APPROVED PACKAGE INSERT FOR AMLOBLOC 5 AND AMLOBLOC 10

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

AMLOBLOC 5 (Tablet)

AMLOBLOC 10 (Tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Amlobloc 5 tablet contains: 5 mg amlodipine besylate equivalent to 5 mg Amlodipine.

Each Amlobloc 10 tablet contains: 10 mg amlodipine besylate equivalent to 10 mg Amlodipine.

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

AMLOBLOC 5

White or almost white, oblong, bevelled tablet, scored on one side and coded “5” on the other side.

AMLOBLOC 10

White or almost white, oblong, bevelled tablet, scored on one side and coded “10” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension

AMLOBLOC is indicated for the treatment of mild to moderate hypertension. AMLOBLOC may be combined with other antihypertensive medicines.

Coronary artery disease (CAD)

Angina pectoris

AMLOBLOC is indicated for the treatment of angina pectoris.

Chronic stable angina

AMLOBLOC is indicated 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. AMLOBLOC may be used alone, as monotherapy, or in combination with other antianginal medicines.

Coronary artery disease

AMLOBLOC is indicated to reduce the risk of coronary revascularosation and the need for hospitalisation due to angina in patients with coronary artery disease.

AMLOBLOC 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

Hypertension and angina pectoris

The initial dose is 5 mg AMLOBLOC once daily, which may be increased to a maximum dose is 10 mg depending on the individual patient's response after 10-14 days therapy.

No dose adjustment of AMLOBLOC is required during combined administration of 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

Use in the elderly:

The usual dosage recommendations are recommended.

Use in renal Failure:

AMLOBLOC may be used in such patients at normal doses. Changes in plasma concentrations are not correlated with degree of renal impairment.

Use in patients with impaired hepatic Impairment:

AMLOBLOC should be administered with caution in these patients.

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 AMLOBLOC on blood pressure in patients less than 6 years of age is not known.

Porphyria:

Safety has not been established.

Method of Administration

For oral use.

4.3 CONTRAINDICATIONS

AMLOBLOC is contra-indicated in patients with:

- Severe hypotension.
- Shock (including cardiogenic shock).
- Hypersensitivity to dihydropyridine derivatives, amlodipine or any of the other ingredients.
- 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)

4.4 Special warnings and precautions for 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).

Use in the elderly

The time to reach peak plasma concentrations of AMLOBLOC is variable and not significantly different between elderly and younger subjects. AMLOBLOC clearance is decreased with resulting increases in AUC (40 – 60 %) and elimination half-life in elderly patients. AUC and

elimination half-life in patients with congestive heart failure (CHF) were increased with age. Elderly patients should start AMLOBLOC therapy at a lower dose.

Use in patients with renal failure

AMLOBLOC may be used at normal doses in patients with renal impairment. Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment. In patient with severe renal impairment, AMLOBLOC doses may need to be reduced. AMLOBLOC is not dialysable.

Use in patients with impaired hepatic function

The half-life of AMLOBLOC is prolonged in patients with impaired liver function. AMLOBLOC should therefore be administered at lower (5 mg) initial dose in these patients.

Use in patients with heart failure

In a long-term, placebo-controlled study (PRAISE-2) of AMLOBLOC in patients with New York Heart Association (NYHA) class III and IV heart failure of non-ischaemic aetiology, AMLOBLOC was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

4.5 Interactions with other medicines and other forms of interaction

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

Simvastatin

Co-administration of multiple doses of 10 mg AMLOBLOC with simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone (see simvastatin professional information).

Grapefruit juice

Co-administration of 240 mL of grapefruit juice with a single oral dose of AMLOBLOC 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of AMLOBLOC. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of AMLOBLOC; therefore, administration of AMLOBLOC 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)

CYP3A4 inhibitors

Co-administration of a 180 mg daily dose of diltiazem with 5 mg AMLOBLOC in elderly hypertensive patients (69 to 87 years of age) resulted in a 57 % increase in AMLOBLOC systemic exposure and a significant further decrease in systolic blood pressure than with AMLOBLOC alone.

Strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of AMLOBLOC. AMLOBLOC should be used with caution when administered with CYP3A4 inhibitors (see section 4.4).

Clarithromycin

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

There is no information on the effect of the combination on the QT interval.

CYP3A4 inducers

There is no data available regarding the effect of CYP3A4 inducers on AMLOBLOC. Concomitant use of CYP3A4 inducers (e.g. rifampicin, hypericum perforatum) may decrease the plasma concentrations of AMLOBLOC. AMLOBLOC should be used with caution when administered with CYP3A4 inducers. In the following studies, there were no significant changes in the pharmacokinetics of either AMLOBLOC or another medicine within the study, when co-administered.

Special studies: Effect of other medicines on AMLOBLOC

Cimetidine

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

Aluminium/magnesium (antacid)

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

Sildenafil

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

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Special studies: Effect of AMLOBLOC on other medicines

Digoxin

Co-administration of AMLOBLOC with digoxin did not change serum digoxin levels or digoxin renal clearance in healthy volunteers.

Ethanol (alcohol)

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

Warfarin

Co-administration of AMLOBLOC with warfarin did not change the warfarin prothrombin response time.

Ciclosporin

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

Tacrolimus

There is a risk of increased tacrolimus blood levels and toxicity when co-administered with AMLOBLOC. In order to avoid toxicity of tacrolimus, administration of AMLOBLOC in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic target of rapamycin (mTOR) inhibitors

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

Medicine/laboratory test interactions

None known.

