Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lotanos Comp 50 mg/12.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of losartan potassium, equivalent to 45.76 mg of losartan, and 12.5 mg of hydrochlorothiazide.

Excipient: 70.31 mg of lactose monohydrate/film-coated tablet.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Round, yellow, film-coated tablet. (diameter 8.1mm)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lotanos Comp 50 mg/12.5 mg film-coated tablets
For the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy.

4.2 Posology and method of administration

Posology
Hypertension

Where possible, titration with the individual components (i.e. losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy with losartan 50 mg or hydrochlorothiazide 12.5 mg to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

The usual maintenance dose is one tablet of Lotanos Comp 50 mg/12.5 mg (losartan 50 mg/HCTZ 12.5 mg) once daily. For patients who do not respond adequately to Lotanos Comp 50 mg/12.5 mg, the dosage may be increased to one tablet of Lotanos Comp 100 mg/25 mg (losartan 100 mg/ HCTZ 25 mg) once daily. The maximum dose is one tablet of Lotanos Comp 100 mg/25 mg once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy. Lotanos Comp 100/12.5 (losartan 100 mg/ HCTZ 12.5 mg) is available for those patients titrated to 100 mg of Losartan who require additional blood pressure control.

Special populations
Use in the elderly:- Dosage adjustment is not usually necessary for the elderly

Use in patients with renal impairment and haemodialysis patient:
No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance 30-50 ml/min). Losartan potassium and hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan/HCTZ tablets must not be used in patients with severe renal impairment (i.e. creatinine clearance ≤30 ml/min) (see section 4.3).

Use in patients with intravascular volume depletion: Losartan / HCTZ should not be used in patients with intravascular volume depletion (e.g., those treated with high-dose diuretics).

Use in patient with hepatic impairment:
Losartan/HCTZ is contraindicated in patients with severe hepatic impairment (see section 4.3).

Paediatric population

Use in children and adolescents (< 18 years): There is no experience in children and adolescents. Therefore, losartan/hydrochlorothiazide should not be administered to children and adolescents.

Method of administration

Losartan potassium/hydrochlorothiazide may be administered with other antihypertensive agents (see sections 4.3, 4.4, 4.5 and 5.1).

The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). Losartan potassium/Hydrochlorothiazide may be administered with or without food.

4.3 Contraindications

- Hypersensitivity to losartan, sulphonamides derivatives (as hydrochlorothiazide) or to any of the excipients listed in section 6.1.
- Therapy resistant hypokalaemia or hypercalcaemia
- Severe hepatic impairment; cholestasis and biliary obstructive disorders
- Refractory hyponatraemia
- Symptomatic hyperuricaemia/gout
- 2nd and 3rd trimesters of pregnancy (see sections 4.4 and 4.6).
- Severe renal impairment (i.e. creatinine clearance < 30 ml/min)
- Anuria
- The concomitant use of Lotanos Comp with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1)

4.4 Special warnings and precautions for use

Losartan

Angiooedema

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

Hypotension and Intravascular volume depletion

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Losartan potassium and Hydrochlorothiazide tablets (see sections 4.2. and 4.3.).

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Therefore, the plasma concentrations of potassium and creatinine clearance values should be closely monitored; especially patients with heart failure and a creatinine clearance between 30-50 ml/ min should be closely monitored.

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

Liver function impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, Losartan potassium and Hydrochlorothiazide tablets should be used with caution in patients with a history of mild to moderate hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore, Losartan potassium and Hydrochlorothiazide tablets is contraindicated in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal function impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system, such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in

renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Renal transplantation
There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan potassium and Hydrochlorothiazide tablets is not recommended.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).
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.

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 - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

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.

Ethnic differences
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black patients than in non-blacks, possibly because of higher prevalence or low-renin states in the black hypertensive population.

Pregnancy:
AIIRAs should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, [including Losartan] (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonist. If intestinal angioedema is diagnosed. Losartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance
As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g., volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia or hypokalaemia which may occur during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustments of antidiabetic agents, including insulin, may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

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

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic induced hyperuricemia.

