**SUMMARY OF PRODUCT CHARACTERISTICS**

**1. NAME OF THE MEDICINAL PRODUCT**

Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg film-coated tablets

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 50 mg losartan potassium, equivalent to 45.76 mg losartan and 12.5 mg hydrochlorothiazide.

Excipient with known effect: lactose 59.98 mg/tablet.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL form**

Film-coated tablet.

Tablets areyellow, oval, moderately biconvex, film-coated tablets with one-sided halving score, tablet dimension 6 mm x 12 mm (oval shape) thickness 3.8 – 4.7 mm. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

**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 by losartan or hydrochlorothiazide alone.

**4.2 Posology and method of administration**

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. Losartan Potassium/Hydrochlorothiazide 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.

*Use in patients with 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).

*Use in patients with hepatic impairment*

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

*Use in patients with intravascular volume depletion*

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

*Older people*

Dosage adjustment is not usually necessary for the older people.

*Paediatric population*

There is no experience in children and adolescents (< 18 years). 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 the active substance, to 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.
* Symptomatic hyperuricaemia/gout.
* 2nd and 3rd trimester of pregnancy (see section 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 m2) (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/Hydrochlorothiazide (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 and potassium containing salt substitutes 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/Hydrochlorothiazide 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/Hydrochlorothiazide 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/Hydrochlorothiazide 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.

*Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyophathy*

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 people than in nonblacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

*Pregnancy*

AIIRAs should not be initiated during pregnancy. 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 (see sections 4.3 and 4.6).

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers 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.

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 hypokalemia which may occur during intercurrent diarrhea 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 adjustment 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 diureticinduced hyperuricemia.

*Hepatic impairment*

Thiazides 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/Hydrochlorothiazide is contraindicated for patients with severe hepatic impairment (see section 4.3 and 5.2).

In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbations or activation of systemic lupus erythematosus was reported after the use of thiazides.

*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).

*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, Losartan Potassium/Hydrochlorothiazide should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

*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.

Losartan Potassium/Hydrochlorothiazide contains lactose. Patients with rare hereditary problems of galactose intolerance, total 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 lower levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

As with the other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diruretics (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 coadministered 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 antiinflammatory 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 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).

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 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 (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 (eg 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 (eg quinidine, hydroquinidine, disopyramide).
* Class III antiarrythmics (eg amiodarone, sotalol, dofetilide, ibutilide).
* Some antipsychotics (eg thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
* Others (eg 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, 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 second and third 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 AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with Losartan Potassium/Hydrochlorothiazide should be stopped immediately and, if appropriate, alternative therapy should be started.

Losartan Potassium/Hydrochlorothiazide therapy exposure 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 5.3 'Preclinical safety data').

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

Infants whose mothers have taken Losartan Potassium/Hydrochlorothiazide should be closely observed for hypotension (see also 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.

Breastfeeding

*Angiotensin II Receptor Antagonists (AIIRAs):*

No information is available regarding the use of Losartan Potassium/Hydrochlorothiazide during breastfeeding. Hydrochlorothiazide is excreted in human milk. Therefore, the use of Losartan Potassium/Hydrochlorothiazide during breastfeeding is not recommended. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

**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**

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 reactions peculiar to this combination of substances were observed.

The adverse reactions were restricted to those which were formerly observed with losartan potassium and/or hydrochlorothiazide.

In controlled clinical trials of essential hypertension, dizziness was the only adverse reaction 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:

|  |  |  |
| --- | --- | --- |
| **System organ class**  | **Adverse reaction**  | **Frequency**  |
| Hepato-biliary disorders  | Hepatitis  | rare  |
| Investigations  | Hyperkalaemia, elevation of ALT  | rare  |
| Nervous system disorders | Dysgeusia | Not known |
| Vascular disorders | Dose-related orthostatic effects | Not known |
| Skin and subcutaneous tissue disorders | Cutaneous lupus erythematosus | Not known |

