PROFESSIONAL INFORMATION FOR

CIPLAVASC 5 & CIPLAVASC 10

SCHEDULING STATUS S3

1 NAME OF THE MEDICINE

CIPLAVASC 5 Tablet

CIPLAVASC 10 Tablet

Amlodipine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CIPLAVASC 5 tablet contains amlodipine besylate equivalent to 5 mg active amlodipine.

Each CIPLAVASC 10 tablet contains amlodipine besylate equivalent to 10 mg active amlodipine**.**

Sugar free.

For the full list of excipients, see **section 6.1**

3 PHARMACEUTICAL FORM

Tablets

CIPLAVASC 5: White, circular, flat, bevelled, uncoated tablet with ‘5’ debossed on one face and central break line on the other.

CIPLAVASC 10: White, circular, flat, bevelled, uncoated tablets with ‘10’ debossed on one face and central break line on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

CIPLAVASC is indicated for the

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

Coronary artery disease (CAD)

CIPLAVASC is indicated:

- for the treatment of angina pectoris.
- for the 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. CIPLAVASC may be used alone, as monotherapy, or in combination with other antianginal medicines.
- to reduce the risk of coronary revascularisation and the need for hospitalisation due to angina in patients with coronary artery disease
- 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

Hypertension and angina pectoris

An initial dose of 5 mg CIPLAVASC once daily is recommended which may be increased to a maximum 10 mg once a day, depending on the individual patient’s response after 10 to 14 days of therapy if there is no improvement.

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

Coronary artery disease

The recommended dosage range is 5 to 10 mg once daily.

Special populations

Use in the elderly

CIPLAVASC used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly but increase of the dosage should take place with care.

Use in patients with hepatic function 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 (see **section 4.4**). The pharmacokinetics of CIPLAVASC have not been studied in severe hepatic impairment. CIPLAVASC should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Use in patients with renal impairment

Changes in CIPLAVASC plasma concentrations are not correlated with the degree of renal impairment; therefore, normal dosage is recommended. CIPLAVASC is not removed by dialysis.

Paediatric population

The recommended antihypertensive oral dose in paediatric patients ages 6 to 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 CIPLAVASC on blood pressure in patients less than 6 years of age is not known.

Method of administration

For oral use.

4.3 Contraindications

CIPLAVASC is contraindicated in:

- hypersensitivity to dihydropyridines derivatives, amlodipine or any of the ingredients of

CIPLAVASC listed in **section 6.1,**

- 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.
- Concomitant use with grapefruit juice (see **section 4.5**).

4.4 Special warnings and precautions for use

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

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**)

Use in the elderly

The time to reach peak plasma concentrations of CIPLAVASC is variable and not significantly different between elderly and younger subjects.

Amlodipine clearance is decreased (40 to 60 %) in the elderly, which results in increases of amlodipine area under the concentration-time curve (AUC) and elimination half-life. Patients with moderate to severe heart failure also show a similar increase in AUC. Therefore, elderly patients should start CIPLAVASC therapy at a lower dose. Dosage increases should be undertaken with care.

Use in patients with renal failure

Although CIPLAVASC is excreted primarily via the kidney, mild renal impairment does not appear to have an effect on plasma concentrations. Severe renal impairment may however require a dosage reduction. Amlodipine cannot be removed by dialysis.

Use in impaired hepatic function

The half-life of CIPLAVASC is significantly prolonged in patients with impaired hepatic function. CIPLAVASC should therefore be administered at lower doses in these patients. Careful monitoring and slow dose titration may be required in severe liver impairment.

Use in patients with heart failure

An increased incidence of pulmonary oedema has been reported.

CIPLAVASC may have a negative inotropic effect. AUC of CIPLAVASC may increase in patients with heart failure. CIPLAVASC should be used with care in congestive heart failure, as the risk of future cardiovascular events and mortality may be increased.

Sodium

This medicine contains less than 1 mmoL sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on CIPLAVASC

Concurrent administration of sublingual nitroglycerin, long-acting nitrates, beta blockers or other antianginal agents with CIPLAVASC may produce additive antihypertensive and antianginal effects. Sublingual nitroglycerin may be used as needed to abort acute angina attacks during CIPLAVASC therapy. Nitrate medicine may be used during CIPLAVASC therapy for angina prophylaxis. CIPLAVASC 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 CIPLAVASC, a gradual decrease of dosage, with medical practitioner supervision, is recommended.

CIPLAVASC may be co-administered with thiazide diuretics, non-steroidal anti-inflammatory medicines, antibiotics, and oral hypoglycaemic medicines.

