PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ASCIVASC 5 mg tablets

ASCIVASC 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

ASCIVASC 5: White to off white round flat faced beveled edge tablets '210' debossed on one side and plain on other side.

ASCIVASC 10: White to off white round flat faced beveled edge tablets '209' debossed on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ASCIVASC is indicated for the treatment of:

- Mild to moderate hypertension, alone or in combination with other

Date amended: 06 August 2023 (Response to PV letter – 14/03/2023)
Date approved: 27 November 2023

antihypertensive medicines.

- Angina pectoris.

4.2 Posology and method of administration

Posology

Hypertension and angina pectoris

Adults

An initial dose of 5 mg ASCIVASC once daily is recommended which may be increased to 10 mg once as day after 10 – 14 days of therapy if there is no improvement.

No dose reduction is required when adding ASCIVASC to thiazide diuretics, beta blockers, or angiotensin-converting enzyme inhibitors.

Special populations

Elderly

Lower initial doses of ASCIVASC 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. ASCIVASC is not dialysable.

Patients with hepatic impairment

The pharmacokinetics of amlodipine have not been studied in hepatic impairment.

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

Paediatric population

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

Method of administration

For oral administration

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

4.3 Contraindications

- Hypersensitivity to amlodipine, dihydropyridines or to any of the excipients (see section 6.1).
- Severe hypotension
- Shock, including cardiogenic shock.
- 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.
- Obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis).
- 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 ASCIVASC, 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 ASCIVASC may increase in patients with heart failure.

ASCIVASC may have a negative inotropic effect.

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

Patients with hepatic impairment

The half-life of ASCIVASC is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. ASCIVASC 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 ASCIVASC is reduced (40 – 60 %) in the elderly, resulting in prolongation of the elimination half-life and higher AUC values. Therefore, elderly patients should start ASCIVASC 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

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

ASCIVASC is not dialysable.

Lithium-induced neurotoxicity

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

General

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

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

ASCIVASC should be used with caution in patients with hypotension.

Diabetes Mellitus

ASCIVASC's effect on insulin and glucose responses may require antidiabetic

therapy to be adjusted.

Interference with diagnostic tests

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

Porphyria

Safety has not been established.

Paediatric patients

Safety and efficacy of ASCIVASC have not been established.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on ASCIVASC

Cytochrome (CYP) 3A4 inhibitors

Concomitant use of ASCIVASC with strong or moderate CYP3A4 inhibitors may give rise to significant increase in ASCIVASC exposure resulting in an increased risk of hypotension. The clinical translation of these pharmacokinetic (PK) variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required in the co-administration of ASCIVASC with one of the following:

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

CYP3A4 inducers

The concomitant use of ASCIVASC with CYP3A4 inducers may result in varying plasma concentration of ASCIVASC. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant use of ASCIVASC and a CYP3A4 inducing medicine, particularly with strong CYP3A4 inducers (e.g. rifampicin and St. John's wort*).*

The effects of ASCIVASC 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 ASCIVASC 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 blockers (such as ASCIVASC) 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 ASCIVASC on other medicines

Antihypertensive medicine

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

ASCIVASC 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 ASCIVASC. In order to avoid toxicity of tacrolimus, administration of ASCIVASC in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

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

Ciclosporin

In renal transplant patients, the co-administration of ciclosporin and amlodipine resulted on variable trough concentrations increases of ciclosporin (0 % – 40 %). Monitoring and appropriate dose adjustments of ciclosporin is advised in renal transplant patients with concomitant administration of ASCIVASC. No drug

interaction studies have been conducted with ciclosporin and ASCIVASC in healthy volunteers or any other populations.

Simvastatin

When compared to the administration of simvastatin alone, studies have shown concomitant use of 80 mg simvastatin and 10 mg ASCIVASC in multiple doses resulted in a 77 % increase of simvastatin exposure. It is advised to limit the dose of simvastatin in patients on ASCIVASC to 20 mg daily.

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

CYP3A4 substrates

ASCIVASC 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 ASCIVASC may produce additive antihypertensive and antianginal effects. Sublingual nitro-glycerine may be used as needed to abort acute angina attacks during ASCIVASC therapy. Nitrate medicine may be used during ASCIVASC therapy for angina prophylaxis.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Breastfeeding

ASCIVASC is excreted in human milk. The use of ASCIVASC 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

Reversible biochemical changes in the head of spermatozoa have been reported in patients treated with calcium channel blockers, such as ASCIVASC. Clinical data regarding the potential effect of ASCIVASC on human fertility are insufficient.

4.7 Effects on ability to drive and use machines

ASCIVASC can have 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 ASCIVASC are known, especially at the start of treatment.

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 summary of adverse reactions

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

with the following frequencies: frequent, less frequent and frequency unknown (cannot be estimated from the available data).

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Purpura, haemorrhage, blood dyscrasias, leukocytopenia, thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity reactions (pruritus, rash, angioedema, erythema multiforme)
Metabolism and nutrition disorders	Less frequent	Hyperglycaemia
Psychiatric disorders	Less frequent	Depression, mood changes (including anxiety), insomnia, confusion
Nervous system disorders	Frequent	Somnolence, dizziness,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		headache (especially at the beginning of the treatment)
	Less frequent	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia, hypertonia, peripheral neuropathy,
Eye disorders	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	Syncope, hypotension (including orthostatic hypotension), vasculitis
Respiratory, thoracic and	Frequent	Dyspnoea

MedDRA system organ class	**Frequency**	**Adverse reactions**
mediastinal disorders		
	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
Hepato-biliary disorders	Less frequent	Hepatitis, jaundice, hepatic enzyme 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	Frequent	Ankle swelling, muscle cramps
	Less frequent	Arthralgia, myalgia, back pain

MedDRA system organ class	**Frequency**	**Adverse reactions**
disorders		
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	increased weight, decreased weight

Exceptional cases of extrapyramidal syndrome have been reported.

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 ASCIVASC. 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 for amlodiine 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 ASCIVASC 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 ASCIVASC 10 mg has been shown to reduce the absorption rate of amlodipine.

Since ASCIVASC 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) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle without changing serum calcium concentrations.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle.

In angina pectoris, amlodipine reduces total ischemic 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 has a minimal effect on cardiac conduction, contraction or heart rate.

5.2 Pharmacokinetic properties

Absorption

Complete absorption of amlodipine is slow following oral administration with peak plasma levels being attained after 6 - 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 about 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 of amlodipine 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

Colloidal silicon dioxide

Dibasic calcium phosphate (anhydrous)

Magnesium stearate

Microcrystalline cellulose (Grade 102)

Sodium starch glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a cool, dry place at or below 25 °C.

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

Store in the original container.

Keep out of reach of children.

6.5 Nature and contents of container

ASCIVASC 5 and 10 mg tablets are packed as follows:

Alu-Alu blister packs of 10 tablets per blister. Three blisters of 10 tablets each are packed in an outer cardboard carton.

White opaque, round HDPE container with child resistant cap containing 90 tablets.

White opaque, round HDPE container with non-child resistant cap containing 500 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

Ascendis Pharma (Pty) Ltd

31 Georgian Crescent East

Bryanston, 2191

South Africa

8 REGISTRATION NUMBERS

ASCIVASC 5: 50/7.1/0557

ASCIVASC 10: 50/7.1/0558

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 June 2022

10 DATE OF REVISION OF THE TEXT

27 November 2023