Date of revision: 24 July 2024

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

AMZAAR® 5/50 Tablets

AMZAAR® 5/100 Tablets

2. QUALITATIVE AND QUANTATIVE COMPOSITION

AMZAAR 5/50 mg Tablets contain 7,84 mg amlodipine camsylate (equivalent to 5 mg amlodipine) and 50 mg of losartan potassium.

AMZAAR 5/100 mg Tablets contain 7,84 mg amlodipine camsylate (equivalent to 5 mg amlodipine) and 100 mg losartan potassium.

AMZAAR contains sugar (mannitol).

AMZAAR 5/50 mg Tablets contain 40 mg mannitol per tablet.

AMZAAR 5/100 mg Tablets contain 40 mg mannitol per tablet.

For full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

AMZAAR 5/50: White modified capsule shaped film-coated tablet, debossed with 222 on one side and the other side is plain.

AMZAAR 5/100: Pink modified capsule shaped film-coated tablet, debossed with 331 on one side and the other side is plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AMZAAR (losartan potassium/amlodipine camsylate) is indicated for the treatment of essential hypertension in patients whose blood pressure is controlled on both the components, taken at the same dose as the separate medicines.

4.2 Posology and method of administration

Posology

The recommended dose of AMZAAR is one tablet per day.

The usual dose of AMZAAR is 5/50 mg daily. The maximum recommended dose of AMZAAR is 5/100 mg daily.

Special populations

Use in patients with renal impairment

No dosage adjustment is necessary in patients with moderate renal impairment (i.e., creatinine clearance 30 to 50 mL/min). For patients with severe renal impairment (i.e., creatinine clearance < 30 mL/min) or patients on dialysis, administration of AMZAAR is contraindicated.

Paediatric population

Use in adolescents and children

Since safety and efficacy of AMZAAR in children equal to or less than 18 years of age has not been established, administration of AMZAAR is not recommended.

Method of administration

AMZAAR may be administered with or without food. It is recommended to take AMZAAR with water.

AMZAAR may be administered with other classes of antihypertensive medicines.

4.3 Contraindications

- Hypersensitivity to any of the ingredients of AMZAAR
- 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 < 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)
- Porphyria
- Lithium therapy: Concomitant administration with AMZAAR may lead to toxic blood concentrations of lithium (see Section 4.5).
- Pregnancy and lactation (see Section 4.6)
- Concomitant administration with renin antagonists such as aliskiren (see Section 4.4 and 4.5)
- Hepatic impairment (see Section 4.4)
- Concomitant use of fluoroquinolones with ACE inhibitors/Renin-Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving AMZAAR the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see Section 4.3 and Section 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 renin antagonists such as aliskiren may increase the risk of hypotension, hyperkalaemia and decrease renal function (including acute renal failure). Dual blockade of RAAS through the combined use of AMZAAR and aliskiren is therefore contraindicated (see section 4.3).

AMZAAR

Hypotension: In patients who are intravascularly volume-depleted (e.g. those treated with diuretics), symptomatic hypotension may occur. Intravascular volume depletion should be corrected prior to administration of AMZAAR.

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan and amlodipine in cirrhotic patients, this formulation is not suitable for patients with hepatic impairment (see section 4.3).

Losartan

Hypersensitivity: Angioedema (see Section 4.8).

Electrolyte/Fluid Imbalance

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes and should be addressed. In a clinical study conducted in type 2 diabetic patients with proteinuria, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group.

Concomitant use of other medicines that may increase serum potassium may lead to hyperkalemia (see Section 4.3 and 4.5).

Renal Function Impairment

As a consequence of inhibiting the renin-angiotensin system, deterioration of renal function including renal failure have been reported in susceptible individuals.

AMZAAR is contraindicated in patients with severe renal function impairment (see Section 4.3).

Concomitant use of fluoroquinolones and ACE inhibitors/Renin-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/renin-angiotensin receptor blockers.

Amlodipine

Angina or Myocardial Infarction: Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of AMZAAR due to the amlodipine, particularly in patients with severe obstructive coronary artery disease.

4.5 Interaction with other medicines and other forms of interaction

In clinical pharmacokinetic trials, no medicine interactions of clinical significance have been identified with co-administration of losartan and hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbitone, ketoconazole and erythromycin. Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

Concomitant use of AMZAAR and potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium, or other medicines that may increase serum potassium (e.g., trimethoprim-containing products) may lead to increases in serum potassium (see Section 4.3 and Section 4.4).

Lithium excretion may be reduced (see Section 4.3).

