PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

AMIZART 50 mg film-coated tablets

AMIZART 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMIZART 50 mg: Each film-coated tablet contains 50 mg losartan potassium.

AMIZART 100 mg: Each film-coated tablet contains 100 mg losartan potassium.

Excipient with known effect:

AMIZART 50 mg: 70,0 mg of lactose monohydrate per film-coated tablet.

AMIZART 100 mg: 140,0 mg of lactose monohydrate per film-coated tablet.

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

AMIZART 50 mg: White to off-white, oval shaped, biconvex, film-coated tablets, debossed "50" on one side and plain on other side.

AMIZART 100 mg: White to off-white, almond shaped, biconvex, film-coated tablets, debossed "100" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AMIZART is indicated for the treatment of hypertension.

Renal protection in type 2 diabetic patients with hypertension and proteinuria.

4.2 Posology and method of administration

AMIZART may be administered with or without food.

AMIZART may be administered with other antihypertensive medicines.

Hypertension

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3 to 6 weeks after initiation of therapy. The dose may be increased to 100 mg once daily.

For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see section 4.4).

No initial dosage adjustment is necessary for the elderly patients or for patients with renal impairment, including patients on dialysis.

A lower dose should be considered for patients with a history of hepatic impairment (see section 4.4).

Renal protection in type 2 diabetic patients with hypertension and proteinuria

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response. AMIZART may be administered with other antihypertensive medicines (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting medicines) as well as with insulin and other commonly used hypoglycaemic medicines (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Method of administration

For oral use.

4.3 Contraindications

AMIZART is contraindicated in patients:

- who are hypersensitive to losartan or any of the ingredients of AMIZART listed in section 6.1.

- with a history of angioedema related to previous therapy with ACE-inhibitors or angiotensin receptor antagonists. These patients must never again be given these medicines.
- with hereditary or idiopathic angioedema.
- with hypertrophic obstructive cardiomyopathy (HOCM).
- with severe renal impairment (creatinine clearance less than 30 ml/min) or for patients with hepatic impairment.
- with aortic stenosis, left ventricular outflow track obstruction.
- with bilateral renal artery stenosis.
- with renal artery stenosis in patients with a single kidney.
- taking concomitant therapy with potassium sparing diuretics such as spirinolactone, triamterene and amiloride.
- the concomitant use of fluoroquinolones with ACE inhibitors/angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in elderly patients.
- with porphyria.
- on lithium therapy - concomitant administration with AMIZART may lead to toxic blood concentrations of lithium.
- pregnancy and lactation (see section 4.6).
- the concomitant use of AMIZART with aliskiren-containing medicines is contraindicated.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving AMIZART, the treatment must be stopped promptly and changed to a different medicine. If a woman is contemplating pregnancy, a different class of medicine should be used (see section 4.6).

Hypersensitivity

Angioedema. Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8).

Hypotension and electrolyte/fluid imbalance

Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of AMIZART, or a lower starting dose should be used. This also applies to children 6 to 18 years of age.

Electrolyte imbalances

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 nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group (see section 4.8). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a creatinine clearance between 30 - 50 mL/min should be closely monitored.

The concomitant use of potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other medicines that may increase serum potassium (e.g. trimethoprim-containing products) with losartan is not recommended (see section 4.5).

Hepatic impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in

patients with severe hepatic impairment. Therefore, AMIZART must not be administered in patients with severe hepatic impairment (see sections 5.2).

Losartan is not recommended in children with hepatic impairment.

Renal impairment

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). Increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. AMIZART is contraindicated in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

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 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.

Use in paediatric patients with renal impairment

Losartan is not recommended in children with glomerular filtration rate < 30 mL/min/1.73 m^2 as no data are available.

Renal function should be regularly monitored during treatment with AMIZART as it may deteriorate. This applies particularly when AMIZART is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Concomitant use of AMIZART and ACE-inhibitors has been shown to impair renal function.

Therefore, concomitant use is not recommended (see section 4.5).

Renal transplantation

There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, the use of losartan is not recommended.

Coronary heart disease and cerebrovascular disease

Excessive blood pressure decreases in patients with ischaemic cardiovascular and cerebrovascular disease and could result in a myocardial infarction or stroke.

