APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BESYLOC 5 mg tablets.

BESYLOC 10 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BESYLOC 5 mg tablet contains amlodipine besylate equivalent to 5 mg amlodipine.

Each BESYLOC 10 mg tablet contains amlodipine besylate equivalent to 10 mg amlodipine.

BESYLOC tablets are sugar-free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

BESYLOC 5 mg: White, round (diameter 8,0 mm), slightly biconvex tablets with bevelled edges, scored on one side.

BESYLOC 10 mg: White, round (diameter 10,5 mm), slightly biconvex tablets, with bevelled edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- treatment of angina pectoris
- treatment of mild to moderate hypertension, alone or in combination with other antihypertensives
- treatment of chronic stable angina - 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. BESYLOC may be used alone, as monotherapy, or in combination with other antianginal medicines
- treatment of coronary artery disease - BESYLOC is indicated to reduce the risk of coronary revascularisation and the need for hospitalisation due to angina in patients with coronary artery disease
- BESYLOC is also indicated to reduce the risk of fatal coronary heart disease and non-fatal myocardial infarction, and to reduce the risk of stroke.

4.2 Posology and method of administration

Posology

BESYLOC can be administered with or without the intake of food.

Grapefruit and grapefruit juice should be avoided (see section 4.5).

Hypertension and Angina pectoris:

Adults:

An initial dose of 5 mg BESYLOC 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.

In hypertension, no dose reduction is required when adding BESYLOC to 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

In the elderly:

The usual dosage regimens are recommended, but increase of the dosage should take place with care (see section 4.4).

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. BESYLOC should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

In patients with renal failure:

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

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 BESYLOC on blood pressure in patients younger than 6 years of age is not known.

Method of administration

Tablet for oral administration.

BESYLOC 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 BESYLOC (see section 6.1)
- 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
- concomitant use with grapefruit juice (see section 4.5)
- safety in children younger than 6 years of age has not been established
- pregnancy and lactation.

4.4 Special warnings and precautions for use

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

BESYLOC 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, BESYLOC may increase the risk of developing heart failure.

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

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

Concomitant use with potent cytochrome CYP3A4 medicines:

The blood pressure lowering effect may be enhanced when potent CYP3A4 inhibitors such as ketoconazole, itraconazole or ritonavir are co-administered (see section 4.5).

Diabetes mellitus:

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

Interference with diagnostic tests:

Calcium channel blockers, such as BESYLOC, 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 BESYLOC therapy at a lower dose.

Use in renal failure:

Although BESYLOC 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 BESYLOC is significantly prolonged in patients with impaired hepatic function, dosage recommendations have not been established. BESYLOC 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.

Use in cardiac failure*:*

Calcium channel blockers, including amlodipine, should be used with caution in patients with hypotension, patients whose cardiac reserve is poor and those with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

BESYLOC should not be used in cardiogenic shock or in patients who have suffered myocardial infarction in the previous 2 to 4 weeks, or in acute unstable angina (see section 4.3).

Porphyria:

Safety has not been established.

Paediatric population

Safety and efficacy have been established in paediatric patients ages 6 - 17 years with recommended doses of 2,5 mg - 5 mg once daily. Safety and efficacy have not been established for doses exceeding 5 mg daily and in patients younger than 6 years of age as the effect of BESYLOC on blood pressure is not known.

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

4.5 Interaction with other medicines and other forms of interaction

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

BESYLOC may enhance the antihypertensive effects of other antihypertensive medicines such as beta blockers. BESYLOC 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 BESYLOC, 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 BESYLOC 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).

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

BESYLOC 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 BESYLOC may be reduced in combination with enzyme-inducing anti-epileptics 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 (see section 4.4).

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. BESYLOC should be used with caution together with CYP3A4 inducers.

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

The use of lithium with BESYLOC 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 co-administered with BESYLOC. In order to avoid toxicity of tacrolimus, administration of BESYLOC 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 BESYLOC 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 BESYLOC to 20 mg daily (see simvastatin professional information).

Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when BESYLOC is co-administered with clarithromycin.

No medicine interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations, with the exception of renal transplant patients. Various studies in renal transplant patients report that co-administration of amlodipine with

ciclosporin increased the trough concentrations of ciclosporin and increased ciclosporin toxicity, from no change up to an average increase of 40 %. Consideration should be given for monitoring ciclosporin levels in renal transplant patients on BESYLOC.

Mechanistic target of rapamycin (mTOR) inhibitors: mTOR inhibitors such as sirolimus, temsirolimus and everolimus are CYP3A substrates. BESYLOC is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, BESYLOC may increase exposure of mTOR inhibitors.

