SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Losartan potassium/hydrochlorothiazide 100 mg/25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Losartan potassium/hydrochlorothiazide 100 mg/25 mg tablet contains 100 mg of losartan (as potassium salt) and 25 mg of hydrochlorothiazide (HCTZ) as the active ingredients.

Each Losartan potassium/hydrochlorothiazide 100 mg/25 mg tablet contains 60.00 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets

Losartan potassium/hydrochlorothiazide 100 mg/25 mg tablet: Yellow, oblong film-coated tablets scored on one side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Losartan potassium/hydrochlorothiazide is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

4.2 Posology and method of administration

Posology

Hypertension

Losartan and hydrochlorothiazide is not for use as initial therapy, but in patients whose blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone.

Dose titration with the individual components (losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

The usual maintenance dose of Losartan potassium/hydrochlorothiazide is one tablet of Losartan potassium/hydrochlorothiazide 50 mg/12.5 mg (losartan 50 mg/HCTZ 12.5 mg) once daily. For patients who do not respond adequately to Losartan potassium/hydrochlorothiazide 50 mg/12.5 mg, the dosage may be increased to one tablet of Losartan potassium/hydrochlorothiazide 100 mg/25 mg (losartan 100 mg/ HCTZ 25 mg) once daily. The maximum dose is one tablet of Losartan potassium/hydrochlorothiazide 100 mg/25 mg once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy.

Renal impairment and haemodialysis patients

No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance 30-50 ml/min). Losartan 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).

Intravascular volume depletion

Volume and/or sodium depletion should be corrected prior to administration of Losartan/HCTZ tablets.

Hepatic impairment

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

Elderly

Dosage adjustment is not usually necessary for the elderly.

Paediatric population

There is no experience in children and adolescents. The safety and efficacy of Losartan potassium/hydrochlorothiazide in children and adolescents (<18 years) has not yet been established. No data is available.

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).

Losartan potassium/hydrochlorothiazide tablets should be swallowed with a glass of water.

Losartan potassium/hydrochlorothiazide may be administered with or without food.

4.3 Contraindications

- Hypersensitivity to losartan, sulphonamide-derived substances (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
- Symtomatic 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 Losartan potassium/hydrochlorothiazide 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

Hypersensitivity

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 Electrolyte/Fluid Imbalance

Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of Losartan potassium, or a lower starting dose should be used (see section 4.2). This also applies to children 6 to 18 years of age.

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalemia was higher in the group treated with Losartan potassium as compared to the placebo group (see section 4.8, 'Hypertension and type 2 diabetes with renal disease - Investigations' and 'Post-marketing experience - Investigations' Therefore, the plasma concentrations of potassium as well as 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 and potassium containing salt substitutes with losartan is not recommended (see section 4.5).

Hepatic impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan must not be administered in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Losartan is not recommended in children with hepatic impairment (see section 4.2).

Renal Impairment

As a consequence of inhibiting the renin-angiotensin 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.

Use in pediatric patients with renal function impairment

Losartan is not recommended in children with glomerular filtration rate < 30ml/min/1.73 m^2 as no data are available (see section 4.2).

Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended (see section 4.5).

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 is not recommended.

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.

There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life threatening cardiac arrhythmias. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution (see section 5.1).

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.

Excipients

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.

Pregnancy

Losartan should not be initiated during pregnancy. Unless continued losartan 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 losartan should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Other warnings and precautions

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

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.

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, Losartan potassium (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after

discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, Losartan potassium should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

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 drugs 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 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.

Clinical trial data have shown 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).

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

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.

Cholestyramine 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 hypokalaemia.

Pressor amines (e.g. adrenaline)

Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarising (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 (probenecid, sulfinpyrazone and 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 sulfinpyrazone may be necessary. Coadministration of a thiazide 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.

Cyclosporine

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 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.

Amphotericin B (parenteral), corticosteroids, ACTH, stimulant laxatives, or glycyrrhizin (found in liquorice).

Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs):

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the 2nd and 3rd trimesters of pregnancy (see sections 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 AIIRA 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 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 sections 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 second and third trimesters 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 Losartan potassium/hydrochlorothiazide during breastfeeding, Losartan potassium/hydrochlorothiazide is not recommended and alternative treatments with better established safety profiles during breastfeeding 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 Losartan potassium/hydrochlorothiazide during breastfeeding is not recommended. If Losartan potassium/hydrochlorothiazide is used during breastfeeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

No studies on the reactions 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

Losartan has been evaluated in clinical studies as follows:

• In a controlled clinical trial in > 3,000 adult patients 18 years of age and older for essential hypertension.