Hepatic impairment
Thiazide should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Losartan potassium and Hydrochlorothiazide tablets is contraindicated for patients with severe hepatic impairment (see section 4.3 and 5.2).

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 based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ 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 minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Acute Respiratory Toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Lotanos Comp should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Other
In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Excipient
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

As with other drug that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium or other drugs that may increase serum potassium (e.g., trimethoprim-containing products) may lead to increases in serum potassium. Co-medication is not advisable.
As with other medicines which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

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

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 antagonists may result in a further deterioration of renal function. These effects are usually reversible.

Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofen, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.

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 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 agent (see sections 4.3, 4.4 and 5.1).

Hydrochlorothiazide

When given concurrently, the following drugs may interact with thiazide diuretics

Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin):
The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Other antihypertensive drugs
Additive effect.

Colestyramine and colestipol resins
Absorption of hydrochlorothiazide is impaired 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.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.
Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)
Possible increased responsiveness to the muscle relaxant.

Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.

Medicinal products used in the treatment of gout (e.g. probenecid, sulfinpyrazole, allopurinol)
Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazole may be necessary. Co-administration of thiazides may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)
Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

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 isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Cyclosporin:
Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

Digitalis glycosides
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when losartan/hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide).
- Class III antiarrythmics (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 IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

Calcium salts
Thiazide diuretics 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 their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see section 4.4).

Carbamazepine
Risk of symptomatic hyponatremia. 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.

Amphotericin B (parenteral), corticosteroids, ACTH or stimulant laxatives, or glycyrrhizin (found in liquorice)
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy
Angiotensin II Receptor Antagonist (AIIRAs)

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4)

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to AIIRAs therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also section 5.3)

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see section 4.3 and 4.4).

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding
Angiotensin II Receptor Antagonists (AIIRAs)
Because no information is available regarding the use of Lotanos Comp during breastfeeding, Lotanos Comp is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Lotanos Comp during breast feeding is not recommended. If Lotanos Comp is used during breast feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, when driving vehicles or operating machinery 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

The adverse reactions below are classified where appropriate by system organ class and frequency according to the following convention:

Very common: ≥1/10
Common: ≥1/100, <1/10
Uncommon: ≥1/1,000, <1/100

Rare: ≥1/10,000, <1/1,000
Very rare: <1/10,000,
not known: cannot be estimated from the available data.

In clinical trials with losartan potassium salt and hydrochlorothiazide, no adverse events peculiar to this combination of substances were observed. The adverse events were restricted to those which were formerly observed with losartan potassium salt and/or hydrochlorothiazide.

In controlled clinical trials for essential hypertension, dizziness was the only adverse reactions reported as substance-related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan and hydrochlorothiazide.

Next to these effects, there are further adverse reactions reported after the introduction of the product to the market as follows:

Hepato-biliary disorders
rare: Hepatitis

Investigation
rare: Hyperkalaemia, elevation of ALT

Additional adverse reactions that have been seen with one of the individual components and may be potential adverse reactions with losartan potassium/hydrochlorothiazide are the following:

Losartan

Blood and lymphatic system disorders
Uncommon: Anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis

Immune system disorders
Rare: Anaphylactic reactions, angioedema, urticaria

Metabolism and nutrition disorders
Uncommon: Anorexia, gout

Psychiatric disorders
Common: Insomnia
Uncommon: Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment

Nervous system disorders
Common: Headache, dizziness
Uncommon: Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope

Eye disorders
Uncommon: Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity.

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus

Cardiac disorders
Uncommon: 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
Uncommon: Vasculitis

Respiratory, thoracic and mediastinal disorders
Common: Cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder
Uncommon: Pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion

Gastrointestinal disorders
Common: Abdominal pain, nausea, diarrhoea, dyspepsia
Uncommon: Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting
Rare: Intestinal angioedema

Hepatobiliary disorders
Not known: Liver function abnormalities

Skin and subcutaneous tissue disorders
Uncommon: Alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating

Musculoskeletal and connective tissue disorders
Common: Muscle cramp, back pain, leg pain, myalgia
Uncommon: Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness
Not known: Rhabdomyolysis

Renal and urinary disorders
Uncommon: Nocturia, urinary frequency, urinary tract infection

Reproductive system and breast disorders
Uncommon: Decreased libido, impotence

General disorders and administration site conditions
Common: Asthenia, fatigue, chest pain
Uncommon: Facial oedema, fever

Investigations
Common: Hyperkalaemia, mild reduction of haematocrit and haemoglobin
Uncommon: Mild increase in urea and creatinine serum levels
Very rare: Increase in hepatic enzymes and bilirubin.