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

Losartan

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

|  |  |  |
| --- | --- | --- |
| **System organ class**  | **Adverse reaction**  | **Frequency**  |
| Blood and lymphatic system disorders  | anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis | uncommon  |
| Cardiac disorders  | 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)  | uncommon  |
| Ear and labyrinth disorders  | vertigo, tinnitus  | uncommon  |
| Eye disorders  | blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity  | uncommon  |
| Gastrointestinal disorders  | abdominal pain, nausea, diarrhea, dyspepsia  | common  |
| constipation, dental pain, dry mouth, flatulence, gastritis, vomiting  | uncommon  |
| pancreatitis | not known  |
| General disorders and administration site conditions  | asthenia, fatigue, chest pain  | common  |
| facial oedema, oedema, fever  | uncommon  |
|  |  |
| Hepatobiliary disorders  | liver function abnormalities  | not known  |
| Immune system disorders  | anaphylactic reactions, angioedema, urticaria | rare  |
| Metabolism and nutrition disorders  | anorexia, gout  | uncommon  |
| Musculoskeletal and connective tissue disorders  | muscle cramp, back pain, leg pain, myalgia  | common  |
| arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness  | uncommon  |
| rhabdomyolysis | not known  |
| Nervous system disorders  | headache, dizziness  | common  |
| nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope  | uncommon  |
|  |  |
| Psychiatric disorders  | insomnia  | common  |
| anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment  | uncommon  |
| nocturia, urinary frequency, urinary tract infection | uncommon |
| Reproductive system and breast disorders  | decreased libido, impotence  | uncommon  |
| Respiratory, thoracic and mediastinal disorders  | cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder  | common  |
| pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion  | uncommon  |
| Skin and subcutaneous tissue disorders  | alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating  | uncommon  |
| Vascular disorders  | vasculitis | uncommon  |
| Investigations  | hyperkalaemia, mild reduction of haematocrit and haemoglobin,  | common  |
| mild increase in urea and creatinine serum levels | uncommon  |
| increase in hepatic enzymes and bilirubin | very rare  |

Hydrochlorothiazide

|  |  |  |
| --- | --- | --- |
| **System organ class**  | **Adverse reaction**  | **Frequency**  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)1 | not known |
| Blood and lymphatic system disorders  | Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia  | uncommon  |
| Immune system disorders  | Anaphylactic reaction  | rare  |
| Metabolism and nutrition disorders  | Anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia  | uncommon  |
| Psychiatric disorders  | Insomnia  | uncommon  |
| Nervous system disorders  | Cephalalgia  | common  |
| Eye disorders  | Transient blurred vision, xanthopsia  | uncommon  |
| Choroidal effusion, acute angle-closure galucoma | not known |
| Vascular disorders  | Necrotizing angiitis (vasculitis, cutaneous vasculitis)  | uncommon  |
| Respiratory, thoracic and mediastinal disorders  | Respiratory distress including pneumonitis and pulmonary oedema | uncommon  |
| Acute respiratory distress syndrome (ARDS) (see section 4.4) | very rare |
| Gastrointestinal disorders  | Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation  | uncommon  |
| Hepato-biliary disorders  | Icterus (intrahepatic cholestatis), pancreatitis  | uncommon  |
| Skin and subcutaneous tissue disorders  | Photosensitivity, urticaria, toxic epidermal necrolysis | uncommon  |
| Musculoskeletal and connective tissue disorders  | Muscle cramps  | uncommon  |
| Renal and urinary disorders  | Glycosuria, interstitial nephritis, renal dysfunction, renal failure  | uncommon  |
| General disorders and administration site conditions  | Fever, dizziness  | uncommon  |

1-Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dosedependent 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 Yellow Card Scheme,

Website: [www.mhra.gov.uk/yellowcard](http://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 overdosage 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 overdosage 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 hemodialysis.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia 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 hyperuricemia.

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 AT1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormon of the renin-angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone.Angiotensin II also stimulates smooth-muscle cell proliferation.

Losartan selectively blocks the AT1 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 rennin 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 AT1 receptor than for the AT2 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 characterized 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. Measurements 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 postdose.

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 effects 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 ECGdocumented 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 coadministration 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 standardized 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 liters. Studies in rats indicate that losartan crosses the bloodbrain 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 14C-labeled 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 oncedaily 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 14C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces.

