APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ZARTAN CO 50/12,5 film coated tablets

ZARTAN CO 100/25 film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZARTAN CO 50/12,5: Each tablet contains 50 mg losartan potassium and 12,5 mg hydrochlorothiazide.

ZARTAN CO 100/25: Each tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

ZARTAN CO tablets contain sugar (lactose monohydrate) in the following quantities: ZARTAN CO 50/12,5 (70,31 mg), ZARTAN CO 100/25 (140,61 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

ZARTAN CO 50/12,5: Round, yellow film coated tablets with a diameter of 7,5 mm.

ZARTAN CO 100/25: Round, yellow film coated tablets with a diameter of 10,5 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The usual starting and maintenance dose is one tablet of ZARTAN CO 50/12,5 once daily. For patients who do not respond adequately, the dosage may be changed to one tablet of ZARTAN CO 100/25 once daily.

The maximum dose is one tablet of ZARTAN CO 100/25 once daily. The maximum antihypertensive effect is attained within three weeks after initiation of therapy.

Special populations

ZARTAN CO should not be initiated in patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics).

Hepatic or renal impairment:

ZARTAN CO should not be considered for patients with a history of hepatic or moderate to severe renal impairment (see sections 4.3 and 4.4).

Elderly patients:

No initial dosage adjustment is necessary for elderly patients. A higher dose (100 mg losartan and 25 mg hydrochlorothiazide) should not be used as initial therapy in the elderly.

Paediatric population

Not applicable.

Method of administration

ZARTAN CO may be administered with other antihypertensive medicines, particularly calcium channel blockers and beta-blockers. ZARTAN CO can be administered with or without food.

Missed dose

Doctors should advise patients who forget to take ZARTAN CO 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, hydrochlorothiazide,

other sulphonamide-derived substances or to any of the ingredients of ZARTAN CO (see section 6.1)

- patients with a history of previous and/or current basal cell carcinoma and/or squamous cell carcinoma of the skin and lip
- anuria or severe renal function impairment (creatinine clearance< 30 mL/min) - hydrochlorothiazide may produce cumulative effects or precipitate uraemia
- severe hepatic impairment
- cholestasis and biliary obstructive disorders - increased plasma concentrations may occur. ZARTAN CO is not recommended since dose titration with losartan is needed
- paediatric use – the safety and efficacy of ZARTAN CO have not been established in paediatric patients
- a history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs). Such 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
- concomitant use of fluoroquinolones with Angiotensin Receptor Blockers (ARBs), such as ZARTAN CO, is contraindicated in patients with moderate to severe renal impairment (Creatinine clearance ≤30 mL/min) and in elderly patients

- aortic stenosis
- concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5)
- porphyria
- hydrochlorothiazide in combination with losartan, as in ZARTAN CO, should not be given to patients with Addison's disease
- lithium therapy: concomitant administration with ZARTAN CO may lead to toxic blood concentrations of lithium
- therapy resistant hypokalaemia or hypercalcaemia
- refractory hyponatraemia
- the concomitant use of ZARTAN CO with renin inhibitors such as aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m^2) (see sections 4.4 and 4.5)
- pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

ZARTAN CO treatment may cause foetal injury.

Should a woman become pregnant while receiving ZARTAN CO, the treatment must be stopped promptly and changed to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Should a woman contemplate pregnancy, the doctor should consider alternative medication (see section 4.6).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Hypotension, syncope, stroke, hyperkalaemia and changes in renal function (including acute renal failure) have been reported with ZARTAN CO in susceptible individuals, especially if combining medicines that affect this system. Dual blockade of the renin-angiotensin-aldosterone system by combining an angiotensin II receptor blocker, such as ZARTAN CO, with an angiotensin converting enzyme inhibitor (ACEI) or aliskiren is therefore not recommended.

Dual blockade of RAAS through the combined use of ZARTAN CO and aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m^2) (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.

Hypotension and electrolyte/fluid imbalance

Patients who are sodium or volume depleted (e.g. those who have received high-dose diuretics). Symptomatic hypotension may occur following the initiation of therapy with ZARTAN CO. Sodium - or volume depletion should be corrected before initiating therapy or a lower starting dose should be used (see section 4.2). Periodic determination of serum electrolytes must be performed at appropriate intervals.

Patients with electrolyte imbalances - the condition may be exacerbated. The correction of electrolyte imbalance prior to administration of ZARTAN CO is recommended.