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive medicines. Therefore, the antihypertensive effect of angiotensin II receptor antagonists such as in AMZAAR or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

In patients with compromised renal function (e.g. elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists such as AMZAAR, may result in a further deterioration of renal function, including possible acute renal failure. Therefore, the

combination should be administered with caution in patients with compromised renal function.

Concomitant use of fluoroquinolones and ACE inhibitors/Renin-Angiotensin receptor blockers may precipitate acute kidney injury (see Section 4.3).

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 such as losartan, a component of AMZAAR and renin antagonists such as aliskiren are associated with a higher frequency of adverse events such as hypotension, syncope, hyperkalaemia and decreased renal function (see Section 4.3 and Section 4.4).

Grapefruit juice contains components that inhibit CYP 450 enzymes and may lower the concentration of the active metabolite of losartan which may reduce the therapeutic effect. Consumption of grapefruit juice should be avoided while taking AMZAAR.

CYP3A4 Inhibitors

Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 1,6 fold increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor

for symptoms of hypotension and oedema when amlodipine is co-administered with CYP3A4 inhibitors.

CYP3A4 Inducers

No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers.

4.6 Pregnancy and lactation

AMZAAR is contraindicated in pregnancy and lactation (see Section 4.3).

Pregnancy

Medicines that act directly on the renin-angiotensin system can cause injury and death to the developing foetus. When pregnancy is detected, discontinue AMZAAR as soon as possible.

Foetal toxicity

Use of medicines that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces foetal renal function and increases foetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with foetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure and death. When pregnancy is detected, discontinue AMZAAR as soon as possible (see Section 4.3).

Neonates with a history of *in utero* exposure to AMZAAR:

If oliguria or hypotension occur, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Breastfeeding

It is not known whether losartan or amlodipine is excreted in human milk. AMZAAR should not be used by mothers who are breastfeeding their infants.

4.7 Effects on ability to drive and use machines

Side effects e.g. dizziness, that have been reported with AMZAAR may affect some patients' ability to drive or operate machinery (see Section 4.8).

4.8 Undesirable effects

Adverse reactions from clinical trials

AMZAAR

The safety of AMZAAR has been evaluated in 325 patients treated with AMZAAR for hypertension in 3 clinical trials for 8 weeks. Adverse reactions have been ranked under headings of frequency using the following convention: Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1 000, < 1/100); Rare (≥ 1/10 000, < 1/1 000); Very rare (< 1/10 000).

The treatment-related adverse events:

Nervous system disorders

Common: Dizziness, headache

Uncommon: Somnolence

Cardiac disorders

Uncommon: Palpitation

Vascular disorders

Uncommon: Flushing, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea, cough

Gastrointestinal disorders

Uncommon: Abdominal discomfort, dyspepsia, nausea, reflux oesophagitis

Skin and subcutaneous tissue disorders

Uncommon: Pruritus (generalised), urticaria (generalised)

Renal and urinary disorder

Uncommon: Pollakiuria

General disorders and administration site conditions

Uncommon: Asthenia, chest discomfort, chest pain, early satiety, peripheral oedema, pitting oedema

Sensory organ disorders

Uncommon: Vertigo

The following adverse reactions have been reported with the components of AMZAAR:

	Double-blind controlled clinical trials with losartan for essential hypertension*		Placebo-Controlled Studies with Amlodipine Besylate** 2,5-10 mg/day		Placebo-Controlled Studies with Amlodipine Besylate***			
	Losartan (n=2085)	**Placebo (n=535)**	**Amlodipine besylate (%) (n=1730)**	**Placebo (%) (n=1250)**	**Amlodipine besylate**		**Placebo**	
					Male =% (n= 1218)	**Female =% (n= 512)**	**Male =% (n=914)**	**Female =% (n=336)**
Body as a Whole								
Abdominal pain	1,7	1,7	1,6	0,3				
Asthenia/ fatigue	3,8	3,9	4,5	2,8				
Chest pain	1,1	2,6						
Oedema/ swelling	1,7	1,9			5,6	14,6	1,4	5,1
Cardiovascular								
Palpitation	1,0	0,4			1,4	3,3	0,9	0,9
Tachycardia	1,0	1,7						
Flushing					1,5	4,5	0,3	0,9
Digestive								
Diarrhoea	1,9	1,9						
Dyspepsia	1,1	1,5						
Nausea	1,8	2,8	2,9	1,9				

Musculoskeletal								
Back pain	1,6	1,1						
Muscle cramps	1,0	1,1						
Nervous/ Psychiatric								
Dizziness	4,1	2,4						
Headache	14,1	17,2	7,3	7,8				
Insomnia	1,1	0,7						
Somnolence			1,4	0,6	1,3	1,6	0,8	0,3
Respiratory								
Cough	3,1	2,6						
Nasal congestion	1,3	1,1						
Pharyngitis	1,5	2,6						
Sinus disorder	1,0	1,3						
Upper respiratory infection	6,5	5,6						

*Adverse experiences reported with losartan occurred in ≥ 1 % of patients, regardless of medicine relationship.
The data are from pooled clinical studies using doses of losartan from 5 – 150 mg.