Heart failure

In patients with heart failure, with or without renal impairment, there is a risk of severe arterial hypotension, and (often acute) renal impairment.

There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life-threatening cardiac dysrhythmias. Therefore, AMIZART should be used with caution in these patient groups. The combination of AMIZART with a beta-blocker should be used with caution (see section 5.1).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

Special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Other warnings and precautions

Losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

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 increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore contraindicated (see section 4.3).

AMIZART should not be used concomitantly with aliskerin (see section 4.3). ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Excipients

AMIZART contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take AMIZART.

4.5 Interactions with other medicines and other forms of interactions

Other antihypertensive medicines may increase the hypotensive action of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50 %. It was found that concomitant treatment of losartan with rifampicin (inducer of metabolism enzymes) gave a

40 % reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).

Concomitant use of other medicines which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin, trimethoprim-containing products), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.

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).

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

When angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients

should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Clinical trial data have 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 (including acute renal failure) compared to the use of a single RAAS-acting medicine (see sections 4.4 and 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing age should ensure adequate contraception.

Pregnancy

The use of AMIZART is contraindicated during pregnancy (see section 4.3).

Patients planning pregnancy should be changed to alternative anti-hypertensive treatments, which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Breastfeeding

AMIZART is contraindicated during lactation (see section 4.3).

It is not known whether losartan is excreted in human milk. Safety of breastfeeding in mothers, taking AMIZART has not been established. However, significant levels of losartan and the active metabolite were shown to be present in rat milk.

Fertility

No data is available on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects of the ability to drive and use machines have been performed. However, when driving vehicles or operating machines, it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8 Undesirable effects

Adverse reaction	**Frequency of adverse reaction by indication**			**Other**	
	Hypertension	**Hypertensive patients with left-ventricular hypertrophy**	**Chronic heart failure**	**Hypertension and type 2 diabetes with renal disease**	**Post-marketing experience**
Blood and lymphatic system disorders					
Anaemia			Frequent		Frequency not known
Thrombocytopaenia					Frequency not known
Immune system disorders					
Hypersensitivity reactions, anaphylactic reactions, angioedema*, and vasculitis**					Less frequent
Psychiatric disorders					
Depression					Frequency not known

Nervous system disorders					
Dizziness	Frequent	Frequent	Frequent	Frequent	
Somnolence	Less frequent				
Headache	Less frequent		Less frequent		
Sleep disorders	Less frequent				
Paraesthesia			Less frequent		
Migraine					Frequency not known
Dysgeusia					Frequency not known
Ear and labyrinth disorders					
Vertigo	Frequent	Frequent			
Tinnitus					Frequency not known
Cardiac disorders					
Palpitations	Less frequent				
Angina pectoris	Less frequent				
Syncope			Less frequent		
Atrial fibrillation			Less frequent		
Cerebrovascular accident			Less frequent		
Vascular disorders					
(Orthostatic) hypotension (including dose-related orthostatic effects)‖	Less frequent		Frequent	Frequent	
Respiratory, thoracic and mediastinal disorders					
Dyspnoea			Less frequent		
Cough			Less frequent		Frequency not known

Gastrointestinal disorders					
Abdominal pain	Less frequent				
Obstipation	Less frequent				
Diarrhoea			Less frequent		Frequency not known
Nausea			Less frequent		
Vomiting			Less frequent		
Hepatobiliary disorders					
Pancreatitis					Frequency not known
Hepatitis					Less frequent
Liver function abnormalities					Frequency not known
Skin and subcutaneous tissue disorders					
Urticaria			Less frequent		Frequency not known
Pruritus			Less frequent		Frequency not known
Rash	Less frequent		Less frequent		Frequency not known
Photosensitivity					Frequency not known
Musculoskeletal and connective tissue disorders					
Myalgia					Frequency not known
Arthralgia					Frequency not known
Rhabdomyolysis					Frequency not known
Renal and urinary disorders					
Renal impairment			Frequent		
Renal failure			Frequent		
Reproductive system and breast disorders					
Erectile dysfunction/ impotence					Frequency not known

