Date: March 2023

PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ZAARIO 50 (50 mg, film coated tablets)

ZAARIO 100 (100 mg, film coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZAARIO 50: Each tablet contains 50 mg losartan potassium. Contains sugar: lactose monohydrate 25 mg/ tablet

ZAARIO 100: Each tablet contains 100 mg losartan potassium. Contains sugar: lactose monohydrate 50 mg/ tablet

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

ZAARIO 50: White to off-white, oval shaped, film coated tablets, scored on one side, debossed with ‘J’ on scored side and ‘50’ on the other side.

ZAARIO 100: White to off-white, capsule shaped, film coated tablets, debossed with ‘J’ on one side and ‘100’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ZAARIO is indicated for the following:

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

4.2 Posology and method of administration

Posology

ZAARIO may be administered with other antihypertensive medicines of a different class.

Hypertension:

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximum antihypertensive effect is achieved 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).

Another formulation should be used for patients requiring a dose of 25 mg.

No initial dosage adjustment is necessary for elderly patients including patients on dialysis. **ZAARIO** is contraindicated in patients with renal impairment,

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 if blood pressure response indicates that it is required. **ZAARIO** may be administered with other antihypertensive medicines (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic medicines (e.g. sulphonylureas, glitazones and glucosidase inhibitors).

Special populations

Use in Elderly

Although consideration should be given to initiating therapy with 25 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.

Method of administration

Losartan tablets should be swallowed whole with a glass of water.

ZAARIO may be administered with or without food.

4.3 Contraindications

- Hypersensitivity to losartan or to any of the inactive ingredients of **ZAARIO** (see 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, left ventricular outflow track obstruction.
- Concomitant therapy with potassium-sparing diuretics, such as spironolactone, triamterene, and amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with **ZAARIO** may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- The concomitant use of **ZAARIO** with renin inhibitors containing products, such as aliskiren, is contraindicated (see section 4.4 and section 4.5).
- Concomitant use of fluoroquinolones with angiotensin-converting enzyme (ACE) inhibitors or renin-angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (see section 4.4).
- **ZAARIO** is not recommended for patients with hepatic impairment.
- Safety and efficacy has not been established in children.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **ZAARIO**, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine. Should a woman contemplate pregnancy, the doctor should consider alternative medication. (See section 4.6.)

Serum potassium levels should be monitored regularly.

Hypersensitivity:

Angioedema may occur in patients treated with **ZAARIO**. Patients with a history of angioedema (swelling of the face, lips, throat and/or tongue) should be monitored closely (see section 4.8).

Hypotension and electrolyte/fluid imbalance:

Symptomatic hypotension may occur after initiation of **ZAARIO**.

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. Volume depletion and electrolyte imbalances should be corrected prior to administration of **ZAARIO** or a lower starting dose should be used (see section 4.2).

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes and should be addressed.

Hepatic impairment:

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a dose of 25 mg should be considered for patients with a history of hepatic impairment (see section 4.2).

Renal impairment:

When impaired renal function is present, changes in renal function as a consequence of inhibiting the renin-angiotensin system, including renal failure, have been reported in susceptible individuals; in some patients these changes in renal function may be reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (less frequently) with acute renal failure and/or death. Similar outcomes have been reported with **ZAARIO**.

Medicines affecting the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with **ZAARIO**; these changes in renal function may be reversible upon discontinuation of therapy. (see section 4.3).

There is no experience in patients who have received kidney transplantation.

Acute kidney injury:

Concomitant use of fluoroquinolones and angiotensin-converting enzyme (ACE) inhibitors or 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 and ACE inhibitors or renin-angiotensin receptor blockers.

Primary hyperaldosteronism:

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

Hyperkalaemia:

Since hyperkalaemia may occur, serum-potassium concentrations should be monitored, especially in the elderly and patients with renal impairment and 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) should be avoided (see section 4.3 and section 4.5).

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 inhibitors, such as 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 **ZAARIO** and renin inhibitors, such as aliskiren is therefore contraindicated (see section 4.3).

ZAARIO should not be used concomitantly with renin inhibitors, such as aliskiren (see section 4.3).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with

diabetic nephropathy.