*Hydrochlorothiazide*

Hydrochlorothiazide is not metabolized 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.

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

**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 F1 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 rate were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

*Tablet core:*

Maize starch, pregelatinised

Cellulose, microcrystalline

Lactose monohydrate

Magnesium stearate

*Film-coating:*

Hypromellose

Macrogol 4000

Quinoline yellow (E104)

Talc

Titanium dioxide (E171).

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

5 years

*HDPE tablet container:*

After first opening of the container, the product should be used within 100 days.

**6.4 Special precautions for storage**

Do not store above 30°C.

Store in the original package in order to protect from moisture.

**6.5 Nature and contents of container**

Al/PVC/PVDC transparent blister, carton.

*Pack sizes*: 10, 14, 28, 30, 56, 60, 84, 90, 98 and 112 film-coated tablets

Polyethylene (HDPE, white) tablet container with a tamper-evident polypropylene (PP, white) closure: 100 film-coated tablets, in a carton box.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

**8. MARKETING AUTHORISATION NUMBER(S)**

PL01656/0068

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 20/5/2009

Date of latest renewal: 8/4/2011

**10. DATE OF REVISION OF THE TEXT**

11/02/2022

**LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON BOX/for blisters and HDPE container**

**1. NAME OF THE MEDICINAL PRODUCT**

Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg film-coated tablets

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 50 mg losartan potassium, equivalent to 45.76 mg losartan and 12.5 mg hydrochlorothiazide.

**3. LIST OF EXCIPIENTS**

Contains lactose.

See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

*Blisters:*

10 film-coated tablets

14 film-coated tablets

28 film-coated tablets

30 film-coated tablets

56 film-coated tablets

60 film-coated tablets

84 film-coated tablets

90 film-coated tablets

98 film-coated tablets

112 film-coated tablets

*HDPE tablet container:*

100 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

For oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

**Keep out of the sight and reach of children.**

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

*HDPE tablet container:*

After first opening of the container, the product should be used within 100 days.

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.

Store in the original package in order to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

**Distributed by:**

Consilient Health (UK) Ltd., No.1 Church Road, Richmond upon Thames, Surrey, TW9 2QE

**12. MARKETING AUTHORISATION NUMBER(S)**

PL01656/0068

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

POM

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg tablets

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC

SN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**LABEL/for HDPE tablet container**

**1. NAME OF THE MEDICINAL PRODUCT**

Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg film-coated tablets

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 50 mg losartan potassium, equivalent to 45.76 mg losartan and 12.5 mg hydrochlorothiazide.

**3. LIST OF EXCIPIENTS**

Contains lactose.

See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

100 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

For oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

**Keep out of the sight and reach of children.**

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

After first opening of the container, the product should be used within 100 days.

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.

Store in the original package in order to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

KRKA

**12. MARKETING AUTHORISATION NUMBER(S)**

PL01656/0068

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

Not applicable.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

Not applicable.

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER (PVC/PVDC//Alu)**

**1. NAME OF THE MEDICINAL PRODUCT**

Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg film-coated tablets

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

KRKA

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Distributor: Consilient Health (UK) Ltd.

**PACKAGE LEAFLET**

**Package leaflet: Information for the user**

**Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg film-coated tablets**

losartan potassium/hydrochlorothiazide

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

* Keep this leaflet. You may need to read it again.
* If you have any further questions, ask your doctor or pharmacist.
* This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
* If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**

1. What Losartan Potassium/Hydrochlorothiazide is and what it is used for

2. What you need to know before you take Losartan Potassium/Hydrochlorothiazide

3. How to take Losartan Potassium/Hydrochlorothiazide

4. Possible side effects

5. How to store Losartan Potassium/Hydrochlorothiazide

6. Contents of the pack and other information

**1. What Losartan Potassium/Hydrochlorothiazide is and what it is used for**

Losartan Potassium/Hydrochlorothiazide is a combination of an angiotensin II receptor antagonist (losartan) and a diuretic (hydrochlorothiazide).

Losartan Potassium/Hydrochlorothiazide is indicated for the treatment of essential hypertension (high blood pressure).

