

**Professional Information for AMLODIPINE/VALSARTAN 5/160 BIOTECH and
AMLODIPINE/VALSARTAN 10/160 BIOTECH**

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

AMLODIPINE/VALSARTAN 5/160 BIOTECH film-coated tablets (5 mg amlodipine and 160 mg valsartan)

AMLODIPINE/VALSARTAN 10/160 BIOTECH film-coated tablets (10 mg amlodipine and 160 mg valsartan)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMLODIPINE/VALSARTAN 5/160 BIOTECH: Each film-coated tablet contains 6,9 mg amlodipine besilate (equivalent to 5 mg amlodipine) and 160 mg valsartan.

AMLODIPINE/VALSARTAN 10/160 BIOTECH: Each film-coated tablet contains 13,9 mg amlodipine besilate (equivalent to 10 mg amlodipine) and 160 mg valsartan.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

AMLODIPINE/VALSARTAN 5/160 BIOTECH: Dark yellow, oval-shaped, biconvex, film-coated tablets debossed with 'L298' on one side and plain on other side.

AMLODIPINE/VALSARTAN 10/160 BIOTECH: Light yellow, oval-shaped, biconvex, film-coated

tablets debossed with 'L300' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild to moderate essential hypertension in patients whose blood pressure is normalised with the individual components in the same doses as the proposed fixed dose combination of AMLODIPINE/VALSARTAN BIOTECH.

4.2 Posology and method of administration

Patients receiving amlodipine and valsartan from separate tablets may be switched to AMLODIPINE/VALSARTAN BIOTECH containing the same component doses.

Posology

The recommended dose is one tablet per day.

Special Populations

In the elderly:

Normal dosage regimens are recommended.

Children and adolescents:

AMLODIPINE/VALSARTAN BIOTECH is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy (see section 4.4).

Renal impairment:

No dosage adjustment is required for patients with mild to moderate renal impairment. In patients with severe renal impairment dosages may need to be reduced (see section 4.4).

Hepatic impairment:

Caution should be exercised when administering AMLODIPINE/VALSARTAN BIOTECH to patients with hepatic impairment or biliary obstructive disorders (see section 4.4).

Method of administration

For oral use.

It is recommended to take AMLODIPINE/VALSARTAN BIOTECH with some water.

4.3 Contraindications

- Hypersensitivity to amlodipine, valsartan, dihydropyridine derivatives, or to any of the inactive ingredients of AMLODIPINE/VALSARTAN BIOTECH listed in section 6.1.
- A history of angioedema related to previous therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Concomitant use of fluoroquinolones with ACE inhibitors/angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (Creatinine clearance \leq 30 mL/min) and in elderly patients.
- Porphyria.
- Lithium therapy: Concomitant administration with AMLODIPINE/VALSARTAN BIOTECH may lead to toxic blood concentrations of lithium (see section 4.5).
- Concomitant use of AMLODIPINE/VALSARTAN BIOTECH with aliskiren-containing products

(see sections 4.4 and 4.5).

- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Haemodynamically unstable heart failure after acute myocardial infarction.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving AMLODIPINE/VALSARTAN BIOTECH, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of AMLODIPINE/VALSARTAN BIOTECH and aliskiren is therefore contraindicated (see section 4.3).

AMLODIPINE/VALSARTAN BIOTECH should not be used concomitantly with aliskiren (see section 4.3).

Sodium- and/or volume-depleted patients

Excessive hypotension was seen in 0,4 % of patients with uncomplicated hypertension treated with amlodipine/valsartan in placebo-controlled studies. In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of AMLODIPINE/VALSARTAN BIOTECH or close medical

supervision at the start of treatment is recommended.

If hypotension occurs with AMLODIPINE/VALSARTAN BIOTECH, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Hyperkalaemia

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels (see sections 4.3 and 4.5).

Renal artery stenosis

AMLODIPINE/VALSARTAN BIOTECH should be used with caution to treat hypertension in patients with unilateral renal artery stenosis since blood urea and serum creatinine may increase in such patients.

Kidney transplantation

To date there is no experience of the safe use of AMLODIPINE/VALSARTAN BIOTECH in patients who have had a recent kidney transplantation.

