PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

VASLOC 5 mg tablets

VASLOC 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Sugar free.

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

VASLOC 5 mg: White to off white, octagonal shaped, uncoated tablets, debossed with “AM 5” on one side and plain on the other side.

VASLOC 10 mg: White to off white, octagonal shaped, uncoated tablets, debossed with “AM 10” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VASLOC 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 VASLOC 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 VASLOC to thiazide diuretics, beta blockers, or angiotensin-converting enzyme inhibitors.

Special populations

Elderly

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

Patients with renal impairment

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

Patients with hepatic impairment

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

Paediatric population

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

Method of administration

For oral administration.

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

4.3 Contraindications

- Hypersensitivity to amlodipine, dihydropyridines or to any of the ingredients of VASLOC.
- Severe hypotension.
- Shock, including cardiogenic shock.
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction (during the first 28 days).
- Unstable angina pectoris.
- Should not be used for acute reduction of blood pressure.
- Pregnancy and lactation (see section 4.6).
- Safety in children has not been established.

4.4 Special warnings and precautions for use

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

Patients with cardiac failure

Patients with heart failure should be treated with caution. Studies in patients with severe heart failure (New York Heart Association (NYHA) class III and IV) have reported a higher incidence of pulmonary oedema in patients treated with amlodipine in comparison to placebo. Calcium channel blockers, including VASLOC, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality. The area under the curve (AUC) of VASLOC may increase in patients with heart failure.

VASLOC may have a negative inotropic effect.

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

Patients with hepatic impairment

The half-life of VASLOC is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. VASLOC should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Elderly patients

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

Patients with renal impairment

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

Lithium-induced neurotoxicity

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

General

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

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

VASLOC should be used with caution in patients with hypotension.

Diabetes mellitus

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

Interference with diagnostic tests

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

Porphyria

Safety has not been established.

Paediatric population

Safety and efficacy have not been established.

4.5 Interactions with other medicines and other forms of interactions

Effects of other medicines on VASLOC

Cytochrome (CYP) 3A4 inhibitors

The concomitant use of VASLOC with strong or moderate CYP3A4 inhibitors, may result in a significant increase in VASLOC exposure, increasing the risk of hypotension. The clinical translation of these pharmacokinetic (PK) variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may be required in the co-administration of VASLOC with one of the following:

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

CYP3A4 inducers

The concomitant use of VASLOC with CYP3A4 inducers may result in varying plasma concentration of VASLOC. The monitoring of blood pressure and dose regulation is advised during and after the concomitant use of VASLOC and a CYP3A4 inducing medicine, particularly a strong CYP3A4 inducing medicine (such as rifampicin and St. John's wort).

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

Grapefruit juice

Administration of **VASLOC** with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene infusion

The co-administration of calcium channel blocking medicine (such as VASLOC) and dantrolene infusion may result in hyperkalaemia and should be avoided in patients susceptible to malignant hyperthermia, as well as in the management of malignant hyperthermia.

Effects of VASLOC on other medicines

Antihypertensive medicine

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

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

Tacrolimus

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

Mechanistic target of Rapamycin (mTOR) inhibitors

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

Ciclosporin

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

Simvastatin

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

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

CYP3A4 substrates

VASLOC is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 and interactions may occur with other medicines, such as quinidine or procainamide, sharing the same metabolic pathway, since both groups possess negative inotropic properties.

Antianginal medicines

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Animal studies have reported reproductive toxicity at high doses of VASLOC.

Breastfeeding

VASLOC is excreted in human milk. The use of VASLOC during breastfeeding is contraindicated (see section 4.3).

The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7 %, with a maximum of 15 %. The effect of amlodipine on infants is unknown.

Fertility

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

4.7 Effects on ability to drive and use machines

VASLOC can have a minor or moderate influence on the ability to drive and use machines. Side effects such as dizziness, headache, fatigue or nausea may impair the ability to react. Caution is advised before driving a vehicle or operating machinery until the effects of VASLOC are known, especially at the start of treatment.

