1.3.1.1 Current Approved Professional Information for Medicines for Human Use

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CALBLOC 5

CALBLOC 10

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CALBLOC 5

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

CALBLOC 10

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

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CALBLOC 5: Brown, smooth, round, biconvex, film coated tablets plain on both sides.

CALBLOC 10: White to off-white, round biconvex, film coated tablets plain on one side and a breakline on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CALBLOC is indicated for the treatment of mild to moderate hypertension. CALBLOC may be combined with other antihypertensives.

Coronary artery disease (CAD)

Angina pectoris

CALBLOC is indicated for the treatment of angina pectoris.

Chronic stable angina

CALBLOC 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. **CALBLOC** may be used alone, as monotherapy, or in combination with other antianginal medicines.

Coronary artery disease

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

CALBLOC 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

An initial dose of 5 mg **CALBLOC** 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 **CALBLOC** to 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 is 10 mg.

Special populations

Use in the elderly

CALBLOC, used at similar doses in elderly or younger patients, is equally well tolerated. Therefore normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care. Elderly patients should start **CALBLOC** therapy at a lower dose. See **Section 4.4**.

Use in patients with impaired hepatic function

CALBLOC should be administered with caution in patients with impaired liver function. Treatment should be initiated at the lowest dose and titrated slowly in these patients. See **Section 4.4**.

Use in renal failure

CALBLOC may be used in such patients at normal doses. Changes in plasma concentrations are not correlated with degree of renal impairment. In patients with severe renal impairment, **CALBLOC** doses may need to be reduced. See **Section 4.4**.

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

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to dihydropyridines, amlodipine, or to any of the excipients of **CALBLOC** listed in **Section 6.1.**
- 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 **CALBLOC** is variable and not significantly different between elderly and younger subjects. **CALBLOC** 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 **CALBLOC** therapy at a lower dose.

Use in patients with renal failure

CALBLOC 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 patients with severe

renal impairment, **CALBLOC** doses may need to be reduced. **CALBLOC** is not dialysable.

Use in patients with impaired hepatic function

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

Use in patients with heart failure

In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with New York Heart Association (NYHA) class III and IV heart failure of non-ischaemic etiology,

amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Benzyl alcohol content in ***CALBLOC 10:***

This medicine contains 0,214 mg of benzyl alcohol in each 10 mg tablet.

Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called 'gasping syndrome') in young children.

Benzyl alcohol should not be given to a new born baby (up to 4 weeks old), unless recommended by the doctor.

Benzyl alcohol should not be given for more than a week to young children (less than 3 years old) as there is an increased risk of accumulation.

Large amounts of benzyl alcohol can build-up in the body and may cause metabolic acidosis in pregnancy and breastfeeding.

Large amounts of benzyl alcohol can build-up in the body and may cause metabolic acidosis in patients with hepatic or renal impairment.

Benzyl alcohol may cause mild local irritation.

4.5 Interaction with other medicines and other forms of interaction

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

Simvastatin

Co-administration of multiple doses of 10 mg amlodipine with simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone.

Grapefruit juice

Co-administration of 240 ml of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 health volunteers had no significant effect on the pharmacokinetics of amlodipine. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of amlodipine; therefore, administration of amlodipine 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 amlodipine in elderly hypertensive patients (69 to 87 years of age) resulted in a 57 % increase in amlodipine systemic exposure and a significant further decrease in systolic blood pressure than with amlodipine alone.

Strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine. Amlodipine 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 amlodipine. Close observation of patients is recommended when amlodipine 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 amlodipine. Concomitant use of CYP3A4 inducers (e.g. rifampicin, *hypericum perforatum*) may decrease the plasma concentrations of amlodipine. Amlodipine should be used with caution when administered with CYP3A4 inducers.

Effects of medicines taken with CALBLOC

Cimetidine

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

Aluminium/magnesium (antacid)

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

Sildenafil

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

Diogoxin

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

Ethanol (alcohol)

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

Warfarin

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

Ciclosporin

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

Tacrolimus

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

Medicine/laboratory test interactions

None known.