** Adverse experiences that were not clearly dose related but were reported with an incidence > 1,0 %.

*** Adverse experiences that appear to be medicine and dose related, there was a greater incidence in women than men.

In hypertensive patients the most common medicine-related side effects were dizziness, asthenia/fatigue and vertigo.

The most common medicine-related side effects in patients with diabetes mellitus were asthenia/fatigue, dizziness, hypotension and hyperkalaemia (see Section 4.4, Hypotension and Electrolyte/Fluid Imbalance).

The following events occurred in < 1 % of patients in controlled clinical trials or under conditions of open trials or where a causal relationship is uncertain; they are listed to alert the medical practitioner to a possible relationship:

Blood and the lymphatic system disorders

Leukopenia, purpura, thrombocytopenia

Immune system disorders

Angioedema

Metabolism and nutrition disorders

Hyperglycaemia, thirst, increased appetite

Psychiatric disorders

Sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalisation, amnesia

Nervous system disorders

Hypoaesthesia, neuropathy peripheral, paraesthesia, tremor, dry mouth, increased sweating, agitation

Eye disorders

Abnormal vision, conjunctivitis, diplopia, eye pain, abnormal visual accommodation, xerophthalmia

Ear and labyrinth disorders

Tinnitus, vertigo

Cardiac disorders

Dysrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, tachycardia, cardiac failure, pulse irregularity, extrasystoles

Vascular disorders

Hypotension, peripheral ischaemia, syncope, postural dizziness, postural hypotension, vasculitis

Respiratory, thoracic and mediastinal disorders

Dyspnoea, epistaxis, coughing, rhinitis, parosmia

Gastrointestinal disorders

Anorexia, constipation, dyspepsia, dysphagia, diarrhoea, flatulence, pancreatitis, vomiting, gingival hyperplasia, gastritis, loose stools, taste perversion

Skin and subcutaneous tissue disorder

Erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, cold and clammy skin

Musculoskeletal, connective tissue and bone disorders

Arthralgia, arthrosis, muscle cramps, myalgia, muscle weakness, twitching, ataxia, hypertonia

Renal and urinary disorders

Micturition frequency, micturition disorder, nocturia, dysuria, polyuria

General disorders and administration site conditions

Allergic reaction, asthenia[1], back pain, hot flushes, malaise, pain, rigors, weight gain, decreased weight, migraine, apathy

[1] These events occurred in < 1 % in placebo-controlled trials, but the incidence of these side effects was between 1 % and 2 % in all multiple dose studies.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Adverse reactions from spontaneous reporting

Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to medicine exposure.

Losartan

Hypersensitivity:

Anaphylactic reactions, 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 losartan; some of these patients previously experienced angioedema with other medicines including ACE inhibitors. Vasculitis, including Henoch-Schönlein purpura, has been reported.

Blood and the lymphatic system disorders

Anaemia, thrombocytopenia

Nervous system disorders

Migraine, dysgeusia

Respiratory thoracic and mediastinal disorders

Cough

Gastrointestinal disorders:

Hepatitis, liver function abnormalities, vomiting

Skin and subcutaneous tissue disorder

Urticaria, pruritus, erythroderma, photosensitivity

Musculoskeletal connective tissue and bone disorders

Myalgia, arthralgia

Reproductive system and breast disorders

Erectile dysfunction/impotence

General disorders and administration site conditions:

Malaise

Amlodipine

The following post-marketing event has been reported where a causal relationship is uncertain: Gynecomastia. In post-marketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalisation, have been reported in association with use of AMZAAR.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

AMZAAR

There are no available clinical data in regard to overdosage of AMZAAR in humans. The overdose on each ingredient of amlodipine and losartan are described.

Losartan

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor the active metabolite can be removed by haemodialysis.

Amlodipine

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Treatment should be symptomatic and supportive.