Other conditions with stimulation of the renin-angiotensin-aldosterone system (RAAS):

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme (ACE) inhibitors has been associated with oliguria and/or progressive uraemia and (less frequently) with acute renal failure and/or death. Similar outcomes are likely with **ZAARIO** therapy. As with other angiotensin converting enzyme inhibitors, losartan, as in ZAARIO, is apparently less effective in lowering blood pressure in the black population than in the non-black population, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Coronary heart disease and cerebrovascular disease:

As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease 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 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 arrhythmias. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis or obstructive hypertrophic cardiomyopathy.

Porphyria:

Limited information is available regarding the effect of antihypertensive medicine in patients with porphyria. Safety of **ZAARIO** has not been established.

ZAARIO contains lactose monohydrate:

Patients with the rare hereditary conditions of lactose or galactose intolerance, e.g. galactosaemia, Lapp lactase deficiency, or glucose-galactose malabsorption should not take **ZAARIO**.

4.5 Interactions with other medicines and other forms of interaction

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

Dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or renin inhibitors, such as aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function compared to the use of a single RAAS-acting medicine (see section 4.3 and section 4.4). Concomitant use of fluoroquinolones and angiotensin-converting enzyme (ACE) inhibitors or renin-angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3 and section 4.4).

Potassium-sparing diuretics, potassium-containing medicine or potassium supplements used concurrently with **ZAARIO** may result in hyperkalaemia since reduction of aldosterone production induced by **ZAARIO** may lead to elevation of serum potassium. Co-medication is not advisable.

As with other medicines which affect the excretion of sodium, lithium excretion may be reduced and serum lithium concentrations increased during concomitant administration of lithium with ACE inhibitors and with angiotensin II antagonists, including losartan, as in **ZAARIO.** Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists (see section 4.3).

Nonsteroidal anti-inflammatory medicines (NSAIDs), including cyclo-oxygenase-2 inhibitors, may reduce the effect of diuretics and the antihypertensive effect of **ZAARIO**. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by

NSAIDs including selective COX-2 inhibitors. Patients taking NSAIDs concomitantly with **ZAARIO** should be adequately hydrated and renal function should be monitored.

ZAARIO is predominantly metabolised by cytochrome P450 CYP2C9 to the active carboxy-acid metabolite and interactions may occur with medicines that effect these enzymes. Fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50 %. Concomitant treatment of **ZAARIO** with rifampicin (inducer of metabolism enzymes) provides a 40 % reduction in plasma concentration of the active metabolite. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential:

Women of childbearing age should ensure adequate contraception.

ZAARIO should be discontinued immediately, when pregnancy is planned or suspected.

Pregnancy:

ZAARIO should not be used in pregnancy (see section 4.3). When pregnancy is detected, **ZAARIO** should be discontinued as soon as possible.

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

Infants whose mothers have taken losartan should be closely observed for hypotension

Lactation:

Safety has not been established. **ZAARIO** should not be used during breastfeeding. Alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a new-born or preterm infant.

4.7 Effects on ability to drive and use machines

Patients should not drive, operate machinery, or do anything else that requires attention until they know how **ZAARIO** will affect them. 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

System Organ Class	Adverse Drug Reaction	Frequency
Infections and infestations	upper respiratory infection	*Frequent*
Blood and the lymphatic system disorders	neutropenia	*Less frequent*
	thrombocytopaenia, anaemia	*Frequency unknown*
Psychiatric disorders	insomnia	*Less frequent*
	depression	*Frequency unknown*
Nervous system disorders	headache, dizziness	*Frequent*
	Fatigue, somnolence, sleep disorders, paraesthesia	*Less Frequent*
	migraine, dysgeusia	*Frequency unknown*
Ear and labyrinth disorders	vertigo	*Frequent*
	tinnitus	*Frequency unknown*
Cardiac disorders	palpitations, tachycardia	*Frequent*
	angina pectoris, syncope, atrial fibrillation, cerebrovascular accident	*Less Frequentt*
Vascular disorders	orthostatic hypotension	*Less frequent*
	vasculitis, including Henoch Schönlein purpura	*Frequency unknown*
Respiratory, thoracic and mediastinal disorders	cough, pharyngitis, nasal congestion, sinus disorder	*Frequent*
	respiratory tract disorders, dyspnoea	*Less frequent*
Gastrointestinal disorders	diarrhoea, nausea, abdominal pain, dyspepsia	*Frequent*
	obstipation, vomiting	*Less frequent*
Skin and subcutaneous tissue disorders	Rash, urticaria, pruritus	*Less frequent*
	erythroderma, photosensitivity	*Frequency unknown*