**2. What you need to know before you take Losartan Potassium/Hydrochlorothiazide**

**Do not take Losartan Potassium/Hydrochlorothiazide**

* if you are allergic to losartan and/or hydrochlorothiazide or any of the other ingredients of this medicine (listed in section 6);
1. if you are more than 3 months pregnant. (It is also better to avoid Losartan Potassium/Hydrochlorothiazide in early pregnancy - see pregnancy section.);
2. if you have severely impaired liver function; cholestasis and biliary obstructive disorders
3. if you have severely impaired kidney function (i.e. creatinine clearance <30 ml/min);
4. if your kidneys are not producing any urine;
5. if you have low potassium, low sodium or high calcium levels which cannot be corrected by treatment;
* if you are suffering from gout.
* if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

**Warnings and precautions**

Talk to your doctor or pharmacist before taking Losartan Potassium/Hydrochlorothiazide.

* if you have previously suffered from swelling of the face, lips, throat or tongue,
* if you take diuretics (water pills),
* if you are on a salt-restricted diet,
* if you have or have had severe vomiting and/or diarrhoea,
* if you have heart failure,
* if you have narrow arteries to your kidneys (renal artery stenosis) or only have one functioning kidney, or you have recently had a kidney transplant,
* if you have narrowing of the arteries (atherosclerosis), angina pectoris (chest pain due to poor heart function),
* if you have ‘aortic or mitral valve stenosis’ (narrowing of the valves of the heart) or ‘hypertrophic cardiomyopathy’ (a disease causing thickening of heart muscle),
* if you are diabetic,
* if you have had gout,
* if you have or have had an allergic condition, asthma or a condition that causes joint pain, skin rashes and fever (systemic lupus erythematosus),
* if you have high calcium or low potassium levels or you are on a low potassium diet,
* if you need to have an anaesthetic (even at the dentist) or before surgery, or if you are going to have tests to check your parathyroid function, you must tell the doctor or medical staff that you are taking Losartan potassium and Hydrochlorothiazide tablets,
* if you suffer from primary hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldosterone by the adrenal gland, caused by an abnormality within the gland),
* if you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking Losartan Potassium/Hydrochlorothiazide,
* if you experienced breathing or lung problems (including inflammation or fluid in the lungs) following hydrochlorothiazide intake in the past. If you develop any severe shortness of breath or difficulty breathing after taking Losartan Potassium/Hydrochlorothiazide, seek medical attention immediately
* if you experience a decrease in vision or eye pain. These could be symptoms of fluid accumulation in the vascular layer of the eye (choroidal effusion) or an increase of pressure in your eye and can happen within hours to weeks of taking Losartan Potassium/Hydrochlorothiazide. This can lead to permanent vision loss, if not treated. If you earlier have had a penicillin or sulfonamide allergy, you can be at higher risk of developing this,
* if you are taking any of the following medicines used to treat high blood pressure:
* an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems,
* aliskiren.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading “Do not take Losartan Potassium/Hydrochlorothiazide”.

You must tell your doctor if you think that you are (or might become) pregnant. Losartan Potassium/Hydrochlorothiazide is not recommended in early pregnancy and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

**Other medicines and Losartan Potassium/Hydrochlorothiazide**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Diuretic agents such as the hydrochlorothiazide contained in Losartan Potassium/Hydrochlorothiazide may interact with other medicines. Preparations containing lithium should not be taken with Losartan Potassium/Hydrochlorothiazide without close supervision by your doctor. Special precautionary measures (e.g. blood tests) may be appropriate if you take potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines, other diuretics (“water tablets”), some laxatives, medicines for the treatment of gout, medicines to control heart rhythm or for diabetes (oral agents or insulins). It is also important for your doctor to know if you are taking other medicines to reduce your blood pressure, steroids, medicines to treat cancer, pain killers, drugs for treatment of fungal infections, or arthritis medicines, resins used for high cholesterol, such as colestyramine, medicines which relax your muscles, sleeping tablets; opioid medicines such as morphine ‘pressor amines’ such as adrenaline or other drugs from the same group; (oral agents for diabetes or insulins).

