PROFESSIONAL INFORMATION FOR ZAARIO PLUS

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ZAARIO PLUS 50/12,5 film coated tablet

ZAARIO PLUS 100/25 film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZAARIO PLUS 50/12,5: Each film coated tablet contains 50 mg losartan potassium and 12,5 mg hydrochlorothiazide.

Contains sugar: lactose monohydrate: 25,00 mg.

ZAARIO PLUS 100/25: Each film coated tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

Contains sugar: lactose monohydrate: 50,00 mg.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

ZAARIO PLUS 50/12,5: Yellow coloured, oval shaped, film coated tablets, debossed with ‘J’ on one side and ‘50+’ on the other side.

ZAARIO PLUS 100/25: Yellow coloured, oval shaped, film coated tablets, debossed with ‘J’ on one side and ‘100+’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZAARIO PLUS is indicated for the treatment of hypertension in patients established on identical doses of the individual medicines.

4.2 Posology and method of administration

ZAARIO PLUS may be administered with other antihypertensive medicines, particularly calcium channel blockers and beta-blockers.

ZAARIO PLUS may be administered with or without food.

The usual starting and maintenance dose is one **ZAARIO PLUS 50/12,5** daily. For patients who do not respond adequately, the dose may be increased to the maximum dose of two tablets of **ZAARIO PLUS 50/12,5**, or one tablet of **ZAARIO PLUS 100/25** (100 mg losartan potassium and 25 mg hydrochlorothiazide), once daily. The maximum antihypertensive effect is achieved within three weeks after initiation of therapy.

ZAARIO PLUS should not be initiated in patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics).
ZAARIO PLUS is contraindicated for patients with severe renal impairment.
ZAARIO PLUS is not recommended for patients with hepatic impairment (see **sections 4.3 and 4.4**).

No initial dosage adjustment of **ZAARIO PLUS 50/12,5** is necessary for elderly patients. **ZAARIO PLUS 100/25** should not be used as initial treatment in elderly patients.

Paediatric population

• Paediatric use – safety and efficacy have not been established in children.

(see section 4.3).

4.3 Contraindications

- Hypersensitivity to losartan, hydrochlorothiazide or any of the inactive ingredients of **ZAARIO PLUS** (see **section 6.1**).
- Hypersensitivity to other sulphonamide-derived medicines, due to the hydrochlorothiazide component.
- Anuria or severe renal function impairment (creatinine clearance < 30 ml/min) – hydrochlorothiazide may produce cumulative effects or precipitate uraemia.
- Hepatic function impairment – increased plasma concentrations may occur (see **section 4.4**).
- Pregnancy and lactation (see **section 4.6**).
- 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).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney or transplanted kidney.
- Aortic stenosis.
- Concomitant therapy with potassium-sparing diuretics, such as spironolactone, triamterene, amiloride (see **section 4.5**).
- Lithium therapy – concomitant administration with **ZAARIO PLUS** may lead to toxic blood concentrations of lithium (see **section 4.5**).

- The concomitant use of **ZAARIO PLUS** with renin inhibitors-containing products, such as aliskiren is contraindicated (see **sections 4.4 and section 4.5**).
- Porphyria.
- Patients with Addison's disease.
- Paediatric use- safety and efficacy have not been established in children.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **ZAARIO PLUS**, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (See **sections 4.3 and 4.6**).

Hypotension and electrolyte/fluid imbalance:

Symptomatic hypotension may occur after initiation of therapy with **ZAARIO PLUS**. Patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics) may experience hypotension. Volume depletion and electrolyte imbalances should be corrected prior to administration of **ZAARIO PLUS** 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. The plasma concentrations of potassium and creatinine clearance values should be closely monitored, especially in patients with heart failure and a creatinine clearance between 30-50 ml/min.

Hepatic and renal impairment:

ZAARIO PLUS is not recommended for patients with hepatic impairment.

ZAARIO PLUS is contraindicated in severe renal impairment (see **sections 4.2 and 4.3**).

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 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 uraemia and (less frequently) with acute renal failure and/or death. Similar outcomes are likely with **ZAARIO PLUS** therapy.

Other medicines affecting the renin-angiotensin system, including **ZAARIO PLUS**, may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney (see **section 4.3**).