Metabolic and endocrine effects

Dosage adjustment of anti-diabetic medicines, including insulin, may be required (see section 4.5), as hydrochlorothiazide may impair glucose therapy.

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

Increases in cholesterol and triglyceride levels may be associated with hydrochlorothiazide 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 ZARTAN CO, attenuates the diuretic-induced hyperuricaemia.

Concomitant use with Lithium

Concomitant administration of lithium may lead to toxic blood concentrations of lithium (see sections 4.3 and 4.5).

Hepatic and renal impairment

ZARTAN CO is not recommended for patients with hepatic impairment or severe renal impairment (see section 4.3 and section 4.2). As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported.

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

ZARTAN CO 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 lorsartan (see section 4.3).

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 sections 4.3 and 4.5).

Renal transplantation

There is no experience in patients with recent kidney transplantation.

Ethnic differences

ZARTAN CO may be less effective in lowering blood pressure in black patients than in non-black patients, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Hypersensitivity

Hypersensitivity reactions may occur, with or without a history of allergy or bronchial asthma, in patients receiving hydrochlorothiazide. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of hydrochorothiazide, as contained in ZARTAN CO.

Non-Melanoma Skin Cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies. Photosensitising actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking ZARTAN CO should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and

promptly report any suspicious skin lesions. Possible preventive measures such as limited 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. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. ZARTAN CO should not be used by patients who have had previous and/or current basal cell carcinoma and/or squamous cell carcinomas of the skin or lip (see section 4.3).

Primary hyperaldosteronism

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

Coronary heart disease and cerebrovascular disease

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 (often acute) renal impairment.

Information on excipients of ZARTAN CO

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

ZARTAN CO contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

The anti-hypertensive effects of ZARTAN CO may be potentiated when taken together with antihypertensive medicines.

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

Losartan potassium

In clinical pharmacokinetic trials no interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (see hydrochlorothiazide, alcohol, barbiturates or narcotics below) ketoconazole and erythromycin.

The concomitant use of ZARTAN CO with renin inhibitors such as aliskiren is contraindicated (see sections 4.3 and 4.4.).

Rifampicin:

Increased metabolism of losartan and its active metabolite. The clinical consequences of this interaction have not been evaluated.

Fluconazole:

Reduces levels of the active metabolite of losartan. The clinical consequences of this interaction have not been evaluated.

Potassium-sparing medicines, potassium supplements or potassium-containing salt substitutes:

An additive hyperkalaemic effect is possible with concomitant use of medicines that block angiotensin II or its effects, with potassium supplements, potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), or salt substitutes containing potassium and other medicines that may increase serum potassium (e.g. trimethoprim-containing products) may lead to increases in serum potassium and can cause hyperkalaemia (see section 4.3).

Lithium:

Lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully, if lithium salts are co-administered with losartan.

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective COX-2 inhibitors, acetylsalicylic acid (aspirin) at anti-inflammatory doses and non-selective NSAIDs:

May attenuate the antihypertensive effect of losartan. Concomitant use of ZARTAN CO 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.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor blockers, as contained in ZARTAN CO, may result in a further deterioration of renal function.

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

Studies 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 4.3 and 4.4).

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

Hydrochlorothiazide

Alcohol, analgesics, or barbiturates:

Concurrent use with hydrochlorothiazide may potentiate orthostatic hypotension.

Anti-diabetic medicines (oral medicines and insulin):

Hydrochlorothiazide may increase blood glucose concentrations. Dosage adjustment of the anti-diabetic medicine may be required.

Other antihypertensive medicines:

Additive hypotensive effect or potentiation.

Cholestyramine and colestipol resins:

The absorption of hydrochlorothiazide may be reduced in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. ZARTAN CO should be administered at least one hour before.

Corticosteroids or ACTH Amphotericin B (parenteral), stimulant laxatives, or glycyrrhizin (found in liquorice):

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 and Non-depolarising skeletal muscle relaxants:

Concurrent use of hydrochlorothiazide may enhance the blockade of non-depolarising neuromuscular blocking medicines, e.g. tubocurarine.

Lithium:

Lithium should not be given with ZARTAN CO. Diuretic medicines reduce the renal clearance of lithium and increase the risk of lithium toxicity.

Refer to the package insert for lithium preparations before use of such preparations with ZARTAN CO (see section 4.3).

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclo-oxygenase-2 inhibitors (COX-2 inhibitors):

May reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium-sparing and hydrochlorothiazide diuretics.