Hydrochlorothiazide

Blood and lymphatic system disorders
Uncommon: Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia

Immune system disorders
Rare: Anaphylactic reaction

Metabolism and nutrition disorders
Uncommon: Anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia

Psychiatric disorders
Uncommon: Insomnia

Nervous system disorders
Common: Cephalalgia

Eye disorders
Uncommon: Transient blurred vision, xanthopsia
Not known: Choroidal effusion, acute myopia, acute angle-closure glaucoma.

Vascular disorders
Uncommon: Necrotizing angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders
Uncommon: Respiratory distress including pneumonitis and pulmonary oedema

Very rare: Acute respiratory distress syndrome (ARDS) (see section 4.4).

Gastrointestinal disorders
Uncommon: Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation

Hepatobiliary disorders
Uncommon: Icterus (intrahepatic cholestasis), pancreatitis

Skin and subcutaneous tissue disorders
Uncommon: Photosensitivity, urticaria, toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramps

Renal and urinary disorders
Uncommon: Glycosuria, interstitial nephritis, renal dysfunction, renal failure

General disorders and administration site conditions
Uncommon: Fever, dizziness

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).

Description of selected adverse reactions
Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

No specific information is available on the treatment of overdose with Lotanos Comp. Treatment is symptomatic and supportive. Therapy with Lotanos Comp 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.

Losartan
Limited data are available in regard to overdose in humans. The most likely manifestation of overdosage 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, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias

The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, ATC code: C 09 DA 01.

Losartan potassium/hydrochlorothiazide combination

Losartan potassium/hydrochlorothiazide is a combination of an angiotensin II receptor antagonist, losartan potassium, and a thiazide diuretic; hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

The antihypertensive effect of the losartan/hydrochlorothiazide combination is sustained for a 24-hour period.

Losartan

Losartan is a synthetically produced oral angiotensin-II receptor (type AT_1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates the proliferation of smooth-muscle cells.

Losartan selectively blocks the AT_1 receptor. In vitro and in vivo, both losartan and its pharmacologically active carboxylic acid metabolite E-3174 inhibit all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.

Losartan potassium does not possess an agonist action and there is also no blockade of other hormone receptors or ion channels that are important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. There is thus no increase in bradykinin-mediated undesirable effects.

During the administration of losartan, the removal of the angiotensin II negative feedback on renin secretion leads to increased plasma-renin activity (PRA). An increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, the antihypertensive action and suppression of the plasma aldosterone concentration are maintained, which indicates effective angiotensin II receptor blockade. After the discontinuation of losartan, the PRA and angiotensin II values fell to the baseline values within three days.

Both losartan potassium and also its active main metabolite have a much greater affinity for the AT_1 receptor than for the AT_2 receptor. On a weight basis the active metabolite is 10 to 40 times more active than losartan.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

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

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group

Hypertension studies

In controlled clinical studies, once-daily administration of losartan potassium to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurement of blood pressure 24 hours post-dose relative to 5-6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose.

Discontinuation of losartan potassium in hypertensive patients did not result in an abrupt rise in blood pressure (rebound). Despite the marked decrease in blood pressure, losartan potassium had no clinically significant effect on heart rate.

Losartan potassium is equally effective in males and females, and in younger (below the age of 65 years) and older hypertensive patients.

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides effect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts.

The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

Onset of diuresis occurs in 1-2 hours. The diuretic effect persists for 10 - 12 hours depending on the dose, the antihypertensive effect persists for up to 24 hours.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Losartan:

Absorption:
Following oral administration, losartan potassium is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites.
Peak plasma concentrations of losartan potassium and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. The systemic bioavailability of Losartan potassium is approx. 33%.