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

ZAARIO PLUS should not be used concomitantly with aliskiren (see **section 4.3**).

Metabolic and endocrine effects:

Patients with diabetes mellitus or hyperglycaemia may require dosage adjustments of antidiabetic medicines, as **ZAARIO PLUS** may impair glucose tolerance.

Hydrochlorothiazide, as contained in **ZAARIO PLUS**, may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Hydrochlorothiazide, as contained in **ZAARIO PLUS** should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy. Hydrochlorothiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide, as in **ZAARIO PLUS**, attenuates the diuretic-induced hyperuricaemia.

Patients with allergy or bronchial asthma:

Hypersensitivity reactions to hydrochlorothiazide may occur in patients suffering from allergy or bronchial asthma.

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 should be avoided (see **section 4.5**).

Systemic lupus erythematosus:

ZAARIO PLUS may exacerbate or activate systemic lupus erythematosus.

Primary hyperaldosteronism:

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

Heart failure:

Caution is advised in patients with heart failure (with or without renal impairment). There is a risk of severe arterial hypotension and renal impairment involved.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:

Caution is advised in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy**.**

Ethnic differences:

Lorsartan, as in **ZAARIO PLUS**, and the other angiotensin antagonists are 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.

Non-melanoma skin cancer

Pharmaco-epidemiological studies have shown an increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative doses of hydrochlorothiazide (HCTZ), as in **ZAARIO PLUS**.
Photosensitising actions of the HCTZ in **ZAARIO PLUS** could act as a possible mechanism of NMSC.

Patients taking **ZAARIO PLUS** should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions, as well as changes to existing ones and promptly report any suspicious skin lesions. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies.

Patients should be advised to limit exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimise the risk of skin cancer. The use of **ZAARIO PLUS** may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Information of excipients of ZAARIO PLUS:

ZAARIO PLUS contains lactose monohydrate.

Patients with the rare hereditary conditions of lactose or galactose intolerance total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Losartan potassium

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 renin inhibitors, such as 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**).

Potassium-sparing diuretics, potassium-containing medicines or potassium supplements used concurrently with **ZAARIO PLUS** may result in

hyperkalaemia since reduction of aldosterone production induced by **ZAARIO PLUS** may lead to elevation of serum potassium.

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 PLUS** (see **section 4.3**).

Nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase-2 inhibitors, may reduce the effect of diuretics and the antihypertensive effect of **ZAARIO PLUS**. Caution should be used in patients taking NSAIDs concomitantly with **ZAARIO PLUS** as the risk of renal impairment may be increased, particularly in those who are not well hydrated. Patients taking NSAIDs concomitantly with **ZAARIO PLUS** should be adequately hydrated and renal function should be monitored.

Rifampicin and fluconazole have been reported to reduce levels of active metabolite, however the clinical responses of the interactions have not been evaluated.

Hydrochlorothiazide

When administered concurrently the following medication may interact with hydrochlorothiazide, as contained in **ZAARIO PLUS**:

Alcohol, analgesics, or barbiturates – Concurrent use with hydrochlorothiazide may potentiate orthostatic hypotension.

Antidiabetic medicines (oral medicines and insulin) – Hydrochlorothiazide may increase blood glucose concentrations. Dosage adjustment of the antidiabetic medicine may be required.

Other antihypertensive medicines – Additive hypotensive effect or potentiation.

Cholestyramine and colestipol resins – The absorption of hydrochlorothiazide may be reduced. **ZAARIO PLUS** should be administered at least one hour before.

Corticosteroids or adrenocorticotrophic hormone (ACTH) – Concurrent use with hydrochlorothiazide may aggravate electrolyte depletion, particularly hypokalaemia.

Beta$_2$-agonists – Enhancement of potassium depleting effect of hydrochlorothiazide.

Sympathomimetics, such as norepinephrine (noradrenaline) – Concurrent use may decrease the response to sympathomimetic medicines.

Neuromuscular blocking medicines – Concurrent use of hydrochlorothiazide may increase the responsiveness to nondepolarising skeletal muscle relaxants, such as atracurium and tubocurarine.

Lithium – Concurrent use of hydrochlorothiazide may reduce the renal clearance of lithium and increase the risk of lithium toxicity.

