SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

Amlodipine 5 Biotech tablets

Amlodipine 10 Biotech tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Amlodipine 5 Biotech: Each tablet contains Amlodipine maleate equivalent to 5 mg Amlodipine.

Amlodipine 10 Biotech: Each tablet contains Amlodipine maleate equivalent to 10 mg Amlodipine.

Sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

Amlodipine 5 Biotech: White to off-white, uncoated, oblong tablet.

Amlodipine 10 Biotech: White to off-white, uncoated, oblong tablet, scored on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Amlodipine 5 and 10 Biotech are indicated for the:

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

4.2 Posology and method of administration

Posology

Hypertension and angina pectoris

Adults

An initial dose of 5 mg Amlodipine 5 Biotech 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 Amlodipine 5 and 10 Biotech to thiazide diuretics, beta-blockers, or angiotensin-converting enzyme inhibitors**.**

4.3. Contraindications

- Hypersensitivity to dihydropyridines or to any of the ingredients listed in section 6.1.

4.4 Special warnings and precautions for use

Elderly patients

Amlodipine clearance is decreased (40 - 60 %) in the elderly, which results in increases of amlodipine concentration in the area under the concentration-time curve (AUG) and elimination half-life. Therefore, elderly patients should start Amlodipine 5 and 10 Biotech therapy at a lower dose.

In the elderly increase of the dosage should take place with care (see sections 4.2 and 5.2).

Patients with renal impairment

Amlodipine 5 and 10 Biotech may be used in such patients at normal doses.

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

Severe renal impairment may however require a dosage reduction. Amlodipine is not dialysable.

Patients with hepatic impairment

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine 5 and 10 Biotech 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.

Use in children

Safety and efficacy have not been established.

Patients with cardiac failure

Patients with heart failure should be treated with caution.

In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1).

Calcium channel blockers, including amlodipine as contained in Amlodipine Biotech, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Porphyria

Safety has not been established.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on amlodipine

CYP3A4 inhibitors

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to

significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored, and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g., rifampicin, hypericum perforatum). 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.

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the coadministration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicines

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

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine, but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine 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. Amlodipine is a weak inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Ciclosporin

No drug interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0 % - 40 %) of ciclosporin were observed.

Consideration should be given for monitoring ciclosporin levels in renal transplant patients on amlodipine, and ciclosporin dose reductions should be made as necessary.

Simvastatin

Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

Concurrent administration of sublingual nitroglycerin, long-acting nitrates, beta-blockers or other antianginal medicines with amlodipine may produce additive antihypertensive and antianginal effects. Sublingual nitroglycerin may be used as needed to abort acute angina attacks during amlodipine therapy. Nitrate medication may be used during amlodipine therapy for angina prophylaxis.

Amlodipine 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 amlodipine, a gradual decrease of dosage with medical practitioner supervision is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of amlodipine in human pregnancy has not been established.

Breastfeeding

Amlodipine 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 amlodipine on infants is unknown.

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on the ability to drive and use machines

Amlodipine 5 and 10 Biotech can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

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.

System organ class	Frequent	Less frequent	Frequency not known
Blood and lymphatic disorders		Thrombo-cytopenia, leukocytopenia.	

Immune system disorders		Allergic reactions.	
Metabolism and nutrition disorders		Hyperglycaemia.	
Psychiatric disorders		Depression, mood changes (including anxiety), insomnia, confusion.	
Nervous system disorders	Dizziness, headache (especially at the beginning of the treatment), somnolence.	Hypertonia, hypoesthesia/ paraesthesia, peripheral neuropathy, tremor, Taste perversion (dysgeusia), syncope.	
Eye disorders	Visual disturbances (including diplopia).		
Ear and Labyrinth disorders		Tinnitus.	
Cardiac disorders	Palpitations.	Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation).	
Vascular disorders	Flushing.	Hypotension, vasculitis.	
Respiratory, Thoracic and	Dyspnoea.	Coughing, rhinitis.	

mediastinal disorders			
Gastrointestinal disorders	Nausea, abdominal pain, dyspepsia, altered bowel habits (including diarrhoea and constipation.	Vomiting, dry mouth, gingival hyperplasia, pancreatitis, gastritis.	
Hepato-biliary disorders		Hepatitis, jaundice, hepatic enzymes increased (mostly consistent with cholestatis).	
Skin and subcutaneous tissue disorders		Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema urticaria, angioedema, erythema multiforme, exfoliative dermatitis, Steven-Johnson syndrome.	Toxic epidermal necrolysis.
Musculoskeletal and connective tissue disorders	Ankle swelling, muscle cramps.	Arthralgia, back pain, myalgia.	
Renal and urinary disorders		Increased urinary frequency, micturition disorder, nocturia.	
Reproductive system and breast disorders		Gynaecomastia, impotence.	

General disorders and administration site conditions	Fatigue, asthenia, oedema.	Pain, chest pain, malaise.	
Investigations		Weight increase, weight decrease.	

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 the medicine. Healthcare 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://sahpra.org.za/wpcontent/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

There is no documented experience with Amlodipine 5 and 10 Biotech overdosage.

Symptoms

Available data 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 less frequently 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.

Treatment

Clinically significant hypotension due to Amlodipine 5 and 10 Biotech overdosage calls for 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.

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

A7.1. Vasodilators, hypotensive medicines

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

ATC code: C08C A01

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.

5.2 Pharmacokinetic properties

Absorption

Complete absorption of amlodipine is slow following oral administration with peak plasma levels being attained after 6 - 12 hours. Amlodipine has a bioavailability of about 64 %. Steady state plasma concentrations are achieved after 7 - 8 days of consecutive dosing.

Distribution

The volume of distribution is about 20 L/kg.

Biotransformation/elimination

Plasma elimination half-life of 35 to 50 hours, allowing for once-daily oral 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (Avicel PH 112)

Calcium hydrogen phosphate anhydrous

Magnesium stearate

Sodium starch glycollate (Type A) (Sodium carboxymethyl starch)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C and protect from moisture

6.5 Nature and contents of the container

White opaque blisters and white opaque plastic securitainers of 30 and 100 tablets.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

Ground Floor, Block K West, Central Park

400, 16th Road, Randjespark

Midrand, 1685

8. REGISTRATION NUMBERS

Amlodipine 5 Biotech: 37/7.1/0378

Amlodipine 10 Biotech: 37/7.1/0379

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTORISATION

27 January 2006

10. DATE OF THE REVISION OF THE TEXT

28 July 2023