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

Biotransformation:
About 14% of an intravenously or orally administered dose of losartan potassium is converted to its active metabolite. Following oral and intravenous administration of 14Clabelled losartan potassium, circulating plasma radioactivity is attributed primarily to losartan potassium and its active metabolite. In approximately 1% of the subjects a minimal conversion of losartan potassium to the active metabolite was found.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination:
Plasma clearance of losartan potassium and its active metabolite is approximately 600 ml/minute and 50 ml/minute, respectively. Following oral administration, plasma concentrations of losartan potassium and its active metabolite decline polyexponentially with a terminal half-life of approximately 2 hours and 6-9 hours, respectively.

Renal clearance of losartan potassium and its active metabolite is approximately 74 ml/minute and 26 ml/minute, respectively. When losartan potassium is administered orally, approximately 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. Both biliary and urinary excretion contributes to the elimination of losartan potassium and its metabolites. Following an oral dose of 14C-labelled losartan potassium in man, approximately 35% of radioactivity is recovered in the urine and 58% in the faeces. Following intravenous administration of 14C-labelled losartan potassium, approximately 43% of the radioactivity is recovered in the urine and 50% in the faeces.

Linearity:
The pharmacokinetics of losartan potassium and its active metabolite are linear with oral losartan potassium doses up to 200 mg. During once-daily dosing, neither losartan potassium nor its active metabolite accumulates significantly in plasma.

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

In female hypertensive patients the plasma levels of losartan potassium 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 potassium and its active metabolite after oral administration were respectively 5 and 1.7 times higher than in young male volunteers (see section 4.2 and 4.4).

Plasma concentrations of losartan potassium are not altered in patients with creatinine clearance above 10 ml/minute. Compared to patients with normal renal function, the AUC for losartan potassium is approximately two times greater in haemodialysis patients.

Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients.

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

Hydrochlorothiazide:

Absorption:
Following oral administration hydrochlorothiazide is absorbed from the gastrointestinal tract at about 80%. The systemic availability is about 70%. Peak plasma concentrations are generally measured after 2-5 hours.

Distribution:
The plasma protein binding of hydrochlorothiazide is 64%; the relative volume of distribution is 0.5 to 1.1 l/kg.

Biotransformation:
In normal volunteers, hydrochlorothiazide is excreted renally to more than 95% unchanged.

Elimination:
The elimination half-life is about 6-8 hours with normal renal function. It is increased with impaired renal function and is about 20 hours in terminally renal insufficiency.

Bioavailability:
Concomitant administration of hydrochlorothiazide and losartan does not appear to affect the pharmacokinetics of either active substance in healthy subjects.

The pharmacokinetic parameters AUCinf and Cmax for losartan and its active metabolite E-3174 and AUCinf, Cmax and urinary recovery 0-24 for hydrochlorothiazide were shown to be bioequivalent when the single compounds were compared to the fixed combination product.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of losartan/hydrochlorothiazide was evaluated in chronic toxicity studies for up to six months duration in rats and dogs after oral administration and the changes observed in these studies with

the combination were mainly produced by the losartan component. The administration of the losartan/hydrochlorothiazide combination induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). There was no evidence of teratogenicity in rats or rabbits treated with the losartan/hydrochlorothiazide combination. Foetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F_1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse foetal and neonatal effects, including renal toxicity and foetal death, occurred when pregnant rats were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Microcrystalline cellulose
Pregelatinised maize starch
Lactose monohydrate
Magnesium stearate

Coating:
Hydroxypropylcellulose
Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Transparent aluminium-PVC/PE/PVDC blisters.

Pack sizes:
Blister: 7, 28, 30, 50, 56, 50x1 (unit dose), 90, 98 (clinic pack), 100 (clinic pack) and 112 film-coated tablets.
HDPE bottle with a PP screw cap with an integrated silica gel dessicant in packs of 112 and 120 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowa Pharmaceuticals Limited
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0074/072/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd May 2008
Date of last renewal: 9th January 2013

10 DATE OF REVISION OF THE TEXT

March 2025