Pressor amines (e.g. adrenaline):

The effect of presser amines may be decreased but not sufficient to preclude their use.

Medicines used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol):

Dosage adjustment of uricosuric medicines may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of hydrochlorothiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic medicines (e.g. atropine, biperiden):

Increase of the bioavailability to hydrochlorothiazide by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic medicines (e.g. cyclophosphamide, methotrexate):

Hydrochlorothiazide may reduce the renal excretion of cytotoxic medicines and potentiate their myelosuppressive effects.

Salicylates:

Salicylates: In case of high dosages of salicylates, hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa:

There have been reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Ciclosporin:

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

Digoxin:

Hydrochlorothiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digoxin-induced cardiac dysrhythmias.

Medicines affected by serum potassium disturbances:

Periodic monitoring of serum potassium and ECG is recommended when ZARTAN CO is administered with medicines affected by serum potassium disturbances (e.g. digoxin and antidysrhythmics) and with the following *torsades de pointes* (ventricular tachycardia)-inducing medicines (including some antidysrhythmics), hypokalaemia being a predisposing factor to *torsades de pointes*:

- class la antidysrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- class Ill antidysrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- others (e.g. bepridil, cisapride, diphemanil, erythromycin JV, halofantrin, mizolastin, pentamidine, vincamine IV).

Calcium salts:

Hydrochlorothiazide may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage should be adjusted accordingly.

Laboratory test interactions:

Because of its effects on calcium metabolism, hydrochlorothiazide may interfere with tests for parathyroid function (see section 4.4).

Carbamazepine:

Risk of symptomatic hyponatraemia. Clinical and biological monitoring is required.

Iodine contrast media:

In case 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 the administration.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing age should use effective contraception.

Pregnancy

ZARTAN CO is contraindicated for use during pregnancy (see section 4.3).

When pregnancy is planned or detected, ZARTAN CO should be discontinued.

Not to be used in pregnancy as teratogenicity has been shown in experimental animals. Medicines affecting the renin-angiotensin system, such as ZARTAN CO, can cause foetal and neonatal morbidity and mortality when administered to pregnant women.

Breastfeeding

ZARTAN CO is contraindicated during lactation.

Losartan and hydrochlorothiazide are excreted in breastmilk but their effect on the nursing infant has not been determined. Thiazides in high doses, causing intense diuresis, can inhibit the milk production. Consequently, mothers on ZARTAN CO should not breastfeed their babies.

Fertility

Not applicable.

4.7 Effects on ability to drive and use machines

ZARTAN CO has a moderate influence on the ability to drive and use machines and can cause side effects such as dizziness or drowsiness. During ZARTAN CO administration, patients should be cautioned against driving or operating machinery until they know how ZARTAN CO affects them.

4.8 Undesirable effects

Tabulated summary of adverse reactions: Losartan potassium

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequent	Upper respiratory infection
Blood and lymphatic system disorders	Less frequent	Symptomatic anaemia, decreased haemoglobin concentrations, neutropenia, thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity: anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue
Endocrine disorders	Less frequent	Acute pancreatitis
Metabolism and nutrition disorders	Less frequent Frequency unknown	Anorexia, gout Hyperkalaemia, hyponatraemia
Psychiatric disorders	Frequent Less frequent	Insomnia Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment
Nervous system disorders	Frequent Less frequent Frequency unknown	Headache, dizziness Migraine, asthenia / fatigue, nervousness, paraesthesia, peripheral neuropathy, tremor, syncope Dysgeusia

Eye disorders	Less frequent	Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity
Ear and labyrinth disorders	Less frequent	Vertigo, tinnitus
Cardiac disorders	Less frequent	Palpitations, tachycardia, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, dysrhythmias (atrial fibrillations, sinus bradycardia, ventricular tachycardia, ventricular fibrillation)
Vascular disorders	Less frequent	Hypotension, oedema/swelling, vasculitis, dose related orthostatic effects
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Cough, nasal congestion, pharyngitis, sinus disorder, chest pain Pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion
Gastrointestinal disorders	Frequent Frequency unknown	Abdominal pain, taste disturbances or complete taste loss, diarrhoea, dyspepsia, nausea Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting, obstipation
Hepatobiliary disorders	Less frequent	Raised liver enzymes values, severe acute hepatotoxicity, cholestasis, hepatitis

Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Urticaria, rash, atypical cutaneous lymphoid infiltrates, vasculitis Photosensitivity, psoriasis, alopecia, dermatitis, dry skin, erythema, flushing, pruritus, sweating, Henoch-Schonlein purpura, ecchymosis, haemolysis
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Back pain, muscle cramps, leg pain, myalgia Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness, rhabdomyolysis
Renal and urinary disorders	Frequent Less frequent	Impaired renal function, renal failure 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 Less frequent Frequency unknown	Asthenia/fatigue, chest pain, oedema/swelling Fever Flu-like symptoms, malaise

Investigations	Frequent Less frequent Frequency unknown	Hyperkalaemia, mild reduction of haematocrit and haemoglobin, hypoglycaemia Mild increase in urea and creatinine serum levels, increase in hepatic enzymes and bilirubin Hyponatraemia

Tabulated summary of adverse reactions:

Hydrochlorthiazide

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Frequency unknown	Sialadenitis
Neoplasms benign and malignant (including cysts and polyps)	Frequency unknown	Non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma)
Blood and lymphatic system disorders	Less frequent	Leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, purpura
Immune system disorders	Frequency unknown	Anaphylactic reaction
Endocrine disorders	Less frequent	Pancreatitis
Metabolism and nutrition disorders	Frequent Less frequent Frequency unknown	Electrolyte imbalance (hyponatraemia), hypokalaemia, hypochloraemic alkalosis Anorexia, hyperuricaemia Hyperglycaemia, glycosuria

Psychiatric disorders	Frequent Frequency unknown	Insomnia Restlessness
Nervous system disorders	Frequent Frequency unknown	Cephalalgia Paraesthesia, headache, dizziness
Eye disorders	Frequency unknown	Vision disturbances, xanthopsia
Ear and labyrinth disorders	Frequency unknown	Vertigo
Vascular disorders	Less frequent	Hypotension, including orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent	Respiratory distress including pneumonitis and pulmonary oedema, necrotising angitis (vasculitis)
Gastrointestinal disorders	Less frequent	Gastric irritation, nausea, vomiting, cramping, diarrhoea, constipation
Hepatobiliary disorders	Less frequent	Jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Purpura, photosensitivity, rash, urticaria, toxic epidermal necrolysis, cutaneous vasculitis Cutaneous lupus erythematosus, erythema multiforme, pseudo-porphyria
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Muscle pain or cramps
Renal and urinary disorders	Frequency unknown	Renal dysfunction, interstitial nephritis, renal failure, glycosuria
Pregnancy, puerperium and perinatal conditions	Less frequent	Dizziness, weakness, restlessness

Tabulated summary of adverse reactions: Losartan potassium and hydrochlorothiazide

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequency unknown	Sialadenitis
Blood and lymphatic system disorders	Frequency unknown	Thrombocytopenia, aplastic anaemia
Immune system disorders	Frequency unknown	Anaphylactic reactions, angioedema
Metabolism and nutrition disorders	Frequency unknown	Electrolyte imbalance including hyponatraemia and hypokalaemia
Psychiatric disorders	Frequency unknown	Restlessness
Nervous system disorders	Frequent Frequency unknown	Dizziness Dysgeusia
Eye disorders	Frequency unknown	Xanthopsia, transient blurred vision
Ear and labyrinth disorders	Frequency unknown	Vertigo
Vascular disorders	Frequency unknown	Vasculitis, including Henoch-Schoenlein purpura, hypotension and/or postural hypotension
Gastrointestinal disorders	Frequency unknown	Vomiting, diarrhoea
Hepatobiliary disorders	Frequency unknown	Hepatitis
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Erythroderma, photosensitivity Purpura

Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Arthralgia, cramping, muscle spasm
Renal and urinary disorders	Frequency unknown	Renal dysfunction, interstitial nephritis, renal failure
General disorders and administrative site conditions	Frequent Frequency unknown	Asthenia, fatigue Fever

Description of selected adverse reactions

Non-melanoma skin cancer:

Based on available data from epidemiological studies, a cumulative dose-dependent association between hydrochlorothiazide and non-melanoma skin cancer (BCC and SCC) has been observed.