• In a controlled clinical trial in 177 hypertensive paediatric patients 6 to 16 years of age

• In a controlled clinical trial in > 9,000 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy (see LIFE Study, section 5.1)

• In controlled clinical trials in > 7,700 adult patients with chronic heart failure (see ELITE I, ELITE II, and HEAAL study, section 5.1)

• In a controlled clinical trial in > 1,500 type 2 diabetic patients 31 years of age and older with proteinuria (see RENAAL study, section 5.1)

In these clinical trials, the most common adverse event was dizziness.

The frequency of adverse events listed below is defined using the following convention:

very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

In controlled clinical trials for essential hypertension, hypertensive patients with left ventricular hypertrophy, chronic heart failure as well as for hypertension and type 2 diabetes mellitus with renal disease, the most common adverse event was dizziness.

Hypertension

In controlled clinical trials for essential hypertension with losartan the following adverse events were reported:

Nervous system disorders
Common: dizziness
Uncommon: somnolence, headache, sleep disorders

Ear and labyrinth disorders
Common: vertigo

Cardiac disorder
Uncommon: palpitations, angina pectoris

Vascular disorders
Uncommon: (orthostatic) hypotension (dose-related orthostatic effects) ‖,

Skin and subcutaneous tissue disorders
Uncommon: rash

Gastrointestinal disorders
Uncommon: abdominal pain, obstipation
Rare: Intestinal angioedema.

General disorders and administration site conditions
Uncommon: asthenia, fatigue, oedema

Investigations
Common: hyperkalaemia
Rare: increased alanine aminotransferase (ALT) §

Hypertensive patients with left ventricular hypertrophy

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy the following adverse events were reported:

Nervous system disorders
Common: dizziness

Ear and labyrinth disorders
common: vertigo

General disorders and administration site conditions
Common: asthenia,fatigue

Chronic heart failure

In a controlled clinical trial in patients with cardiac insufficiency the following adverse events were reported:

Blood and lymphatic system disorders
Common: anaemia

Nervous system disorders
Common: dizziness
Uncommon: headache

Rare: paraesthesia

Cardiac disorders
Rare: syncope, artrial fibrillation, cerebrovascular accident

Vascular disorders
Common: (orthostatic) hypotension (including dose- related orthostatic effects) ‖

Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea, cough

Gastrointestinal disorders
Uncommon: diarrhoea, nausea, vomiting
Rare: Intestinal angioedema.

Skin and subcutanous tissue disorders
Uncommon: urticaria, pruritus, rash

Renal and urinary disorders
Common: renal impairment, renal failure

General disorders and administration site conditions
Uncommon: asthenia, fatigue

Investigations
Uncommon: hyperkalaemia†
Common: increase in blood urea, serum creatinine, and serum potassium

Hypertension and type 2 diabetes with renal disease

In a controlled clinical trial in type 2 diabetic patients with proteinuria (RENAAL study, see section 5.1) the most common drug-related adverse events which were reported for losartan are as follows:

Nervous system disorders
Common: dizziness

Vascular disorders
Common: (orthostatic) hypotension (including dose- related orthostatic effects)

General disorders and administration site conditions
Common: asthenia, fatigue

Investigations
Common: hypoglycaemia, hyperkalaemia‡

Post-marketing experience

The following adverse events have been reported in post-marketing experience:

Blood and lymphatic system disorders:
Not known: anaemia, thrombocytopenia

Immune system disorders

Rare: hypersensitivity reactions, anaphylactic reactions, angioedema*, and vasculitis**

Psychiatric disorders
Not known: depression

Nervous system disorders
Not known: migraine, dysgeusia

Ear and labyrinth disorders
Not known: tinnitus

Respiratory, thoracic and mediastinal disorders
Not known: cough

Gastrointestinal disorders
Not known: diarrhoea

Hepatobiliary disorders
Rare: hepatitis
Not known: liver function abnormalities, pancreatitis

Skin and subcutaneous tissue disorders
Not known: urticaria, pruritus, rash, photosensitivity

Muscoskeletal and connective tissue disorders
Not known: myalgia, arthralgia, rhabdomyolysis