4.8 Undesirable effects

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

The following adverse reactions have been reported during treatment with VASLOC:

System Organ Class	**Frequency**	
Blood and lymphatic system disorders	Less frequent	Leukocytopenia, thrombocytopenia, purpura, haemorrhage, blood dyscrasias
Immune system disorders	Less frequent	Hypersensitivity reactions (pruritus, rash, angioedema, erythema multiforme)
Metabolism and nutrition disorders	Less frequent	Hyperglycaemia
Pshychiatric disorders	Less frequent	Depression, mood changes (including anxiety), insomnia, confusion
Nervous system disorders	Frequent	Somnolence, dizziness, headache (especially at the beginning of treatment)

	Less frequent	Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia, hypertonia, peripheral neuropathy
Eye disorders	Less frequent	Visual disturbance (including diplopia)
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Frequent	Palpitations
	Less frequent	Dysrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), myocardial infarction
Vascular disorders	Frequent	Flushing
	Less frequent	Hypotension (including orthostatic hypotension), syncope, vasculitis
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea
	Less frequent	Cough, rhinitis
Gastrointestinal disorders	Frequent	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)
	Less frequent	Vomiting, dry mouth, pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	Less frequent	Hepatitis, jaundice, hepatic enzymes increased (mostly consistent with cholestasis)

Skin and subcutaneous tissue disorders	Less frequent	Alopecia, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria, angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
	Frequency unknown	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Frequent	Ankle swelling, muscle cramps
	Less frequent	Arthralgia, myalgia, back pain
Renal and urinary disorders	Less frequent	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Less frequent	Impotence, gynaecomastia
General disorders and administration site conditions	Frequent	Oedema, fatigue, asthenia, peripheral oedema
	Less frequent	Chest pain, pain, malaise, taste perversion
Investigations	Less frequent	Weight increase, weight decrease

Exceptional cases of extrapyramidal syndrome have been reported.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of VASLOC 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 Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms of overdose

In overdose side effects may be exaggerated and exarcebated.

Available data suggest that large overdosage could result in excessive peripheral vasodilatation, and possible reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Management of overdose

Clinically significant hypotension due to VASLOC overdosage requires active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. In healthy volunteers the use of charcoal up to 2 hours after administration of VASLOC 10 mg has been shown to reduce the absorption rate of amlodipine.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1 Vasodilators, hypotensive medicines

Pharmacotherapeutic group: Selective calcium channel blockers with mainly vascular effects. Dihydropyridine derivatives. ATC Code: C08CA01.

Mechanism of action

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist). It inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle without affecting serum calcium concentrations. Direct relaxation of vascular smooth muscle forms the basis of the antihypertensive action.

In angina pectoris, amlodipine reduces total ischaemic burden by the following action:
Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
Amlodipine exerts its activity by binding to the dihydropyridine binding sites. It exerts minimal action on cardiac conduction, contraction and heart rate.

5.2 Pharmacokinetic properties

Absorption

Complete absorption of amlodipine is slow following oral administration with peak plasma levels being attained after 6 to 12 hours.
The absorption of amlodipine is unaffected by the concomitant intake of food.

Distribution

Amlodipine has a bioavailability of about 64 % and peak plasma levels are attained after 6 to 12 hours. The volume of distribution is approximately 20 L/kg.

Biotransformation

The plasma elimination half-life is 35 to 50 hours, allowing for once-daily oral dosing. Steady state plasma concentrations are achieved after 7 to 8 days of consecutive dosing. Metabolism is via the liver and is extensive with less than 10 % of amlodipine appearing unchanged in the urine. Metabolites are inactive and primarily (up to 60 %) excreted via the kidney.

Special populations

Hepatic impairment

Limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase AUC of approximately 40 - 60 % and a lower initial dose may be required.

Renal impairment

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly

The time to reach peak plasma concentrations is similar in elderly and younger patients (see section 4.2).

Amlodipine clearance tends to be decreased with resulting increases in AUC of approximately 40 - 60 % and elimination half-life in elderly patients, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Paediatric population

Data reported in children below 6 years is limited.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, microcrystalline cellulose, magnesium stearate, colloidal silica anhydrous, sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store at or below 30 °C in the original package.

Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

The tablets are packed in PVC/PVDC/Aluminium foil blisters strips. The blister strips are packed in cartons containing 28 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Smart Pharmaceuticals (Pty) Ltd

247 Voortrekker Road

Kraaifontein, Cape Town

7570

8. REGISTRATION NUMBERS

VASLOC 5 mg: 46/7.1/0565

VASLOC 10 mg: 46/7.1/0566

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 April 2022

10. DATE OF REVISION OF THE TEXT

6 April 2022