Hepatic impairment

Valsartan is mostly eliminated unchanged via the bile. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Particular caution should be exercised when administering AMLODIPINE/VALSARTAN BIOTECH to patients with mild to moderate hepatic impairment or biliary obstructive disorders.

In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Renal impairment

No dosage adjustment of AMLODIPINE/VALSARTAN BIOTECH is required for patients with mild to moderate renal impairment (GFR > 30 mL/min/1,73 m²). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease.

Angioedema

Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue, has been reported in patients treated with valsartan. Some of these patients previously experienced angioedema with other medicines, including ACE inhibitors. AMLODIPINE/VALSARTAN BIOTECH should be discontinued immediately in patients who develop angioedema and should not be re-administered.

Heart failure/post-myocardial infarction

As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive uremia and with acute renal failure and/ or death. Similar outcomes have been reported with valsartan. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

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

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

Aortic and mitral valve stenosis

As with all other vasodilators, special caution is indicated in patients suffering from mitral stenosis or significant aortic stenosis that is not high grade.

Concomitant use of fluoroquinolones and ACE inhibitors/ angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE inhibitors/ angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3).

Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors/ angiotensin receptor blockers whether used separately and/or concomitantly.

4.5 Interaction with other medicines and other forms of interaction

To be taken into account with concomitant use

Other antihypertensive medicines

Commonly used antihypertensive medicines (e.g. alpha blockers, diuretics) and other medicines which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

Interactions linked to amlodipine

Concomitant use not recommended*Grapefruit or grapefruit juice*

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.

Caution required with concomitant use*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. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

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.

CYP3A4 inducers (anticonvulsant medicines [e.g. carbamazepine, phenobarbitone, phenytoin, fosphenytoin, primidone], rifampicin, *Hypericum perforatum*).

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 medicine particularly with strong CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum*).

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. It is recommended to limit the

dose of simvastatin to 20 mg daily in patients on amlodipine.

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 hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Tacrolimus

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

To be taken into account with concomitant use

Others

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

Interactions linked to valsartan

Concomitant use not recommended

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, including valsartan (see section 4.3). Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diurectic is also used, the risk of lithium toxicity may presumably be increased further with amlodipine/valsartan.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels

If a medicine that affects potassium levels is to be prescribed in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day), and non-selective NSAIDs

When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir)

The results of an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren

Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see sections 4.3 and 4.4).

Others

In monotherapy with valsartan, no interactions of clinical significance have been found with the

following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

Concomitant use of fluoroquinolones and ACE inhibitors/ angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE inhibitors/ angiotensin receptor blockers may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see section 4.3). When pregnancy is planned or confirmed, treatment with AMLODIPINE/VALSARTAN BIOTECH should be discontinued.

Women of childbearing potential/contraception in males and females

Women of childbearing age should ensure effective contraception.

Pregnancy

AMLODIPINE/VALSARTAN BIOTECH is contraindicated during pregnancy (see section 4.3).

Medicines affecting the renin-angiotensin system, such as AMLODIPINE/VALSARTAN BIOTECH, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Breastfeeding

AMLODIPINE/VALSARTAN BIOTECH is contraindicated during lactation. 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

There are no clinical studies on fertility with amlodipine/valsartan e.g. AMLODIPINE/VALSARTAN BIOTECH.

4.7 Effects on ability to drive and use machines

Dizziness or weariness may occasionally occur. This should be taken into account by patients taking AMLODIPINE/VALSARTAN BIOTECH.

4.8 Undesirable effects

| System class | organ | Description | Frequency | | |
|---|----------------|--|--------------------------|---------------|-----------|
| | | | Amlodipine/ valsartan | Amlodipine | Valsartan |
| Infections and infestations | | Nasopharyngitis | Frequent | -- | -- |
| | | Influenza | Frequent | -- | -- |
| Blood and lymphatic system disorders | | Decrease in haemoglobin and in haematocrit | -- | -- | Not known |
| | | Leukopenia | -- | Less frequent | -- |
| | | Neutropenia | -- | -- | Not known |
| | | Thrombocytopenia, sometimes with purpura | -- | Less frequent | Not known |
| Immune system disorders | | Hypersensitivity | Less frequent | Less frequent | Not known |
| Metabolism and nutrition disorders | | Anorexia | Less frequent | -- | -- |
| | | Hypercalcaemia | Less frequent | -- | -- |
| | | Hyperglycaemia | -- | Less frequent | -- |
| | | Hyperlipidaemia | Less frequent | -- | -- |
| | Hyperuricaemia | Less frequent | -- | -- | |