Musculoskeletal, connective tissue and bone disorders	back pain, muscle cramps	*Frequent*
	leg pain	*Less frequent*
	myalgia, arthralgia, rhabdomyolysis	*Frequency unknown*
Renal and urinary disorders	Renal failure, renal impairment	*Frequent*
Hepatobiliary disorders	hepatitis	*Less frequent*
	pancreatitis, liver function abnormalities	*Frequency unknown*
Immune system disorders	hypersensitivity reactions, anaphylactic reactions, angioedema (including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue), vasculitis	*Less frequent*
Reproductive system and breast disorders	erectile dysfunction/impotence	*Frequency unknown*
General disorders and administrative site conditions	asthenia, fatigue, oedema/swelling, chest pain	*Frequent*
	malaise	*Frequency unknown*
Investigations	hyperkalaemia, increased alanine aminotransferase (ALT), increase in blood urea, serum creatinine and serum potassium, hypoglycaemia	*Frequent*
	liver function abnormalities, hyponatraemia	*Frequency unknown*

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.

Reporting can also be done directly to Unicorn Pharmaceuticals (Pty) Ltd at: vigilance@unicornpharma.co.za

4.9 Overdose

Symptoms:

The symptoms of an overdosage of **ZAARIO** would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.

Treatment:

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 **ZAARIO** nor the active metabolite can be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3 Vascular medicines - other hypotensives.

Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA01

Losartan is a synthetic, orally active nonpeptide angiotensin II receptor antagonist with high affinity and selectivity for the AT_1 receptor. Both losartan and its principal active metabolite have a far greater affinity for the AT_1-receptor than for the AT_2-receptor. The active metabolite is 10- to 40-times more active than losartan on a weight for weight basis. Angiotensin II is a potent vasoconstrictor, a primary active hormone of the renin-angiotensin system and a major 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 and its pharmacologically active carboxylic acid metabolite (E-3174) blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by inhibiting the binding of angiotensin II to the AT_1 receptor, regardless of the source or route of synthesis.

Losartan is a specific antagonist of the angiotensin II receptor type AT_1; it does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit angiotensin converting enzyme (ACE) (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT_1 receptor, such as the potentiation of bradykinin-mediated effects or the generation of oedema are not associated with losartan. This provides a pharmacodynamic distinction between losartan and ACE inhibitors. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity, during losartan administration. A 2 to 3-fold increase in angiotensin II in plasma comes as a result of increases in plasma renin activity. However, antihypertensive activity and suppression of plasma aldosterone concentration are apparent, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin levels decline to untreated levels within 3 days.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration, bioavailability is approximately 33 %. It undergoes first-pass metabolism to form an active carboxylic acid metabolite (which has greater pharmacological activity than losartan) and some inactive metabolites. About 14 % of orally administered dose is converted to its active metabolite. The mean peak concentrations of losartan and its active metabolite are reached in 1 hour and 3 – 4 hours respectively.

Distribution:

Both losartan and carboxylic acid metabolite are greater than, or equal to 99 % bound to plasma proteins. The distribution volume 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 ^{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 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 doses up to 200 mg.

The terminal half-life of losartan is about 2 hours and that of its active metabolite is 6 – 9 hours. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Losartan is excreted in the urine, and in the faeces, as unchanged losartan and metabolites. Following oral dosing of ^{14}C-labeled losartan in man, about 35 % of the dose is excreted in the urine and about 60 % in the faeces. Neither losartan nor the active metabolite can be removed by haemodialysis.

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.

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 impaired renal function and a creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the area under the curve (AUC) for losartan is approximately 2-fold greater in patients on haemodialysis.

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.

5.3 Preclinical safety data

Not Applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch and titanium dioxide.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture.

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

6.5 Nature and contents of container

ZAARIO 50: White opaque PVC/PE/PVdC silver aluminium blisters, containing 10 tablets per blister, in an outer cardboard carton. 30 tablets per outer carton pack.

ZAARIO 100: White opaque PVC/PE/PVdC silver aluminium blisters, containing 10 tablets per blister, in an outer cardboard carton. 30 tablets per outer carton pack.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Corner of Searle & Pontac Streets

Woodstock, Cape Town

8001

enquiries@unicornpharma.co.za

8 REGISTRATION NUMBER(S)

ZAARIO 50: 46/7.1.3/0714

ZAARIO 100: 46/7.1.3/0715

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 June 2018

10 DATE OF REVISION OF THE TEXT

12/05/2023