Reproductive system and breast disorders
Not known: erectile dysfunction / impotence

General disorders and administration site conditions
Not known: malaise

Investigations
Not known: hyponatraemia

**Including swelling of the larynx, glottis, face, lips, pharynx, and/or tongue (causing airway obstruction); in some of these patients angiooedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors*

***Including Henoch-Schönlein purpura*

‖Especially in patients with intravascular depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics

†Common in patients who received 150 mg losartan instead of 50 mg

‡In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan tablets developed hyperkalaemia >5.5 mmol/l and 3.4% of patients treated with placebo

§Usually resolved upon discontinuation

The following adverse events occurred more often in patients receiving losartan than placebo:

Muscoskeletal and connective tissue disorders
Not known: back pain

Renal and urinary disorders
Not known: urinary tract infections

General disorders and administration site conditions
Not known: flu-like symptoms

Renal and urinary disorders

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy (see section 4.4)

Paediatric population

The adverse reaction profile for paediatric patients appears to be similar to that seen in adult patients. Data in the paediatric population are limited.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No specific information is available on the treatment of overdose with Losartan potassium/hydrochlorothiazide. Treatment is symptomatic and supportive. Therapy with Losartan potassium/hydrochlorothiazide 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 overdose would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

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

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) 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 hemodialysis has not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, ATC code: C09DA01

Losartan-Hydrochlorothiazide

The components of Losartan potassium/hydrochlorothiazide have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricaemia.

The antihypertensive effect of Losartan potassium/hydrochlorothiazide is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of Losartan potassium/hydrochlorothiazide had no clinically significant effect on heart rate. In clinical trials, after 12 weeks of therapy with losartan 50 mg/hydrochlorothiazide 12.5 mg, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mmHg.

Losartan potassium/hydrochlorothiazide is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (<65 years) and older (≥65 years) patients and is effective in all degrees of hypertension.

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 smooth-muscle cell proliferation.

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

Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, 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). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of the plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After the discontinuation of losartan, PRA and angiotensin II values fell within 3 days to the baseline values.

Both losartan and its principal active metabolite have a far greater affinity for the AT_1 receptor than for the AT_2 receptor. The active metabolite is 10- to 40-times more active than losartan on a weight for weight basis.

In a study specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan or hydrochlorothiazide was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In nondiabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally losartan causes a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent in chronic therapy.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma norepinephrine.

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan produced positive hemodynamic and neurohormonal effects characterised by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and norepinephrine, respectively. The occurrence of hypotension was dose related in these heart failure patients.

Hypertension Studies

In controlled clinical studies, once-daily administration of losartan 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 70 – 80 % of the effect seen 5-6 hours post-dose.

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

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

LIFE Study

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or once daily atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure.

The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001, 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

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

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.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect 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 and 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 co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours 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

Absorption

Losartan

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardised meal.

Distribution

Losartan

Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide

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

Biotransformation

Losartan

About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

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

Elimination

Losartan

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

Characteristics in Patients

Losartan-Hydrochlorothiazide

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.

Losartan

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.

Pharmacokinetic studies showed that the AUC of losartan in Japanese and non-Japanese healthy male subjects is not different. However, the AUC of the carboxylic acid metabolite (E-3174) appears to be different between the two groups, with an approximately 1.5 fold higher exposure in Japanese subjects than in non-Japanese subjects. The clinical significance of these results is not known.

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential, toxicity to reproduction and development. 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 reactions, 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

Each Losartan potassium/hydrochlorothiazide 100 mg/25 mg tablet contains the following inactive ingredients:

Core:

microcrystalline cellulose (E460)

lactose monohydrate

pregelatinised maize starch

magnesium stearate (E572)

Film-coating:

hypromellose(E464)

titanium dioxide (E171)

macrogol/PEG 400

Iron oxide yellow (E172)

Indigo carmine aluminum lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Losartan potassium/hydrochlorothiazide 100 mg/25 mg:

PVC/PE/PVDC aluminium blister with 7, 10, 14, 28, 30, 50, 56, 90, 98 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Medreich Plc

Warwick House

Plane Tree Crescent

Feltham

TW13 7HF

8 MARKETING AUTHORISATION NUMBER(S)

PL 21880/0144

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/10/2024

10 DATE OF REVISION OF THE TEXT

21/02/2025