4.6 Fertility, pregnancy and lactation

Safety of **CALBLOC** in pregnancy or lactation has not been established.

Large amounts of benzyl alcohol can build-up in the body and may cause metabolic acidosis in pregnancy or breastfeeding.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment with **CALBLOC**.

4.8 Undesirable effects

System Organ Class	**Frequent**	**Less frequent**
Blood and lymphatic system disorders		leuokopenia, thrombocytopenia
Immune system disorders		allergic reactions with pruritus, rash, angioedema and erythema multiforme

Metabolism and nutrition disorders		hyperglycaemia
Psychiatric disorders		insomnia, mood changes
System Organ Class	**Frequent**	**Less frequent**
Nervous system disorders	somnolence, dizziness, headache	tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia, hypertonia, peripheral neuropathy, extrapyramidal disorder
Eye disorders		visual disturbances
Ear and labyrinth disorders		tinnitus
Cardiac disorders	palpitations	myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), chest pain
Vascular disorders	flushing	hypotension, vasculitis
Respiratory, thoracic and mediastinal disorders		dyspnoea, rhinitis, cough
Gastrointestinal disorders	abdominal pain, nausea	vomiting, dyspepsia (including gastritis), altered bowel habits, dry mouth, pancreatitis, gingival hyperplasia
Hepatobiliary disorders		hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestatis)
Skin and subcutaneous tissue disorders		alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, angioedema, erythema multiforme, urticaria

Musculoskeletal and connective tissue disorders		arthralgia, myalgia, muscle spasms, back pain
Renal and urinary disorders		micturition disorder, nocturia, pollakiuria
Reproductive system and breast disorders		erectile dysfunction, gynaecomastia
General disorders and administration site conditions		asthenia, pain, malaise
Investigations		weight gain, weight decreases

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing 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 Reaction Reporting Form", found online under SAHPRA's publications.

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Available data for amlodipine 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 ventilator support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment

Administration of activated charcoal to healthy volunteers immediately after or up to 2 hours after **CALBLOC** 10 mg ingestion has been shown to significantly decrease **CALBLOC** absorption. Activated charcoal given 6 hours after **CALBLOC** had no effect. Clinically significant hypotension due to **CALBLOC** 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. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacotherapeutic group: Calium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC code: C08CA01

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 perioheral arterioles and this 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 35 – 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

CALBLOC 5:

Tablet Core (Inactive)

Calcium hydrogen phosphate

Croscarmellose sodium

Magnesium stearate

Maize starch

Microcrystalline cellulose

Purified talc

Purified water

Film Coating (Inactive)

Colour tabcoat brown

Polyethylene glycol

Purified water

Composition of Colour tabcoat brown TC 8010

Hydroxy propyl methyl cellulose

Polyethylene glycol

Red iron oxide Cl No. 77491

Titanium dioxide Cl No. 77891

CALBLOC 10:

Tablet Core (Inactive)

Calcium hydrogen phosphate

Magnesium stearate

Maize starch

Microcrystalline cellulose

Purified talc

Purified Water

Film Coating (Inactive)

Benzyl alcohol

Hydroxy propyl methyl cellulose

Polyethylene glycol

Purified talc

Purified Water

Titanium dioxide Cl No. 77891

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

CALBLOC 5 and CALBLOC 10

30's

Three blister packs (composed of transparent PVC and silver coloured aluminium foil backing) of 10 tablets in a carton.

100's

Ten blister packs (compose of transparent PVC and silver coloured aluminium foil backing) of 10 tablets in a carton.

Two blister packs (composed of transparent PVC and silver coloured aluminium foil backing) of 50 tablets in a carton.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd.

14 Lautre Road

Stormill Ext. 1

Roodepoort

1724

South Africa

8. REGISTRATION NUMBER(S)

CALBLOC 5: A38/7.1/0652

CALBLOC 10: A38/7.1/0653

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 November 2004

10. DATE OF REVISON OF THE TEXT

03 August 2023