Nonsteroidal anti-inflammatory drugs (NSAIDs) – May reduce the diuretic, natriuretic and antihypertensive effects of diuretics (see **section 4.3**).

Probenecid, sulfinpyrazone and allopurinol – Concurrent use of hydrochlorothiazide, as contained in **ZAARIO PLUS** may raise the level serum uric acid. A dosage adjustment of probenecid or sulfinpyrazone may be necessary. Coadministration of **ZAARIO PLUS** may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic medicines – Concurrent use with hydrochlorothiazide, as contained in **ZAARIO PLUS**, increases the bioavailability to thiazide-type diuretics by decreasing gastrointestinal mobility and stomach emptying rate.

Cytotoxic medicines – Concurrent use of hydrochlorothiazide, as contained in **ZAARIO PLUS**, may reduce the renal excretion of cytotoxic medicines and potentiate the myelosuppressive effects.

Salicylates – In the event of high dosages of salicylates hydrochlorothiazide, as contained in **ZAARIO PLUS**, may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa – Concurrent use with hydrochlorothiazides, as contained in **ZAARIO PLUS**, may result in haemolytic anaemia in isolated cases and caution is advised.

Ciclosporin – Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout type complications.

Digitalis glycosides – Thiazide-induced hypokalaemia or hypomagnesaemia can initiate digitalis-induced cardiac dysrhythmias during concomitant treatment with **ZAARIO PLUS**.

Medicinal products affected by serum potassium disturbances – Periodic monitoring of serum potassium and electrocardiogram (ECG) is recommended when **ZAARIO PLUS** is used concomitantly with medicines affected by serum potassium disturbances (e.g. digitalis glycosides and antidysrhythmic medicines), and with the following torsades de pointes (ventricular tachycardia)-inducing medicines (including some antidysrhythmic medicines), hypokalaemia being a predisposing factor to torsades de pointes.

- Class Ia antidysrythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antidysrythmics (e.g. amiodarone, sotalol)
- Some antipsychotics (amisulpride, haloperidol, sulpiride)
- Others (e.g bepridil, cisapride, diphemanil, erythromycin IV, halofatrin, mizolastin, pentamide, terfendadine, vincinamide IV)

Calcium salts – Concurrent use with hydrochlorothiazides, as contained in **ZAARIO PLUS**, may increase serum calcium levels due to decreased excretion.

Carbamazepine – Concurrent use may impose a risk of symptomatic hyponatremia and therefore monitoring is required.

Iodine contrast media – In the event of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before administration.

Amphotericin B (parenteral), corticosteroids, adrenocorticotrophic hormone (ACTH), stimulant laxatives to glycyrrhizin –

Hydrochlorothiazide, as contained in **ZAARIO PLUS**, may intensify electrolyte imbalance, particularly hypokalaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy:

ZAARIO PLUS should not to be used in pregnancy (see **section 4.3**).

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

Women of childbearing potential:

Women of childbearing age should ensure adequate contraception.

ZAARIO PLUS should be discontinued as soon as possible, when pregnancy is planned or suspected (see **sections 4.3 and 4.4**).

Lactation:

Safety has not been established. **ZAARIO PLUS** should not be used during breastfeeding (see **section 4.3**).

4.7 Effects on the ability to drive and use machines

ZAARIO PLUS is not likely to impair the ability to drive and use machinery. However, patients should be advised not to drive, operate machinery, or do anything else that requires attention until they know how **ZAARIO PLUS** affects them.

4.8 Undesirable effects

Losartan potassium

The following adverse reactions have been reported for losartan in clinical studies and in post-marketing experience:

Blood and the lymphatic system disorders:

Less frequent: neutropenia, anaemia, Henoch-Schönlein purpura, ecchymosis,haemolysis

Frequency unknown: thrombocytopenia

Immune system disorders:

Less frequent: anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue; in some of these patients angioedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors

Metabolism and nutrition disorders:

Less frequent: anorexia, gout

Psychiatric disorders:

Frequent: insomnia

Less frequent: anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment

Nervous system disorders:

Frequent: headache, dizziness

Less frequent: fatigue, nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope

Frequency unknown: dysgeusia

Eye disorders:

Less frequent: blurred vision, burning/stinging eye, decrease in visual acuity, conjunctivitis

Ear and labyrinth disorders:

Less frequent: vertigo, tinnitus

Cardiac disorders:

