in die neus (rinitis).

Rapportering van newe-effekte
Indien jy newe-effekte ondervind, bespreek dit met jou dokter, apteker of verpleegkundige. Dit sluit enige moontlike newe-effekte wat nie in hierdie inligtingsblad gelys word nie, in.

Jy kan ook newe-effekte aan SAHPRA rapporteer deur die "6.04 Adverse Drug Reaction Reporting Form" te voltooi. Dit is 'n vorm om ongunstige geneesmiddelreaksies te rapporteer. Hierdie vorm is aanlyn onder SAHPRA se publikasies beskikbaar: https://www.sahpra.org.za/Publications/Index/8

Deur newe-effekte te rapporteer, kan jy help om meer inligting rakende die veiligheid van hierdie medisyne te verskaf.

5. Hoe om APRATE te berg

BERG ALLE MEDISYNES BUITE BEREIK VAN KINDERS.

Bêre by of onder 30 °C.

Neem alle ongebruikte medisyne terug na jou apteker.
Moenie ongebruikte medisyne in dreine en rioolstelsels (bv. toilette) wegdoen nie.

6. Inhoud van die verpakking en ander inligting

Wat APRATE bevat
- Die aktiewe bestanddeel is amlodipienbesilaat.

APRATE 5 mg:
Elke tablet bevat amlodipienbesilaat gelykstaande aan 5 mg amlodipien.

APRATE 10 mg:
Elke tablet bevat amlodipienbesilaat gelykstaande aan 10 mg amlodipien.

Die ander bestanddele is mikrokristallyne sellulose, kalsiumwaterstoffosfaat, watervrye magnesiumstearaat en natriumstyselglikolaat.

APRATE 5 mg:
1. PVC/PE/Aclar-aluminiumstulpstrook
   Tablette word verpak in 250 mikron wit ondeursigtige PVC-film gelamineer met 25 mikron PE bedek met 23 mikron Aclar en 25 mikron bedrukte aluminiumfoelie.
   Elke stulpstrook bevat 10 tablette.
   Verpakkingsgrootte: 30's – Elke karton bevat 3 stulpstroke met 10 tablette elk.
2. PVC/PVdC-aluminiumstulpstrook
   Tablette word verpak in wit ondeursigtige 250 mikron PVC-film gelamineer met 90 gm^2 PVdC en 25 mikron bedrukte aluminiumfoelie. Elke stulpstrook bevat 10 tablette.
   Verpakkingsgrootte: 30's – Elke karton bevat 3 stulpstroke met 10 tablette elk.
3. HDPE-houer:
   Tablette word verpak in 'n HDPE-houer met 'n geriffelde deksel en induksieseëllaag.
   Verpakkingsgrootte: 30's.

APRATE 10 mg:
1. PVC/PE/Aclar-aluminiumstulpstrook
   Tablette word verpak in 250 mikron wit ondeursigtige PVC-film gelamineer met 25 mikron PE bedek met 23 mikron Aclar en 25 mikron bedrukte aluminiumfoelie. Elke stulpstrook bevat 10 tablette.
   Verpakkingsgrootte: 30's – Elke karton bevat 3 stulpstroke met 10 tablette elk.
2. PVC/PVdC-aluminiumstulpstrook
   Tablette word verpak in wit ondeursigtige 250 mikron PVC-film gelamineer met 90 gm^2 PVdC en 25 mikron bedrukte aluminiumfoelie. Elke stulpstrook bevat 10 tablette.
   Verpakkingsgrootte: 30's – Elke karton bevat 3 stulpstroke met 10 tablette elk.
3. HDPE-houer:
   Tablette word verpak in 'n HDPE-houer met 'n geriffelde deksel en induksieseëllaag.
   Verpakkingsgrootte: 30's.

Hoe APRATE lyk en inhoud van die verpakking
APRATE 5 mg:
Wit tot naaswit, plat, vaatjievormige, onbedekte tablette met afgeskuinste rande, met "C" aan die een kant en "58" aan die ander kant ingepers.

APRATE 10 mg:
Wit tot naaswit, plat, ronde, onbedekte tablette met afgeskuinste rande, met "C" aan die een kant en "59" aan die ander kant ingepers.

Houer van Registrasiesertifikaat
AUROGEN SOUTH AFRICA (EDMS) BPK.
Woodhill Office Park, Gebou 1,
Phillip Engelbrechtlaan 53,
Meyersdal, Uitbr. 12,
1448, Johannesburg.

Datum van registrasie
18 April 2008

Hierdie inligtingsblad is laas hersien
30 Desember 2023

Registrasienommers
SUID AFRIKA:
APRATE 5 mg: 41/7.1/0754
APRATE 10 mg: 41/7.1/0755

NAMIBIË NS2:
APRATE 5 mg: 10/7.1/0248
APRATE 10 mg: 10/7.1/0249