The largest study included a population comprised of 71 533 cases of BCC and 8 629 cases of SCC matched to 1 430 833 and 172 462 population controls, respectively. High cumulative hydrochlorothiazide use (≥ 50 000 mg) was associated with an adjusted-odds ratio (OR) of 1,29 (95 % CI: 1,23 - 1,35) for BCC and 3,98 (95 % CI: 3,68 - 4,31) for SCC. A cumulative dose-response relationship was observed for both BCC and SCC. Another study evaluated the association between lip cancer (SCC) and exposure to hydrochlorothiazide: 633 cases of lip cancer were matched with 63 067 population controls. A cumulative dose-response relationship was demonstrated with an adjusted OR of 2,1 (95 % CI: 1,7 - 2,6) for ever-use, increasing to an OR of 3,9 (95 % CI: 3,0 - 4,9) for high use (≥ 25 000 mg) and an OR of 7,7 (95 % CI: 5,7 - 10,5) for the highest cumulative dose (≥ 100 000 mg).

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

Losartan potassium signs and symptoms:

The most likely manifestation of overdosage 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. Neither losartan nor the active metabolite can be removed by haemodialysis.

Hydrochlorothiazide signs and symptoms

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.

Management of overdose

No specific information is available on the treatment of overdose with ZARTAN CO. Treatment is symptomatic and supportive. Therapy with ZARTAN CO should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vascular medicines

ATC code: C09DA01

Pharmacological classification: A 7.1.3 Other hypotensives.

Mechanism of action

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

Losartan:

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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.

Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle cell proliferation.

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.

Hydrochlorothiazide:

Hydrochlorothiazide is a thiazide diuretic and antihypertensive medicine, the mechanism of the antihypertensive effect of hydrochlorothiazide is unknown. Hydrochlorothiazide does not usually affect normal blood pressure. It affects the distal renal tubular mechanism of electrolyte reabsorption.

Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium, magnesium and bicarbonate. After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Losartan and Hydrochlorothiazide in combination:

Losartan and hydrochlorothiazide are additive in their antihypertensive efficacy.

5.2 Pharmacokinetic properties

Losartan

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 - 4 hours, respectively.

There was no clinically significant effect on the plasma concentration profile, when losartan was administered with a standardised meal.

Distribution:

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

Biotransformation:

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

Elimination:

Plasma clearance of losartan and its metabolite is about 600 mL/min and 50 mL//min, respectively.

Renal clearance of losartan and its metabolite is about 74 mL/min and 26 mL/min, respectively.

When administered orally, about 4 % of a losartan 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 metabolite are linear with oral losartan doses up to 200 mg.

Losartan is excreted in the urine, and in the faeces via bile, as unchanged losartan and metabolites. Following oral dosing about 35 %

of the dose is excreted in the urine and about 58 % in the faeces. The terminal elimination half-life of losartan is 2 hours and its active metabolite is 6 to 9 hours.

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

Hydrochlorothiazide

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney.

The plasma half-life has been observed to vary between 5,6 and 14,8 hours after 24-hour observation. It is reported to have a bioavailability of about 65 - 70 %. At least 61 % of the oral dose is eliminated unchanged within 24 hours.

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Losartan Potassium-Hydrochlorothiazide

Hydrochlorothiazide 12,5 mg does not alter the pharmacokinetics of losartan 50 mg and vice versa.

Pharmacokinetics in special patient groups

The elderly:

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

Liver disease:

Following oral administration of ZARTAN CO 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.

Kidney disease:

No dosage adjustment is required in patients with mild to moderate renal impairment.

ZARTAN CO is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see section 4.3).

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Pregelatinised maize starch

Film coating:

Hydroxypropyl cellulose

Hypromellose

Titanium oxide

Yellow iron oxide

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 light and moisture.

Do not remove from the outer carton until required for use.

6.5 Nature and contents of container

ZARTAN CO 50/12,5 and ZARTAN CO 100/25 are packed into silver aluminium/clear transparent PVC/PE/PVDC blister packs of 10 tablets.

3 blister strips are packed into a printed outer carton (30 tablets).

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 CO 50/12,5: A42/7.1.3/1068

ZARTAN CO 100/25: A42/7.1.3/1069

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 05 August 2011

10. DATE OF REVISION OF THE TEXT

27 September 2024

NAMIBIA:

ZARTAN CO 50/12,5: NAM NS2 12/7.1.3/0070

ZARTAN CO 100/25: NAM NS2 12/7.1.3/0071

ZAMBIA:

ZARTAN CO 50/12,5: ZAM POM 051/022

APPROVED PROFESSIONAL INFORMATION

ZARTAN CO 100/25: ZAM POM 051/023