Your doctor may need to change your dose and/or to take other precautions:

* If you are taking an ACE-inhibitor or aliskiren (see also information under the headings “Do not take Losartan Potassium/Hydrochlorothiazide ” and “Warnings and precautions”)

Please also inform your doctor when it is planned to apply iodine contrast media about taking Losartan Potassium/Hydrochlorothiazide.

**Losartan Potassium/Hydrochlorothiazide with food, drink and alcohol**

This medicinal product may be taken with or without food.

You are advised not to drink alcohol whilst taking these tablets: alcohol and Losartan Potassium/Hydrochlorothiazide tablets may increase each other’s effects.

Dietary salt in excessive quantities may counteract the effect of Losartan Potassium/Hydrochlorothiazide tablets.

**Pregnancy and breastfeeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Losartan Potassium/Hydrochlorothiazide before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Losartan Potassium/Hydrochlorothiazide. Losartan Potassium/Hydrochlorothiazide is not recommended during pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breastfeeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. Losartan Potassium/Hydrochlorothiazide is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

**Use in children and adolescents**

There is no experience with the use of Losartan Potassium/Hydrochlorothiazide in children. Therefore, Losartan Potassium/Hydrochlorothiazide should not be given to children.

**Use in elderly patients**

Losartan Potassium/Hydrochlorothiazide works equally well in and is equally well tolerated by most older and younger adult patients. Most older patients require the same dose as younger patients.

**Driving and using machines**

When you begin treatment with this medication, you should not perform tasks which may require special attention (for example, driving an automobile or operating dangerous machinery) until you know how you tolerate your medicine.

**Losartan Potassium/Hydrochlorothiazide contains lactose**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

**3. How to take Losartan Potassium/Hydrochlorothiazide**

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure. Your doctor will decide on the appropriate dose of Losartan Potassium/Hydrochlorothiazide depending on your condition and whether you are taking other medicines. It is important to continue taking Losartan Potassium/Hydrochlorothiazide for as long as your doctor prescribes it in order to maintain smooth control of your blood pressure.

High Blood Pressure

The usual dose of Losartan Potassium/Hydrochlorothiazide for most patients with high blood pressure is 1 tablet of Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg per day to control blood pressure over the 24-hour period. This can be increased to 2 tablets once daily of Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg film-coated tablets or changed to 1 tablet daily of Losartan Potassium/Hydrochlorothiazide 100 mg/25 mg film-coated tablets (a stronger strength) per day. The maximum daily dose is 2 tablets per day of Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg film-coated tablets or 1 tablet daily of Losartan Potassium/Hydrochlorothiazide 100 mg/25 mg film-coated tablets.

**If you take more Losartan Potassium/Hydrochlorothiazide than you should**

In case of an overdose, contact your doctor immediately so that medical attention may be given promptly. Overdose can cause a drop in blood pressure, palpitations, slow pulse, changes in blood composition, and dehydration.

**If you forget to take Losartan Potassium/Hydrochlorothiazide**

Try to take Losartan Potassium/Hydrochlorothiazide daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience the following, stop taking Losartan Potassium/Hydrochlorothiazide tablets and tell your doctor immediately or go to the casualty department of your nearest hospital:

A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing).

This is a serious but rare side effect, which affects more than 1 out of 10,000 patients but fewer than 1 out of 1,000 patients. You may need urgent medical attention or hospitalisation.

The following side effects have been reported:

*Common (may affect up to 1 in 10 people):*

* Cough, upper airway infection, congestion in the nose, sinusitis, sinus disorder,
* Diarrhoea, abdominal pain, nausea, indigestion,
* Muscle pain or cramps, leg pain, back pain,
* Insomnia, headache, dizziness,
* Weakness, tiredness, chest pain,
* Increased potassium levels (which can cause an abnormal heart rhythm), decreased haemoglobin levels.

