PROFESSIONAL INFORMATION FOR

CIPLAVASC 5 AND

CIPLAVASC 10

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

CIPLAVASC 5 (Tablets)

CIPLAVASC 10 (Tablets)

COMPOSITION:

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

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

The inactive ingredients are colloidal silicon dioxide (Aerosil 200), dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose (Avicel pH 102) and sodium starch glycolate.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1 Vasodilators, hypotensive medicines.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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). 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.

The dilatation of the main coronary arteries and coronary arterioles in both normal and ischemic regions results 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.

Pharmacokinetic properties:

Absorption and distribution:

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 % and a plasma elimination half-life of 35 to 50 hours, allowing for once-daily oral dosing. Bioavailability is not affected by food. Steady state plasma concentrations are achieved after 7 to 8 days of consecutive dosing. The volume of distribution is about 20 ℓ/kg. About 97,5 % of amlodipine is bound to plasma proteins.

Metabolism and 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.

Special populations:

Hepatic impairment:

Decreased clearance of amlodipine may occur, causing a longer half-life and an increase in AUC of about 40 – 60 %.

INDICATIONS:

CIPLAVASC is indicated for the:

- Treatment of angina pectoris.
- Treatment of mild to moderate hypertension, alone or in combination with other antihypertensives.

CONTRAINDICATIONS:

CIPLAVASC is contraindicated in:

- Patients with hypersensitivity to amlodipine or any of the ingredients of **CIPLAVASC**.
- Patients with hypersensitivity to dihydropyridines.
- 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.

Safety in pregnancy and lactation has not been established (see **"PREGNANCY AND LACTATION"**).

WARNINGS AND SPECIAL PRECAUTIONS:

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

Use in the elderly:

Amlodipine clearance is decreased (40 – 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 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 children:

Safety and efficacy has not been established.

Use in 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.

Porphyria:

Safety has not been established.

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.

INTERACTIONS:

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 medication 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.

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 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.

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.

Effect of CIPLAVASC of other medicines:

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 % – 40 %). Dose reduction of ciclosporin should be considered and ciclosporin levels should be closely monitored.

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.

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 in healthy male volunteers.

CIPLAVASC has no effect on protein binding of phenytoin and indomethacin.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established (see **"CONTRAINDICATIONS"**). It is not known whether amlodipine is excreted in breast milk.

DOSAGE AND DIRECTIONS FOR USE:

Hypertension and angina pectoris:

Adults:

An initial dose of 5 mg **CIPLAVASC** 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 **CIPLAVASC** to thiazide diuretics, beta blockers, or angiotensin-converting enzyme inhibitors.

SIDE-EFFECTS:

Blood and lymphatic system disorders:

Less frequent: Purpura, thrombocytopenia, leucopenia, leukocytopenia.

Immune system disorders:

Less frequent: Allergic reactions with pruritus, rash, angioedema, and erythema multiforme, Stevens-Johnson syndrome.

Metabolism and nutrition disorders:

Less frequent: Hyperglycaemia.

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, dygeusia (taste perversion).

Eye disorders:

Frequent: Visual disturbances (including diplopia).

Ear and labyrinth disorders:

Less frequent: Tinnitus.

Cardiac disorders:

Frequent: Peripheral oedema, palpitations.

Less frequent: Syncope, myocardial infarction, dysrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation).

Vascular disorders:

Frequent: Flushing.

Less frequent: Hypotension (including orthostatic hypotension), vasculitis.

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea.

Less frequent: Coughing, rhinitis.

Gastrointestinal disorders:

Frequent: Nausea, abdominal pain, dyspepsia, altered bowel habits (including diarrhoea and constipation).

Less frequent: Vomiting, dry mouth, gingival hyperplasia, pancreatitis, gastritis.

Hepatobiliary disorders:

Less frequent: Hepatitis, jaundice, raised liver enzymes (mostly consistent with cholestasis).

Skin and subcutaneous tissue disorders:

Less frequent: Alopecia, skin discolouration, hyperhidrosis (increased sweating), pruritus, rash, exanthema, urticaria, exfoliative dermatitis, Quincke oedema, photosensitivity.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Ankle swelling, muscle cramps.

Less frequent: Arthralgia, back pain, myalgia.

Renal and urinary disorders:

Less frequent: Increased urinary frequency, micturition disorder, nocturia.

Reproductive system and breast disorders:

Less frequent: Impotence, gynaecomastia.

General and administrative site disorders:

Frequent: Fatigue, oedema, asthenia.

Less frequent: Pain, weight increase/decrease, chest pain, malaise.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no documented experience with **CIPLAVASC** overdosage. Gastric lavage may be of benefit. 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.

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. Intravenous calcium gluconate may be of benefit in reversing the effects of calcium channel blockade.

Since amlodipine is highly protein-bound, dialysis will probably not be of benefit.

TREATMENT IS SYMPTOMATIC AND SUPPORTIVE.

IDENTIFICATION:

CIPLAVASC 5: White, circular, flat, bevelled, uncoated tablet with '5' debossed on one face and central breakline on the other.

CIPLAVASC 10: White, circular, flat, bevelled, uncoated tablet with '10' debossed on one face and central breakline on the other.

PRESENTATION:

CIPLAVASC 5 and **CIPLAVASC 10** are both available in aluminium blister strips of 14 or 10 tablets packed in blister packs, each containing 28 or 30 tablets.

STORAGE INSTRUCTIONS:

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

CIPLAVASC 5: A39/7.1/0117

CIPLAVASC 10: A39/7.1/0120

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

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