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|------------------------------------|-----------------------------------|---------------|---------------|---------------|
| | Hypokalaemia | Frequent | -- | -- |
| | Hyponatraemia | Less frequent | -- | -- |
| Psychiatric disorders | Depression | -- | Less frequent | -- |
| | Anxiety | Less frequent | -- | -- |
| | Insomnia/sleep disturbances | -- | Less frequent | -- |
| | Mood swings | -- | Less frequent | -- |
| | Confusion | -- | Less frequent | -- |
| Nervous system disorders | Coordination abnormal | Less frequent | -- | -- |
| | Dizziness | Less frequent | Frequent | -- |
| | Dizziness postural | Less frequent | -- | -- |
| | Dysgeusia | -- | Less frequent | -- |
| | Extrapyramidal syndrome | -- | Not known | -- |
| | Headache | Frequent | Frequent | -- |
| | Hypertonia | -- | Less frequent | -- |
| | Paraesthesia | Less frequent | Less frequent | -- |
| | Peripheral neuropathy, neuropathy | -- | Less frequent | -- |
| | Somnolence | Less frequent | frequent | -- |
| | Syncope | -- | Less frequent | -- |
| | Tremor | -- | Less frequent | -- |
| | Hypoesthesia | -- | Less frequent | -- |
| Eye disorders | Visual disturbance | Less frequent | Less frequent | -- |
| | Visual impairment | Less frequent | Less frequent | -- |
| Ear and labyrinth disorders | Tinnitus | Less frequent | Less frequent | -- |
| | Vertigo | Less frequent | -- | Less frequent |
| Cardiac disorders | Palpitations | Less frequent | Frequent | -- |
| | Syncope | Less frequent | -- | -- |
| | Tachycardia | Less frequent | -- | -- |
| | Dysrhythmias (including | -- | Less frequent | -- |

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|--|--|---------------|----------------|---------------|
| | bradycardia, ventricular | | | |
| | tachycardia, and atrial fibrillation) | | | |
| | Myocardial infarction | -- | Less frequent | -- |
| Vascular disorders | Flushing | -- | Frequent | -- |
| | Hypotension | Less frequent | Less frequent | -- |
| | Orthostatic hypotension | Less frequent | -- | -- |
| | Vasculitis | -- | Less frequent | Not known |
| Respiratory, thoracic and mediastinal disorders | Cough | Less frequent | Less frequent | Less frequent |
| | Dyspnoea | -- | Less frequent | -- |
| | Pharyngolaryngeal pain | Less frequent | -- | -- |
| | Rhinitis | -- | Less frequent | -- |
| | Abdominal discomfort, abdominal pain upper | Less frequent | Frequent | Less frequent |
| Gastrointestinal disorders | Change of bowel habit | -- | Less frequent | -- |
| | Constipation | Less frequent | Less frequent | -- |
| | Diarrhoea | Less frequent | Less frequent | -- |
| | Dry mouth | Less frequent | Less frequent | -- |
| | Dyspepsia | -- | Less frequent | -- |
| | Gastritis | -- | Less frequent | -- |
| | Gingival hyperplasia | -- | Less frequent | -- |
| | Nausea | Less frequent | Frequent | -- |
| | Pancreatitis | -- | Less frequent | -- |
| | Vomiting | -- | Less frequent | -- |
| | Liver function test abnormal, including blood bilirubin increase | -- | Less frequent* | Not known |
| Hepato-biliary disorders | Hepatitis | -- | Less frequent | -- |
| | Intrahepatic cholestasis, jaundice | -- | Less frequent | -- |

