Master: GEMVALAZ 5/160 and 10/160 Reg No.: 49/7.1.3/0167-8
Duplicate: VALGAMEZ 5/160 and 10/160 Reg No.: 49/7.1.3/0169.167-8

This submission: Compliant Response to Clinical Evaluation Recommendation: Amlodipine- Risk of non-cardiogenic pulmonary oedema

Date of this submission 07/06/2023

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

GEMVALAZ *5/160 mg tablet* *(5 mg amlodipine and 160 mg valsartan)*

GEMVALAZ *10/160 mg tablet* (10 mg amlodipine and 160 mg valsartan)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GEMVALAZ 5/160 mg:	Each film-coated tablet contains 6,93 mg amlodipine besylate (equivalent to 5 mg amlodipine base) and 160 mg valsartan)
GEMVALAZ 10/160 mg:	Each film-coated tablet contains 13,87 mg amlodipine besylate (equivalent to 10 mg amlodipine base) and 160 mg valsartan)

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

GEMVALAZ 5/160 mg: Dark yellow colored, oval film coated tablet debossed on one side with AV2 and plain on the other side

GEMVALAZ 10/160 mg: Beige colored, oval film coated tablet debossed on one side with AV3 and plain on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Signed: Carlyn Aiyer

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 GEMVALAZ

4.2 Posology and method of administration

Patients receiving valsartan and amlodipine from separate tablets may be switched to GEMVALAZ containing the same component doses.

Posology

The recommended dose is one tablet per day (the 2 strengths are listed under section 2).

Special populations

In Elderly:

Normal dosage regimens are recommended.

Children and adolescents:

GEMVALAZ 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 GEMVALAZ to patients with hepatic impairment or biliary obstructive disorders (see sections 4.4 and 4.8).

Method of administration

For oral use

It is recommended to take GEMVALAZ with some water.

4.3 Contraindications

- Hypersensitivity to amlodipine, valsartan, or to dihydropyridine derivatives, or to any of the inactive ingredients of GEMVALAZ listed in section 6.1.
- A history of angioedema related to previous therapy with 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 ≤ 30ml/min) and in elderly patients.
- Porphyria.

- Lithium therapy: Concomitant administration with GEMVALAZ may lead to toxic blood concentrations of lithium. (see section 4.5).
- The concomitant use of GEMVALAZ with aliskiren-containing products is contraindicated. (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. (Section 4.6).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving GEMVALAZ, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see section 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 GEMVALAZ and aliskiren is therefore contraindicated (see section 4.3).

GEMVALAZ should not be used concomitantly with aliskiren. (see section4.3).

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 GEMVALAZ or close medical supervision at the start of treatment is recommended.

If hypotension occurs with GEMVALAZ, 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 Section 4.3 and 4.5).

Renal artery stenosis

GEMVALAZ 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 GEMVALAZ in patients who have had 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 GEMVALAZ 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 GEMVALAZ 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 angiotensin-converting enzyme (ACE) inhibitors. GEMVALAZ should be discontinued immediately in patients who develop angioedema and should not be re-administered.

Signed: Carlyn Aiyer

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 ureamia 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

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 medicnes [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 diuretic 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 drugs (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 has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers 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, indomethacin, 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 GEMVALAZ should be discontinued.

Women of childbearing potential / Contraception in males and females

Women of childbearing age should ensure effective contraception.

Pregnancy

GEMVALAZ is contraindicated during pregnancy(see section 4.3)

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

Breastfeeding

GEMVALAZ 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. GEMVALAZ

Signed: Carlyn Aiyer

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 GEMVALAZ.

4.8 Undesirable effects

System Organ Class	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	--	--
	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 bradycardia, ventricular	--	Less frequent	--

	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	--
Gastro-intestinal disorders	Abdominal discomfort, abdominal pain upper	Less frequent	Frequent	Less frequent
	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	--
Hepato-biliary disorders	Liver function test abnormal, including blood bilirubin increase part of below	--	Less frequent*	Not known
	Hepatitis	--	Less frequent	--
	Intrahepatic cholestasis,	--	Less frequent	--

	jaundice			
Skin and subcutaneous tissue disorders	Alopecia	--	Less frequent	--
	Angioedema	--	Less frequent	Not known
	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	--
Musculo-skeletal and connective tissue disorders	Arthralgia	Less frequent	Less frequent	--
	Back pain	Less frequent	Less frequent	--
	Joint swelling	Less frequent	--	--
	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 urinary disorders	Micturition disorder	--	Less frequent	--
	Nocturia	--	Less frequent	--
	Pollakiuria	Less frequent	Less frequent	--
	Polyuria	Less frequent	--	--
	Renal failure and impairment	--	--	Not known
	Impotence	--	Less frequent	--
Repro-ductive system and breast disorders	Erectile dysfunction	Less frequent	--	--
	Gynaecomastia	--	Less frequent	--
General disorders and administration site conditions	Asthenia	Frequent	Less frequent	--
	Discomfort, malaise	--	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 part of investigations	--	--	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 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://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

There is no experience of overdose with GEMVALAZ. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially 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

If ingestion is recent, induction of vomiting or gastric lavage 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 GEMVALAZ 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

GEMVALAZ 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 did not influence the response to GEMVALAZ.

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 does not change 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 reduction of 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 amlodipine/valsartan 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.

Distribution

Volume of distribution is approximately 21L /kg. In vitro studies with amlodipine have shown that approximately 97,5 % of circulating compound 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 (Cmax) 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 (t½α <1 h and t½ß 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

- silica colloidal anhydrous,
- magnesium stearate,
- starch pre-gelatinized (starch 1500),
- microcrystalline cellulose,
- Iron oxide yellow,
- talc,
- purified water,
- Opadry (03F82330) yellow {HPMC 2910/ Hypromellose 6cP, Iron Oxide Yellow, Macrogol/ PEG 4000, Titanium dioxide, talc} and
- Opadry (03F83059) orange {HPMC 2910/ Hypromellose 6cP Titanium Dioxide, Macrogol/ PEG 4000, talc}.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Shelf Life: 36 months

6.4 Special precautions for storage

Store at or below 25 ºC in original package.

Protect from moisture.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Carton contains 28 or 30 tablets packed in cold form blister pack, which is packed into an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

14 Lautre Road,

Stormill, Ext.1, Roodepoort,

Johannesburg, 1724

South Africa

8. REGISTRATION NUMBER

Gemvalaz 5/160: 49/7.1.3/0167

Gemvalaz 10/160: 49/7.1.3/0167

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 March 2022

10. DATE OF REVISION OF THE TEXT

08 November 2023