Less frequent: hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitation, arrhythmias (atrial fibrillations, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation)

Vascular disorders:

Less frequent: vasculitis

Frequency unknown: dose related orthostatic effects

Respiratory, thoracic and mediastinal disorders:

Frequent: cough, pharyngitis, nasal congestion, sinus disorder, sinusitis, upper respiratory infection, sinus disorder

Less frequent: pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion

Gastrointestinal disorders:

Frequent: diarrhoea, nausea, abdominal pain, dyspepsia

Less frequent: gastrointestinal disturbances, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting, obstipation

Frequency unknown: pancreatitis

Hepatobiliary disorders:

Frequency unknown: liver function abnormalities

Skin and subcutaneous tissue disorders:

Less frequent: rash, urticaria, pruritus, ecchymosis, alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, sweating

Musculoskeletal, connective tissue and bone disorders:

Frequent: back pain, muscle cramps, myalgia, leg pain

Less frequent: arthralgia, arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness

Frequency unknown: rhabdomyolysis

Renal and urinary disorders:

Frequent: renal impairment, renal failure

Less frequent: impaired renal function, nocturia, urinary frequency, urinary tract infection

Reproductive system and breast disorders:

Less frequent: decreased libido, erectile dysfunction/impotence

General disorders and administrative site conditions:

Frequent: asthenia/fatigue, oedema/swelling, chest pain

Less frequent: facial oedema, fever, malaise

Frequency unknown: flu-like symptoms

Investigations:

Frequent: hyperkalaemia, elevated alanine aminotransferase ALT, mild reduction of haemacrit and haemoglobin, hypoglycaemia

Less frequent: mild increase with urea and creatinine serum levels, increase in hepatic enzymes and bilirubin,

Frequency unknown: hyponatraemia

Hydrochlorothiazide

The following adverse reactions have been reported for hydrochlorothiazide in clinical studies and in post-marketing experience:

Blood and the lymphatic system disorders:

Less frequent: thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, purpura, aplastic anaemia

Immune system disorders:

Less frequent: anaphylactic reaction

Metabolism and nutrition disorders:

Less frequent: anorexia, hyperuricaemia, hyperglycaemia, hyponatraemia, hypokalaemia

Psychiatric disorders:

Less frequent: restlessness, insomnia

Nervous system disorders:

Frequent: cephalgia

Less frequent: paraesthesia, headache

Eye disorders:

Frequency unknown: yellow vision (xanthopsia), transient blurred vision

Vascular disorders:

Less frequent: hypotension (including orthostatic hypotension), necrotizing angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal *disorders:*

Less frequent: respiratory distress, including pneumonitis and pulmonary oedema

Gastrointestinal disorders:

Less frequent: sialadenitis, nausea, vomiting, diarrhoea, constipation, pancreatitis, gastric irritation, spasms, stomach irritation

Hepatobiliary disorders:

Less frequent: jaundice (intrahepatic cholestatic jaundice), icterus (intrahepatic cholestasis), pancreatitis

Skin and subcutaneous tissue disorders:

Less frequent: rash, urticaria, photosensitivity, toxic epidermal necrolysis

Frequency unknown: cutaneous lupus erythematosus

Musculoskeletal, connective tissue and bone disorders:

Less frequent: muscle cramps

Neoplasms benign, malignant and unspecified (incl. cysts and polyps):

Frequency unknown: Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)

Renal and urinary disorders:

Less frequent: glucosuria, interstitial nephritis, renal dysfunction, renal failure

General disorders and administrative site conditions:

Less frequent: fever, dizziness

Frequency unknown: weakness

Losartan potassium and hydrochlorothiazide

Nervous system disorders:

Frequent: dizziness

General disorders and administrative site conditions:

Frequent: asthenia/fatigue.

Post marketing studies:

Blood and the lymphatic system disorders:

Frequency unknown: Thrombocytopenia

Immune system disorders:

Frequency unknown: 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 rarely in patients treated with losartan; some of these patients previously experienced angioedema with other medicine including ACE - inhibitors

Vascular disorders:

Frequency unknown: Vasculitis, including Henoch-Schoenlein purpura

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Cough

Gastrointestinal disorders:

Frequency unknown: Diarrhoea, vomiting

Hepatobiliary disorders:

Less Frequent: Hepatitis

Skin and subcutaneous tissue disorders:

Frequency unknown: Urticaria, erythroderma has been reported with losartan.