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|-------------------------|-----------------------------------|---------------|---------------|-----------|
| Skin and | Angioedema | -- | Less frequent | Not known |
| subcutaneous | Alopecia | -- | Less frequent | |
| tissue disorders | Dermatitis bullous | -- | -- | Not known |
| | Erythema | Less frequent | -- | -- |
| | Erythema multiforme | -- | Less frequent | -- |
| | Exanthema | Less frequent | Less frequent | -- |
| | Hyperhidrosis | Less frequent | Less frequent | -- |
| | Photosensitivity reaction | -- | Less frequent | -- |
| | Pruritus | Less frequent | Less frequent | Not known |
| | Purpura | -- | Less frequent | -- |
| | Rash | Less frequent | Less frequent | Not known |
| | Skin discolouration | | Less frequent | -- |
| | Urticaria and other forms of rash | -- | Less frequent | -- |
| | Exfoliative dermatitis | -- | Less frequent | -- |
| | Stevens-Johnson syndrome | -- | Less frequent | -- |
| | Quincke oedema | -- | Less frequent | -- |
| | Toxic epidermal necrolysis | -- | Not known | -- |
| | Arthralgia | Less frequent | Less frequent | -- |
| Musculoskeletal | Back pain | Less frequent | Less frequent | -- |
| and connective | Joint swelling | Less frequent | -- | -- |
| tissue disorders | Muscle spasm | Less frequent | Less frequent | -- |
| | Myalgia | -- | Less frequent | Not known |
| | Ankle swelling | -- | Frequent | -- |
| | Sensation of heaviness | Less frequent | -- | -- |
| | Increased blood creatinine | -- | -- | Not known |
| Renal and | Micturition disorder | -- | Less frequent | -- |
| urinary | Nocturia | -- | Less frequent | -- |
| disorders | Pollakiuria | Less frequent | Less frequent | -- |
| | Polyuria | Less frequent | -- | -- |

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|---|------------------------------|---------------|---------------|---------------|
| | Renal failure and impairment | -- | -- | Not known |
| | Impotence | -- | Less frequent | -- |
| Reproductive system and breast disorders | Erectile dysfunction | Less frequent | -- | -- |
| | Gynaecomastia | -- | Less frequent | -- |
| General disorders and administration site conditions | Discomfort, malaise | -- | Less frequent | -- |
| | Asthenia | Frequent | Less frequent | |
| | Fatigue | Frequent | Frequent | Less frequent |
| | Facial oedema | Frequent | -- | -- |
| | Flushing, hot flush | Frequent | -- | -- |
| | Non cardiac chest pain | -- | Less frequent | -- |
| | Oedema | Frequent | Frequent | -- |
| | Oedema peripheral | Frequent | -- | -- |
| | Pain | -- | Less frequent | -- |
| | Pitting oedema | Frequent | -- | -- |
| | Increased serum potassium | -- | -- | Not known |
| Investigations | Increased weight | -- | Less frequent | -- |
| | Decreased weight | -- | Less frequent | -- |

* Mostly consistent with cholestasis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of AMLODIPINE/VALSARTAN BIOTECH is important. It allows continued monitoring of the benefit/ risk balance of AMLODIPINE/VALSARTAN BIOTECH. 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://www.sahpra.org.za/Publications/Index/8>.

4.9 Overdose

Symptoms

There is no experience of overdose with AMLODIPINE/VALSARTAN BIOTECH. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Available data for amlodipine suggest that gross overdosage could result in excessive peripheral vasodilation 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 ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment

If ingestion is recent, induction of vomiting may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to AMLODIPINE/VALSARTAN BIOTECH overdose 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.

Both valsartan and amlodipine are unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3 Vascular medicines – other hypotensives.

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II

antagonists, combinations; angiotensin II antagonists and calcium channel blockers, *ATC code*: C09DB01.

AMLODIPINE/VALSARTAN BIOTECH combines two antihypertensive compounds with separate mechanisms of action: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II (Ang II) antagonist class of medicines.

Amlodipine/valsartan

The combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range. The antihypertensive effect of a single dose of the combination persisted for 24 hours.

Age, gender and race does not influence the response to AMLODIPINE/VALSARTAN BIOTECH.

Amlodipine

The amlodipine component of amlodipine/valsartan inhibits the transmembrane entry 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, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

Haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine has minimal effect on sinoatrial nodal function or atrioventricular conduction in intact animals or humans.