CYP3A4 inhibitors

Strong or moderate CYP3A4 inhibitors (e.g. protease inhibitors, azole antifungals, macrolides such as erythromycin or clarithromycin, verapamil or diltiazem) may lead to increased plasma concentrations of CIPLAVASC resulting in an increased risk of hypotension. These effects may be more pronounced in the elderly. Dose reduction and clinical monitoring may be required (see **section 4.4**).

CYP3A4 inducers

Clinical data regarding the effect of CYP3A4 inducers on amlodipine is not available. Administration of CIPLAVASC concomitantly with CYP3A4 inducers (e.g. rifampicin, hypericum perforatum) may lead to lower plasma concentrations of amlodipine and caution should be exercised.

Grapefruit Juice

Grapefruit or grapefruit juice may increase the blood pressure lowering effects of CIPLAVASC in some patients. Co-administration of grapefruit or grapefruit juice with CIPLAVASC is, therefore, not recommended. (see **section 4.3**)

Dantrolene (infusion)

Due to the risk of hyperkalaemia observed with co-administration of calcium blockers, such as CIPLAVASC, with intravenous dantrolene, it is recommended that co-administration be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Cimetidine

Co-administration with cimetidine did not alter the pharmacokinetics of CIPLAVASC.

Aluminium/magnesium (antacid)

Co-administration of an aluminium/magnesium antacid with a single dose of CIPLAVASC had no significant effect on the pharmacokinetics of CIPLAVASC.

Sildenafil

A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of CIPLAVASC. When CIPLAVASC and sildenafil were used in combination, each medicine independently exerted its own blood pressure lowering effect.

Effect of CIPLAVASC on other medicines

Simvastatin

Co-administration of simvastatin with amlodipine results in a 77 % increased bioavailability of simvastatin. Simvastatin doses in patients on CIPLAVASC should be limited to 20 mg daily.

Tacrolimus

Co-administration with CIPLAVASC may increase the blood concentration of tacrolimus. In order to avoid toxicity, the administration of CIPLAVASC requires close monitoring of tacrolimus blood level concentrations and dose adjustments of tacrolimus where appropriate.

Ciclosporin

Studies involving the interaction of ciclosporin and amlodipine has not been conducted in any population except for renal transplant patients. Variable trough concentration increases of ciclosporin were observed (0 % to 40 %). Dose reduction of ciclosporin should be considered and ciclosporin levels should be closely monitored.

Warfarin, Atorvastatin and digoxin

CIPLAVASC does not affect the pharmacokinetics of atorvastatin, digoxin or warfarin. The co-administration of CIPLAVASC does not alter the effect of warfarin on prothrombin response time.

Ethanol (alcohol)

Single and multiple 10 mg doses of CIPLAVASC had no significant effect on the pharmacokinetics of ethanol.

Digoxin

Co-administration of CIPLAVASC with digoxin did not change serum digoxin levels or digoxin renal clearance.

CIPLAVASC has no effect on protein binding of phenytoin and indomethacin

Mechanistic target of rapamycin (mTOR) inhibitors

mTOR inhibitors such as sirolimus, temsirolimus and everolimus are CYP3A substrates. CIPLAVASC is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, CIPLAVASC may increase exposure of mTOR inhibitors.

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

The safety of CIPLAVASC in pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses.

Breastfeeding

CIPLAVASC is excreted in human milk. 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 CIPLAVASC on infants is unknown**.**

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Data regarding the potential effect of CIPLAVASC on fertility is insufficient.

4.7 Effects on ability to drive and use machines

CIPLAVASC can have minor or moderate effect on the ability to drive and operate machines, caution should be exercised especially at the beginning of treatment. The ability to react may be impaired if a patient taking CIPLAVASC suffers from dizziness, headache, fatigue or nausea.

4.8 Undesirable effects

Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	*Less frequent*	Thrombocytopenia, leukopenia, leukocytopenia.
Immune system disorders	*Less frequent*	Allergic reactions including pruritus, rash, angioedema and erythema multiforme
Metabolism and nutrition disorders	*Less frequent*	Hyperglycaemia

MedDRA system organ class	Frequency	Adverse reactions
Psychiatric disorders	*Less frequent*	Depression, insomnia, mood changes (including anxiety), confusion.
Nervous system disorders	*Frequent*	Dizziness, headache (especially at the beginning of the treatment), somnolence
	Less frequent	Hypertonia, hypoaesthesia, paraesthesia, peripheral neuropathy, tremor, dysgeusia syncope, extrapyramidal disorder
Eye disorders	*Less frequent*	Visual disturbances (including diplopia), Visual impairment
Ear and labyrinth disorders	*Less frequent*	Tinnitus
Cardiac disorders	*Frequent*	Palpitations
	Less frequent	Myocardial infarction, dysrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), chest pain
Vascular disorders	*Frequent*	Flushing
	Less frequent	Hypotension, vasculitis
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea, rhinitis, cough
Gastrointestinal disorders	*Frequent*	Nausea, abdominal pain
	Less frequent	Vomiting, dyspepsia, altered bowel habits (including diarrhoea and