Non-cardiogenic pulmonary oedema has been rarely reported as a consequence of amlodipine overdose, that may manifest with a delayed onset (24 – 48 hours post-ingestion) and require ventilatory support or may result in a fatal outcome. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

5. PHARMACOLOGICAL PROPERTIES

A.7.1.3 Other hypotensives

5.1 Pharmacodynamic properties

Losartan and amlodipine have complementary hypotensive activity: Losartan potassium is an angiotensin II receptor blocker (ARB), and amlodipine is a calcium channel blocker (CCB). Losartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Losartan

Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system, and a major determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation. A second angiotensin II receptor has been identified as the AT2 receptor subtype, but it plays no known role in cardiovascular homeostasis.

Losartan is a synthetic, orally active compound. Based on binding and pharmacological bioassays, it binds selectively to the AT1 receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.

Losartan binds selectively to the AT1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT1 receptor, such as the potentiation of bradykinin-mediated effects or the generation of oedema (losartan 1,7 %; placebo 1,9 %), are not associated with losartan.

Amlodipine

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. 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. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionised compound (pKa=8,6), and its kinetic interaction with the calcium channel receptor is characterised by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

5.2 Pharmacokinetic properties

Absorption

Losartan

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33 %. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3 to 4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the medicine was administered with a standardised meal.

Amlodipine

After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90 %. The bioavailability of amlodipine is not altered by the presence of food.

Distribution

Losartan

Both losartan and its active metabolite are equal to or > 99 % bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Amlodipine

Ex vivo studies have shown that approximately 93 % of the circulating medicine is bound to plasma proteins in hypertensive patients.

Metabolism

Losartan

About 14 % of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about 1 % of individuals studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Amlodipine

Amlodipine is extensively (about 90 %) converted to inactive metabolites via hepatic metabolism with 10 % of the parent compound and 60 % of the metabolites excreted in the urine.

Elimination

Losartan

Plasma clearance of losartan and its active metabolite is about 600 mL/min and 50 mL/min, respectively. Renal clearance of losartan and its active metabolite is about 74 mL/min and 26 mL/min, respectively. When losartan is administered orally, about 4 % of the dose is

excreted unchanged in the urine, and about 6 % of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6 to 9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labelled losartan in man, about 35 % of radioactivity is recovered in the urine and 58 % in the faeces. Following an intravenous dose of ^{14}C-labelled losartan in man, about 43 % of radioactivity is recovered in the urine and 50 % in the faeces.

Amlodipine

Elimination from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Losartan

The plasma concentrations of losartan and its active metabolite observed in elderly male hypertensives are not significantly different from those observed in young male hypertensives.

Plasma concentrations of losartan were up to 2-fold higher in female hypertensives as compared to male hypertensives. Concentrations of the active metabolite were not different in males and females. This apparent pharmacokinetic difference is not judged to be of clinical significance.

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were respectively, 5-fold and 1,7-fold greater than those seen in young male volunteers.

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 mL/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

Amlodipine

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40 to 60 %, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1,25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

AMZAAR contains the following inactive ingredients: Butylated hydroxytoluene, sodium starch glycolate, microcrystalline cellulose, D-mannitol, povidone, crospovidone, magnesium stearate, hypromellose, hydroxypropylcellulose, titanium oxide, and talc.

AMZAAR contains sugar (mannitol).

AMZAAR 5/100 mg Tablets also contain iron oxide red and iron oxide yellow.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C. Keep the blister in the carton until required for use. Protect from moisture.

6.5 Nature and contents of container

AMZAAR is packaged in push-through aluminium blisters of 30 tablets. The material used to fabricate the blister cavity is a laminate consisting of silver polyvinylchloride (PVC)/aluminium/polyamide film. The lidding material is a push through aluminium foil with heat seal coating one side and print primer on the other. The blisters are packed in a carton.

6.6 Special precautions for disposal

Not applicable

7. HOLDER OF CERTIFICATE OF REGISTRATION

Organon South Africa (Pty) Ltd

Spaces, 1st Floor

22 Magwa Crescent, Gateway West

Waterfall City, Midrand, 2090

South Africa

8. REGISTRATION NUMBER(S)

AMZAAR 5/50: 46/7.1.3/0559

AMZAAR 5/100: 46/7.1.3/0560

9. DATE OF FIRST AUTHORISATION

Date of registration of the medicine: 20 March 2018

10. DATE OF REVISION OF THE TEXT

Date of revision: 24 July 2024

WPC-MK0954F-022020; WPC-MK0954F-102021; SAHPRA PV Directive PVC87 Item #6.6.5 ACE Inhibitors & Fluoroquinolones dated 03.05.2019.; SAHPRA Directive Amlodipine Risk of Non-cardiogenic pulmonary oedema dated 14 March 2023