Valsartan

Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT₁, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT₁ receptor blockade with valsartan may stimulate the unblocked receptor subtype AT₂, which appears to counterbalance the effect of the AT₁ receptor. Valsartan does not exhibit any partial agonist activity at the AT₁ receptor and has much (about 20,000-fold) greater affinity for the AT₁ receptor than for the AT₂ receptor.

Administration of valsartan to patients with hypertension results in a drop in blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4 - 6 hours. The antihypertensive effect persists over 24 hours after administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2 - 4 weeks and is sustained during long-term therapy. Abrupt withdrawal of valsartan has not been associated

with rebound hypertension or other adverse clinical events.

Valsartan has been demonstrated to significantly reduce hospitalisations in patients with chronic heart failure (NYHA class II-IV). The benefits were greatest in patients not receiving either an ACE inhibitor or a beta blocker. Valsartan has also been shown to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

5.2 Pharmacokinetic properties

Amlodipine/valsartan

Following oral administration of amlodipine/valsartan, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6 - 8 hours, respectively. The rate and extent of absorption of the amlodipine/valsartan combination are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets.

Amlodipine

Absorption

After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6 - 12 hours. Absolute bioavailability has been calculated as between 64 % and 80 %. Amlodipine bioavailability is unaffected by food ingestion. (See absorption of combination tablet below).

Distribution

Volume of distribution is approximately 21 L/kg. *In vitro* studies with amlodipine have shown that approximately 97,5 % of circulating medicine is bound to plasma proteins in hypertensive patients.

Biotransformation

Amlodipine is extensively (approximately 90 %) metabolised in the liver to inactive metabolites.

Elimination

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7 - 8 days. Ten per cent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

Valsartan**Absorption**

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2 – 4 hours. Mean absolute bioavailability is 23 %. Food decreases exposure (as measured by AUC) to valsartan by about 40 % and peak plasma concentration (C_{max}) by about 50 %, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution

The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94 - 97 %), mainly serum albumin.

Biotransformation

Valsartan is not transformed to a high extent as only about 20 % of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10 % of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination

Valsartan shows multiexponential decay kinetics ($t_{1/2\alpha} < 1$ h and $t_{1/2\beta}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83 % of dose) and urine (about 13 % of dose), mainly as unchanged

medicine. Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0,62 L/h (about 30 % of total clearance). The half-life of valsartan is 6 hours.

Special populations

Paediatric population (age below 18 years)

No pharmacokinetic data are available in the paediatric population.

Elderly (age 65 years or over)

Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70 % in the elderly than in the young, therefore caution is required when increasing the dosage.

Renal impairment

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. As expected for a compound where renal clearance accounts for only 30 % of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Patients with mild to moderate renal impairment may therefore receive the usual initial dose.

Hepatic impairment

Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase of approximately 40 - 60 % in AUC. On average, in patients with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Caution should be exercised in patients with liver disease (see section 4.2).

Linearity

Valsartan and amlodipine exhibit linear pharmacokinetics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Colloidal silicon dioxide (E551)

Crospovidone (E1201)

Magnesium stearate (E572)

Microcrystalline cellulose (E460(i))

Coating:

Opadry Yellow (containing hypromellose (E464), iron oxide red (E172), iron oxide yellow (E172), macrogol (E1521), talcum (E553b) and titanium dioxide (E171)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

36 months (for 30's packed in HDPE bottles only).

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture.

For blister packs: Keep the blister strips in the outer carton until required for use.

For HDPE packs: Keep in the outer container until required for use.

6.5 Nature and contents of container

AMLODIPINE/VALSARTAN 5/160 BIOTECH and AMLODIPINE/VALSARTAN 10/160 BIOTECH

are packed in silver aluminium/aluminium blister strips containing 30, 90 or 100 film-coated tablets and white opaque high-density polyethylene (HDPE) round bottles with a screw cap or child resistant cap containing 30 or 500 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special 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/VALSARTAN 5/160 BIOTECH: 50/7.1.3/0851

AMLODIPINE/VALSARTAN 10/160 BIOTECH: 50/7.1.3/0852

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 May 2021

10. DATE OF REVISION OF THE TEXT

24 May 2023