MedDRA system organ class	Frequency	Adverse reactions
		constipation), dry mouth, gingival hyperplasia, pancreatitis, gastritis
Hepato-biliary disorders	*Less frequent*	Hepatitis, jaundice, raised liver enzymes (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders	*Less frequent*	Alopecia, skin discolouration, hyperhidrosis, pruritus, rash, angioedema exanthema, urticaria, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity, purpura
	Frequency unknown	Toxic Epidermal Necrolysis
Musculoskeletal and connective tissue disorders	*Frequent*	Ankle swelling
	Less frequent	Arthralgia, muscle cramps, back pain, myalgia
Renal and urinary disorders	*Less frequent*	Increased urinary frequency, micturition disorder, nocturia
Reproductive system and breast disorders	*Less frequent*	Impotence, gynaecomastia, Erectile dysfunction
General disorders and administration site conditions	*Frequent*	Fatigue, oedema
	Less frequent	Pain, malaise, asthenia

MedDRA system organ class	Frequency	Adverse reactions
Investigations	*Less frequent*	Weight increase, weight decrease.

Paediatric population

Paediatric patients (ages 6 to 17 years)

Adverse events are similar to those of adults. The most frequent adverse events are:

MedDRA system organ class	**Adverse reactions**
Nervous system disorders	Headache, dizziness
Vascular disorders	Vasodilation
Respiratory, thoracic, and mediastinal disorders	Epistaxis
Gastrointestinal disorders	Abdominal pain
General disorders and administration site conditions	Asthenia

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Symptoms

Gross overdosage could result in excessive peripheral vasodilation and possibly reflex tachycardia, resulting in marked and probably prolonged systemic hypotension up to and including shock with fatal outcome.

Treatment

There is no documented experience with CIPLAVASC overdosage. Clinically significant hypotension due to CIPLAVASC 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.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of CIPLAVASC overdose that may manifest with a delayed onset (24 to 48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment is symptomatic and supportive. Intravenous calcium gluconate may be of benefit in reversing the effects of calcium channel blockade.

Administration of activated charcoal immediately after or up to 2 hours after CIPLAVASC 10 mg ingestion may significantly decrease CIPLAVASC absorption. Activated charcoal given 6 hours after CIPLAVASC has no effect.

Since CIPLAVASC is highly protein-bound, dialysis may not be of benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 7.1 Vasodilators, hypotensive, antihypertensive medicines include other antihypertensive medicines e.g. ACE-inhibitors, ARBs, RAAS, etc

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

ATC code C08CA01

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, reducing total peripheral resistance (afterload) and myocardial energy 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.

The dilatation of the main coronary arteries and coronary arterioles in both normal and ischemic regions result in increased myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Clinically significant reductions of blood pressure in both the supine and standing position throughout a 24-hour interval are observed in patients with hypertension on a once daily dose of amlodipine. Acute hypotension does not occur due to the slow onset of action.

A once daily dose of amlodipine increases the total exercise time, time to angina onset, and time to 1 mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption in patients with angina.

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. Amlodipine has a bioavailability of about 64 %, allowing for once-daily oral dosing. Steady state plasma concentrations are achieved after 7 to 8 days of consecutive dosing. The volume of distribution is about 20 L/kg.

Bioavailability is not affected by food. About 97,5 % of amlodipine is bound to plasma proteins.

Biotransformation and elimination

The plasma elimination half-life of 35 to 50 hours. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide (Aerosil 200),

Dibasic calcium phosphate,

Magnesium stearate,

Microcrystalline cellulose (Avicel pH 102),

Sodium starch glycolate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

6.5 Nature and contents of container

CIPLAVASC 5 and CIPLAVASC 10 are both available in PVC/aluminium foil blister strips of 14 or 10 tablets packed in an outer carton each 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

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap

Mispel Street

Bellville, 7530

8 REGISTRATION NUMBER(S)

CIPLAVASC 5: A39/7.1/0117

CIPLAVASC 10: A39/7.1/0120

Namibia: NS2	
CIPLAVASC 5:	06/7.1/0223
CIPLAVASC 10:	06/7.1/0224

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 11 February 2005

Latest renewal: Not applicable.

10 DATE OF REVISION OF THE TEXT

17 December 2025