Photosensitivity has been reported with losartan and hydrochlorthiazide as contained in **ZAARIO PLUS.**

Investigations:

Less Frequent: Hyperkalaemia, elevation of ALT

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ZAARIO PLUS is important. It allows continued monitoring of the benefit/risk balance of ZAARIO PLUS. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

Report all side effects to Unicorn Pharmaceuticals (Pty) Ltd to

enquiries@unicornpharma.co.za

By reporting side effects, you can help provide more information on the safety of ZAARIO PLUS.

4.9 Overdose

Losartan potassium

The most likely symptoms of an overdose 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.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digoxin has also been administered, hypokalaemia may accentuate cardiac dysrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological Class: A 7.1.3 Vascular medicines - other hypotensives

5.1 Pharmacodynamic properties

Pharmacodynamic properties:

ZAARIO PLUS is a combination of losartan potassium (an angiotensin II receptor type AT1 antagonist) and hydrochlorothiazide (a diuretic).

Losartan potassium

Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system and a major determinant of the pathophysiology of hypertension. Losartan is a synthetic angiotensin II receptor antagonist with high affinity and selectivity for the AT_1 receptor Losartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by inhibiting the binding of angiotensin II to the AT_1 receptor.

Losartan is a specific antagonist of the angiotensin II receptor type AT_1; it does not inhibit angiotensin-converting enzyme (ACE) (kininase II), the enzyme that degrades bradykinin. 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.

Hydrochlorothiazide

Hydrochlorothiazide is a diuretic and antihypertensive medicine**.** The mechanism of the antihypertensive effect of thiazides is unknown. It affects the distal renal tubular mechanism of electrolyte reabsorption, increasing the excretion of sodium and chloride ions in approximately equivalent amounts, and consequently of water.

Natriuresis may be accompanied by some loss of potassium, magnesium and bicarbonate.

Losartan potassium-hydrochlorothiazide

Losartan and hydrochlorothiazide are additive in their anti-hypertensive efficacy.

5.2 Pharmacokinetic properties:

Losartan potassium

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. The mean peak concentrations of losartan and its active metabolite are reached in 1 hour and 3 to 4 hours respectively.

Distribution:

Both losartan and the carboxylic acid metabolite are greater than, or equal to 99 % bound to plasma proteins, primarily albumin. The distribution volume of losartan is 34 litres.

Metabolism:

Metabolism is primarily by cytochrome P450 isoenzymes CYP2C9 and CYP3A4. About 14 % of an orally administered dose is converted to its active metabolite.

Elimination:

The terminal half-life of losartan is about 2 hours and that of its active metabolite is 6 to 9 hours.

Losartan is excreted in the urine, and in the faeces, as unchanged losartan and metabolites. Following oral dosing, 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.

Patients with renal impairment:

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.

Patients with hepatic impairment:

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.

Hydrochlorothiazide

The oral bioavailability is about 70 %. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney; > 95 % is excreted via urine. The plasma half-life has been observed to vary between 5,6 and 14,8 hours after 24 hours of observation. At least 61 % of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental barrier but not the blood-brain barrier.

Losartan potassium-hydrochlorothiazide

In a pharmaceutical study 12,5 mg hydrochlorothiazide does not alter the pharmacokinetics of 50 mg losartan and vice versa.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients:

Lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch and Opadry Yellow (containing [titanium dioxide, hypromellose, hydroxypropyl cellulose, Quinoline Yellow aluminium lake colourant] hydroxypropyl cellulose, hypromellose, Quinoline Yellow aluminium lake colourant, titanium dioxide).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 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

Silver-grey aluminium/aluminium blister strips containing 10 tablets each.

Each outer carton contains 3 blister strips of 10 tablets each.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharaceuticals (Pty) Ltd

Corner of Searle & Pontac Streets

Cape Town

South Africa 8001

8. REGISTRATION NUMBER

ZAARIO PLUS 50/12,5: A 46/7.1.3/0712

ZAARIO PLUS 100/25: A 46/7.1.3/0713

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 October 2021

10. DATE OF REVISION OF THE TEXT

Not applicable.