Medicine/laboratory test interactions: None known.

Cimetidine, aluminium/magnesium (antacid) and sildenafil do not affect the pharmacokinetics of amlodipine.

BESYLOC does not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ethanol.

Amlodipine has been administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and oral hypoglycaemic medicines.

In vitro data from studies with human plasma indicate that BESYLOC

has no effect on protein binding of the medicines tested (digoxin, phenytoin, warfarin, or indomethacin).

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

BESYLOC in pregnancy and lactation is contraindicated (see section 4.3). Since teratogenic effects were noted in animals, amlodipine should not be administered to pregnant women.

Breastfeeding

BESYLOC is excreted in human milk and therefore should not be administered in lactating women (see section 4.3).

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

4.7 Effects on ability to drive and use machines

Amlodipine can have minor or moderate influence on the ability to drive and use machines.

BESYLOC can cause side effects such as dizziness, headache, fatigue or nausea therefore the ability to react may be impaired.

During BESYLOC 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 commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

b. Tabulated list of adverse effects

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent	Purpura, thrombocytopenia, leucocytopenia, 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 Less frequent	Headache, somnolence, dizziness Hypertonia, hypoaesthesia/ paraesthesia, peripheral neuropathy, tremor, increased sweating, dysgeusia, extrapyramidal disorder
Eye disorders	Less frequent	Visual disturbances
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Frequent Less frequent	Palpitations Myocardial infarction, dysrhythmia (including ventricular tachycardia and atrial fibrillation), chest pain, bradycardia
Vascular disorders	Frequent Less frequent	Flushing, peripheral oedema Hypotension (including orthostatic hypotension), syncope, vasculitis
Respiratory, thoracic and mediastinal disorders	Less frequent	Coughing, dyspnoea, rhinitis
Gastrointestinal disorders	Frequent Less frequent	Nausea, abdominal pain, altered bowel habits Vomiting, dyspepsia, pancreatitis, constipation, diarrhoea, dry mouth, gingival hyperplasia
Hepatobiliary 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, urticaria, Quincke oedema
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Ankle swelling 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	Sexual dysfunction, gynaecomastia
General disorders and administrative site conditions	Frequent Less frequent	Facial oedema, upper extremity oedema, fatigue Taste perversion, asthenia, malaise, pain
Investigations	Less frequent	Weight increase/decrease

Paediatric population

Paediatric patients (ages 6 - 17 years)

Adverse events were similar to those seen in adults.The most frequently reported adverse events were:

System Organ Class	**Frequency**	**Side effects**
Nervous system disorders	Frequent	Headache, dizziness
Vascular disorders	Frequent	Vasodilation

Respiratory, thoracic and mediastinal disorders	Less frequent	Epistaxis
Gastrointestinal disorders	Frequent	Abdominal pain
General disorders and administrative site conditions	Frequent	Asthenia

Severe adverse events (predominantly headache) were experienced by 7,2 % with amlodipine 2,5 mg, 4,5 % with amlodipine 5 mg, and 4,6 % with placebo. The most common cause of discontinuation from the study was uncontrolled hypertension. There were no discontinuations due to laboratory abnormalities. There was no significant change in heart rate.

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

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 BESYLOC 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.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: C 08 CA 01

Pharmacological classification: A 7.1 Vasodilators, hypotensive medicine.

Mechanism of action

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 II-IV 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:

The absolute bioavailability of the unchanged compound is estimated as 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:

The 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. Amlodipine is predominantly metabolised by the liver to inactive metabolites.

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.

5.3 Preclinical safety data

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis).

In another rat study in which male rats were treated with amlodipine besylate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0,5, 1,25, and 2,5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no medicinal product related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch

Sodium starch glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store at or below 30 °C.

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

6.5 Nature and contents of container

BESYLOC 5 mg: OPA/AL/PVC film and heat sealing aluminium foil blisters of 30 tablets, contained in a printed outer carton.

BESYLOC 10 mg: OPA/AL/PVC film and heat-sealing aluminium foil blisters of 30 tablets, contained in a printed outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

APPROVED PROFESSIONAL INFORMATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

BESYLOC 5 mg: A41/7.1/0560

BESYLOC 10 mg: A41/7.1/0561

9. DATE OF FIRST AUTHORISATION

August 2015

10. DATE OF REVISION OF THE TEXT

28 January 2025

NAM:

BESYLOC 5 mg: NS2 08/7.1/0155

BESYLOC 10 mg: NS2 08/7.1/0156