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 AMLOBLOC in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses.

Lactation

AMLOBLOC 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 AMLOBLOC on infants is unknown.

4.7 Effects on ability to drive and use machines

AMLOBLOC can cause dizziness. The patient's ability to drive or use machinery should be individually assessed.

4.8 Undesirable effects

Blood and lymphatic system disorders:

Less frequent: Leukocytopenia, thrombocytopenia

Immune system disorders:

Less frequent: Allergic reaction including pruritus, rash, angioedema and erythema multiforme

Metabolism and nutrition disorders:

Less frequent: Hyperglycaemia

Endocrine disorders:

Less frequent: Gynaecomastia

Nervous system disorders:

Frequent: Headache (especially at the beginning of the treatment), fatigue, dizziness, asthenia, and somnolence

Less frequent: Malaise, dry mouth, paraesthesia, increased sweating, tremor, hypoaesthesia, taste disorders, peripheral neuropathy, dysgeusia, syncope, paraesthesia, hypertonia, extrapyramidal disorder

Eye disorders:

Less frequent: Visual ~~disturbances~~ impairment

Ear and labyrinth disorders:

Less frequent: Tinnitus

Psychiatric disorders:

Less frequent: Sleep disorder, irritability, depression, confusion, mood changes including anxiety.

Cardiac disorders:

Frequent: Palpitations

Less frequent: Syncope, tachycardia, chest pain, at the beginning of treatment aggravation of angina pectoris may happen, cases of myocardial infarction and dysrhythmias (including extrasystole, ventricular tachycardia, bradycardia and atrial dysrhythmias) and chest pain have been reported in patients with coronary artery disease, but a clear association with amlodipine has not been established.

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 (including gastritis), altered bowel habits, dry mouth, gingival hyperplasia, pancreatitis

Hepato-biliary disorders:

Less frequent: Hepatic enzyme elevations (mostly consistent with cholestasis), jaundice and hepatitis

Skin and subcutaneous tissue disorders:

Less frequent: Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, angioedema, erythema multiforme, urticaria

Musculoskeletal, connective tissue ~~and bone~~ disorders:

Less frequent: Muscle cramps, back pain, myalgias and arthralgia

Renal and urinary disorders:

Less frequent: Increased micturition frequency, nocturia, pollakiuria

Reproductive system and breast disorders:

Less frequent: Erectile dysfunction, gynaecomastia

General disorders and administrative site conditions:

Frequent: Peripheral oedema, fatigue

Less Frequent: Asthenia, pain, malaise

Investigations:

Less frequent: weight increase, weight 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:

MedDRA System Organ Class	**Undesirable effects**
Nervous system disorders	Headaches, dizziness
Vascular disorders	Vasodilation
Respiratory, thoracic, and mediastinal disorders	Epistaxis
Gastrointestinal disorders	Abdominal pain
General disorders and administration site conditions	Asthenia

4.9 Overdose

Overdosage could result in excessive peripheral vasodilation and possibly reflex tachycardia, with subsequent marked and prolonged systemic hypotension. Shock with fatal outcome has 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.

Administration of activated charcoal immediately after or up to 2 hours after AMLOBLOC 10 mg ingestion has been shown to significantly decrease AMLOBLOC absorption. Activated charcoal given 6 hours after AMLOBLOC had no effect. Clinically significant hypotension due to AMLOBLOC overdosage may need active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. Treatment is symptomatic and supportive. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Since AMLOBLOC is highly protein-bound, dialysis is not likely to be of benefit.

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. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1 Vasodilators, hypotensive, antihypertensive medicines include other antihypertensive medicines e.g. ACE-inhibitors, ARBs, RAAS etc. ATC code: C08 CA01

Mechanism of Action

Amlodipine is a dihydropyridine, calcium ion influx inhibitor (calcium channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has

not been fully determined, but in experimental animals, 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. Unloading of the heart reduces myocardial energy consumption and oxygen requirements.

5.2 Pharmacokinetic properties

Absorption

After oral administration of therapeutic doses, amlodipine is absorbed with peak blood levels between 6 and 12 hours post dose. Absolute bioavailability has been estimated to be approximately 64%. The volume of distribution is approximately 21 L/kg. Absorption of amlodipine is unaffected by consumption of a low-fat breakfast.

In vitro studies have shown that approximately 97,5% of circulating amlodipine is bound to plasma proteins.

Biotransformation/elimination

The terminal plasma elimination half-life is about 135-50 hours. Steady state plasma levels are reached after 7-8 days of consecutive dosing.

Amlodipine is extensively metabolised by the liver to inactive metabolites. 10% of the parent compound and 60% of the metabolites are excreted in the urine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate anhydrous, magnesium stearate, microcrystalline cellulose, sodium starch glycolate (Type A)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 mg, 10 mg: 36 months

6.4 Special precautions for storage

Store at or below 25 °C, in original packaging

6.5 Nature and contents of container

Packs of 30's and/or 100's in Alu/PVC blister or Al/OPA/al/PVC blisters or polyethylene containers with tamper evident closures.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8 REGISTRATION NUMBER

AMLOBLOC 5: A40/7.1/0435

AMLOBLOC 10: A40/7.1/0436

9 DATE OF FIRST AUTHORISATION

02 February 2007

10 DATE OF REVISION OF THE TEXT

28 March 2023

[1]Company Reg. No.: 1990/001979/07