*Uncommon (may affect up to 1 in 100 people):*

* Anaemia, red or brownish spots on the skin (sometimes especially on the feet, legs, arms and buttocks, with joint pain, swelling of the hands and feet and stomach pain), bruising, reduction in white blood cells, clotting problems and bruising,
* Loss of appetite, increased uric acid levels or frank gout, increased blood sugar levels, abnormal blood electrolyte levels,
* Anxiety, nervousness, panic disorder (recurring panic attacks), confusion, depression, abnormal dreams, sleep disorders, sleepiness, memory impairment,
* Pins and needles or similar sensations, pain in the extremities, trembling, migraine, fainting,
* Blurred vision, burning or stinging in the eyes, conjunctivitis, worsening eyesight, seeing things in yellow,
* Ringing, buzzing, roaring or clicking in the ears,
* Low blood pressure, which may be associated with changes in posture (feeling light-headed or weak when you stand up, angina (chest pain), abnormal heartbeat, cerebrovascular accident (TIA, “mini-stroke”), heart attack, palpitations,
* Inflammation of blood vessels, which is often associated with a skin rash or bruising,
* Sore throat, breathlessness, bronchitis, pneumonia, water on the lungs (which causes difficulty breathing), nosebleed, runny nose, congestion,
* Constipation, wind, stomach upsets, stomach spasms, vomiting, dry mouth, inflammation of a salivary gland, toothache,
* Jaundice (yellowing of the eyes and skin), inflammation of the pancreas,
* Hives, itching, inflammation of the skin, rash, redness of the skin, sensitivity to light, dry skin, flushing, sweating, hair loss,
* Pain in the arms, shoulders, hips, knees or other joints, joint swelling, stiffness, muscle weakness,
* Frequent urination including at night, abnormal kidney function including inflammation of the kidneys, urinary infection, sugar in the urine,
* Decreased sexual appetite, impotence,
* Swelling of the face, fever.

*Rare (may affect up to 1 in 1,000 people)*

* Hepatitis (inflammation of the liver), abnormal liver function tests

*Very rare (may affect up to 1 in 10,000 people)*

* Acute respiratory distress (signs include severe shortness of breath, fever, weakness, and confusion).

*Not known* ***(****frequency cannot be estimated from the available data)*

* Skin and lip cancer (Non-melanoma skin cancer).
* Rhabdomyolisis.
* Disturbed taste (dysgeusia).
* Decrease in vision or pain in your eyes due to high pressure (possible signs of fluid accumulation in the vascular layer of the eye (choroidal effusion) or acute angle-closure glaucoma).

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme,

Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

**5. How to store Losartan Potassium/Hydrochlorothiazide**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Store in the original package in order to protect from moisture.

*HDPE tablet container:*

After first opening of the container, the product should be used within 100 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

**6. Contents of the pack and other information**

**What Losartan Potassium/Hydrochlorothiazide contains**

* + The active substances are losartan potassium and hydrochlorothiazide. Each film-coatedtablet contains 50 mg losartan potassium, equivalent to 45.76 mg losartan and 12.5 mg hydrochlorothiazide.
	+ The other ingredients are: pregelatinised maize starch; microcrystalline cellulose; lactose monohydrate and magnesium stearate in the tablet core and hypromellose; macrogol 4000; quinoline yellow (E104); talc; titanium dioxide (E171) in the film coating.

See section 2 “Losartan Potassium/Hydrochlorothiazide contains lactose”.

**What Losartan Potassium/Hydrochlorothiazide looks like and contents of the pack**

* + Losartan Potassium/Hydrochlorothiazide tablets areyellow, oval, moderately biconvex, film-coated tablets with one-sided halving score, tablet dimension 6 mm x 12 mm (oval shape) thickness 3.8 – 4.7 mm. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. See section 2 “Losartan Potassium/Hydrochlorothiazide contains lactose”.

Tablets are supplied in cartons containing:

* + 10, 14, 28, 30, 56, 60, 84, 90, 98 and 112 film-coated tablets in Al/PVC/PVDC transparent blisters
	+ 100 film-coated tablets in white plastic tablet container with white tamper-evident screw closure.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

**Manufacturers:**

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

TAD Pharma GmbH, Heinz-Lohmann-Straße 5, 27472 Cuxhaven, Germany

KRKA-POLSKA Sp. z o.o., ul. Równoległa 5, 02-235 Warszawa, Poland

**Distributed by:**

Consilient Health (UK) Ltd., No. 1 Church Road, Richmond upon Thames, Surrey, TW9 2QE.

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