General disorders and administrative site conditions					
Asthenia	Less frequent	Frequent	Less frequent	Frequent	
Fatigue	Less frequent	Frequent	Less frequent	Frequent	
Oedema	Less frequent				
Malaise					Frequency not known
Investigations					
Hyperkalaemia	Frequent		Less frequent†	Frequent‡	
Increased alanine aminotransferase (ALT)§	Less frequent				
Increase in blood urea, serum creatinine, and serum potassium			Frequent		
Hyponatraemia					Frequency not known
Hypoglycaemia				Frequent	

*Including swelling of the larynx, glottis, face, lips, pharynx, and/or tongue (causing airway obstruction); in some of these patients' angioedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors.

**Including Henoch-Schönlein purpura.

‖Especially in patients with intravascular depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics.

†Common in patients who received 150 mg losartan instead of 50 mg.

‡In a clinical study conducted in type 2 diabetic patients with nephropathy, 9,9 % of patients treated with Losartan tablets developed hyperkalaemia > 5,5 mmol/l and 3,4 % of patients treated with placebo.

§ Usually resolved upon discontinuation.

The following additional adverse reactions occurred more frequently in patients who received losartan than placebo (frequencies not known): back pain, urinary tract infection, and flu-like symptoms.

Renal and urinary disorders

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy (see section 4.4).

Paediatric population

The adverse reaction profile for paediatric patients appears to be similar to that seen in adult patients. Data in the paediatric population are limited.

Reporting of suspected adverse reactions

Reporting of 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

Symptoms of overdose

Limited data are available with regard to overdose in humans. The most likely manifestation of overdose would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.

Treatment of overdose

If symptomatic hypotension should occur, supportive treatment should be instituted.

Measures are depending on the time of medicinal product intake and kind and severity of symptoms. Stabilisation of the cardiovascular system should be given priority. After oral intake, the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonist, plain ATC Code: C09CA01

Pharmacological classification: A 7.1.3 Other hypotensives

Losartan is a synthetic oral angiotensin-II receptor (type AT_1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 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.

Losartan selectively blocks the AT_1 receptor. *In vitro* and *in vivo* 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 its synthesis.

Losartan does not have an agonist effect nor does it 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, there is no potentiation of undesirable bradykinin-mediated effects.

5.2 Pharmacokinetic properties

Absorption

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 3 - 4 hours, respectively.

Distribution

Both losartan and its active metabolite are ≥ 99 % bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Biotransformation

About 14 % of an intravenously- or orally-administered dose of losartan is converted to its active metabolite.

Following oral and intravenous administration of 14C-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 one percent of individuals studied.

In addition to the active metabolite, inactive metabolites are formed.

Elimination

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 - 9 hours,

respectively. During once daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

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

Characteristics in patients

In elderly hypertensive patients, the plasma concentrations of losartan and its active metabolite do not differ essentially from those found in young hypertensive patients.

In female hypertensive patients, the plasma levels of losartan were up to twice as high as in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women.

In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma levels of losartan and its active metabolite after oral administration were respectively 5 and 1,7 times higher than in young male volunteers (see section 4.2 and 4.4).

Plasma concentrations of losartan are not altered in patients with a creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2 times higher in haemodialysis patients. The 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.

Pharmacokinetics in paediatric patients

The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0,54 to 0,77 mg/kg of losartan (mean doses).

The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughly similar pharmacokinetic parameters of losartan following oral

administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/toddlers was comparatively high.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse reactions on the late foetal development, resulting in foetal death and malformations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, purified talc and magnesium stearate.

The film-coating contains hypromellose, titanium dioxide, talc and polyethylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years

6.4 Special precautions for storage

Store at or below 30 °C in the original package.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

The film-coated tablets are packed in PVC/PE/PVDC/Aluminium foil blister strips. The blister strips are packed in cartons containing 28 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Smart Pharmaceuticals (Pty) Ltd

247 Voortrekker Road

Kraaifontein, Cape Town

7570

8. REGISTRATION NUMBERS

AMIZART 50 mg: 46/7.1.3/0716

AMIZART 100 mg: 46/7.1.3/0717

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 April 2022

10. DATE OF REVISION OF THE TEXT

12 April 2022

AMI/C/PI/A