SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ZARTAN 12,5 mg film coated tablets

ZARTAN 25 mg film coated tablets

ZARTAN 50 mg film coated tablets

ZARTAN 100 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ZARTAN 12,5 mg film coated tablet contains 12,5 mg losartan potassium

Each ZARTAN 25 mg film coated tablet contains 25 mg losartan potassium

Each ZARTAN 50 mg film coated tablet contains 50 mg losartan potassium

Each ZARTAN 100 mg film coated tablet contains 100 mg losartan potassium

ZARTAN contains mannitol (50,95 mg, 101,90 mg, 203,80 mg and 407,60 mg in ZARTAN 12,5 mg, 25 mg, 50 mg and 100 mg respectively).

ZARTAN is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

ZARTAN 12,5 mg is a white, coated, round biconvex 6 mm tablet embossed “1L”.

ZARTAN 25 mg is a white, coated, round biconvex 8 mm tablet embossed “2L”.

ZARTAN 50 mg is a white, coated, round biconvex, scored 10 mm tablet embossed “3L”.

ZARTAN 100 mg is a white, coated, oval biconvex 9,2 x 18,3 mm tablet embossed “4L”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZARTAN 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

Hypertension

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

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. ZARTAN may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha-

or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Special populations

Patients with intravascular volume-depletion

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).

Renal impairment

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

Hepatic impairment

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

Elderly

No dose adjustment is necessary in elderly patients.

Paediatric population

Safety and efficacy in children has not been established.

Method of administration

For oral use.

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

ZARTAN may be administered with or without food.

Missed dose

Doctors should advise patients who forget to take ZARTAN to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- Hypersensitivity to losartan potassium or to any of the ingredients of ZARTAN (see section 6.1).
- Concomitant use of fluoroquinolones with Angiotensin receptor blockers, such as ZARTAN, is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance ≤ 30 mL/min) and in elderly patients.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 mL/min) or for patients with hepatic impairment.

- 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, amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with ZARTAN may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- The concomitant use of ZARTAN with renin inhibitors, such as aliskiren-containing products, is contraindicated (see section 4.4).

Paediatric use

The safety and efficacy in children has not been established.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving ZARTAN, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see 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 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 ZARTAN and renin

inhibitors such as aliskiren, is therefore contraindicated (see section 4.3). ZARTAN should not be used concomitantly with renin inhibitors such as aliskiren (see section 4.3).

Fluoroquinolones

Concomitant use of fluoroquinolones and ARBs, such as ZARTAN, 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 fluroquinolones or ARBs, such as ZARTAN, whether used separately and/or concomitantly.

Volume depletion

Patients with volume-depletion (e.g. those treated with high-dose diuretics) may experience hypotension, which may be minimised by initiating treatment with a low dose of ZARTAN. Halving of the dose should be considered for patients with a history of hepatic impairment (see section 4.2).

Electrolyte imbalance

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 generally be avoided (see section 4.5).

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. These changes in renal function may be reversible upon discontinuation of ZARTAN
therapy, in some patients.

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 are likely with ZARTAN therapy.

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. These changes in renal function may be reversible upon discontinuation of ZARTAN therapy.

Liver function 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).

Porphyria

Limited information is available regarding the effect of antihypertensive medicines in patients with porphyria. Safety of losartan in patients with porphyria has not been fully established and is therefore contraindicated (see section 4.3).

Information on excipients of ZARTAN

ZARTAN contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or 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).

Combinations containing any of the following medicines, depending on the amount present, may also interact with ZARTAN:

Fluoroquinolones

Concomitant use of fluoroquinolones and ARBs, such as ZARTAN 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).

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) (selective COX-2 inhibitors, acetylsalicylic acid and at anti-inflammatory doses and non-selective NSAIDs) may antagonise the antihypertensive effect of ZARTAN. Concomitant use may lead to an increased risk of worsening renal function, including possible acute renal failure and an increase in serum potassium, especially in patients with poor pre-existing renal function. 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.

Sympathomimetics

Concurrent use with sympathomimetics may reduce the antihypertensive effects of ZARTAN.

Potassium

Potassium-sparing diuretics, potassium containing medicine or potassium supplements used concurrently with ZARTAN may result in hyperkalaemia since reduction of aldosterone production induced by ZARTAN may lead to elevation of serum potassium.

Concomitant use with medicines which retain potassium (e.g. amiloride, triamterene, spironolactone) or increase potassium levels (e.g. heparin), and/or potassium salt substitutes containing potassium may lead to increases in serum potassium and co-medication is not advised.

Lithium

Concomitant administration of lithium with ZARTAN may increase serum lithium concentrations and toxicity. Co-administration should be with caution and serum lithium levels should be monitored.

In clinical pharmacokinetic trials, no interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital, ketoconazole and erythromycin.

Rifampin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing age should ensure effective contraception.

Pregnancy

Safety in pregnancy and lactation has not been established (see section 4.3).

When pregnancy is planned or confirmed, ZARTAN should be discontinued.

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

Breastfeeding

It is not known whether losartan is excreted in human milk. Safety of breast feeding in mothers taking ZARTAN has not been established. However, significant levels of losartan and the active metabolite

were shown to be present in rat milk (see section 4.3.).

4.7 Effects on ability to drive and use machines

Dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased. Patients should be advised to be cautious when driving vehicles or operating machinery or performing potentially hazardous tasks until they are reasonably certain that their performance is not affected by ZARTAN.

4.8 Undesirable effects

Summary of the safety profile

Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequent	Upper respiratory tract infections
Blood and lymphatic system disorders	Less frequent Frequency unknown	Symptomatic anaemia, decreased haemoglobin concentrations Neutropenia, thrombocytopenia
Immune system disorders	Less frequent	Angioedema (involving swelling of the face, lips, and / or tongue), anaphylaxis, vasculitis
Endocrine disorders	Less frequent	Acute pancreatitis
Psychiatric disorders	Frequent	Insomnia
Nervous system disorders	Frequent Less frequent	Headache, vertigo Dizziness, migraine, dysgeusia
Cardiac disorders	Less frequent	Palpitations, tachycardia
Vascular disorders	Less frequent Frequency unknown	Hypotension Oedema /swelling, vasculitis, including Henoch-Schönlein purpura
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, nasal congestion, pharyngitis, sinus disorder
Gastrointestinal disorders	Less frequent Frequency unknown	Diarrhoea, dyspepsia, nausea, abdominal pain Taste disturbances, complete taste loss, vomiting

Hepatobiliary disorders	Frequency unknown	Raised liver enzymes values, severe acute hepatotoxicity, cholestasis, hepatitis
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Urticaria, rash Pruritus, erythroderma, photosensitivity, atypical cutaneous lymphoid infiltrates
Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Back pain, muscle cramps, leg pain Myalgia, arthralgia
Renal and urinary disorders	Frequency unknown	Impaired renal function
Reproductive system and breast disorders	Frequency unknown	Erectile dysfunction, impotence
General disorders and administrative site conditions	Frequent Frequency unknown	Asthenia/fatigue, chest pain, oedema/swelling Malaise*
Investigations	Frequent Frequency unknown	Hyperkalaemia, elevations of alanine amino transferase (ALT), hyponatraemia Liver function abnormalities

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8.

An email can be sent directly to the company,

pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

The symptoms of an overdosage of ZARTAN would be hypotension and tachycardia.

Bradycardia could occur from parasympathetic (vagal) stimulation.

Management of overdose:

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain

ATC code: C09CA01

Pharmacological classification: A 7.1.3 Other hypotensives

Mechanism of action

Losartan is a non-peptide angiotensin II receptor antagonist with high affinity and selectivity for the AT1 receptor, without binding to or blocking other hormone receptors or ion channels important in cardiovascular regulation. Angiotensin II is a potent vasoconstrictor, a primary active hormone of the renin-angiotensin system and a major determinant of the pathophysiology of hypertension. Losartan blocks the

vasoconstrictor and aldosterone-secreting effects of angiotensin II by inhibiting the binding of angiotensin II to the AT1 receptor.

Losartan is a specific antagonist of the angiotensin II receptor type AT1; it does not inhibit 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. 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 an intravenously or 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 metabolites are greater than, or equal to 99 % bound to plasma proteins. The distribution volume of losartan is 34 litres.

Biotransformation:

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

Elimination:

The terminal half-life of losartan is 2 hours and its active metabolite is 6 - 9 hours. Losartan is excreted in the urine, and in the faeces, as unchanged active ingredients and metabolites. Following oral dosing, about 35 % of the dose is excreted in the urine and about 58 % in the faeces. Neither losartan nor the active metabolite can be removed by haemodialysis.

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 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

Tablet core:

Croscarmellose sodium

Magnesium stearate

Mannitol

Microcrystalline cellulose

Povidone

Film coating:

Hypromellose

Propylene glycol

Purified talc

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place at or below 25 ºC.

Keep blisters in carton until required for use.

6.5 Nature and contents of container

ZARTAN 12,5, 25, 50 and 100 mg tablets are packed in PVC/PVDC/Aluminium blister strips of 10 tablets. Three strips will be packed in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

ZARTAN 12,5 mg: A41/7.1.3/0288

ZARTAN 25 mg: A41/7.1.3/0286

ZARTAN 50 mg: A41/7.1.3/0287

ZARTAN 100 mg: A41/7.1.3/0289

9. DATE OF FIRST AUTHORISATION

Date of registration: 07 November 2011

10. DATE OF REVISION OF THE TEXT

30 August 2023

NAMIBIA

ZARTAN 12,5 mg: NS2 08/7.1.3/0065

ZARTAN 25 mg: NS2 08/7.1.3/0066

ZARTAN 50 mg: NS2 08/7.1.3/0067

ZARTAN 100 mg: NS2 08/7.1.3/0086