

New Zealand Data Sheet

Losartan HCTad[®] 50mg/12.5mg

Losartan potassium/Hydrochlorothiazide film-coated tablets, 50 mg/12.5 mg

Presentation

One Losartan HCTad tablet contains losartan potassium 50 and hydrochlorothiazide (HCT) 12.5 mg.

Losartan HCTad tablets are yellow, oval, slightly biconvex, film-coated tablets. Diameter: 6 mm x 12 mm (oval). Thickness: 3.8 mm – 4.7 mm.

Indications

Hypertension

Losartan HCTad is indicated for the treatment of hypertension, for patients in whom combination therapy is appropriate.

Reduction in the risk of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy

Losartan HCTad is a combination of losartan and hydrochlorothiazide. In patients with hypertension and left ventricular hypertrophy, losartan, often in combination with hydrochlorothiazide, reduces the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy (see Warnings and Precautions, Ethnic differences).

Dosage and Administration

Losartan HCTad may be administered with other antihypertensive agents.

Losartan HCTad may be administered with or without food.

Hypertension

The usual starting and maintenance dose of Losartan HCTad (losartan 50 mg/HCT 12.5 mg) is one tablet once daily. For patients who do not respond adequately to Losartan HCTad, the dosage may be increased to two tablets once daily. The maximum dose is two tablets once daily. In general the antihypertensive effect is attained within three weeks after initiation of therapy.

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

Losartan HCTad is not recommended for patients with severe renal impairment (creatinine clearance \leq 30 mL/min) or for patients with hepatic impairment.

No initial dosage adjustment of Losartan HCTad is necessary for elderly patients.

Reduction in the risk of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy

The usual starting dose is 50 mg of losartan once daily. If goal blood pressure is not reached with losartan 50 mg, therapy should be titrated using a combination of losartan and a low dose of hydrochlorothiazide (12.5 mg*) and, if needed, the dose should then be increased to losartan 100 mg and hydrochlorothiazide 12.5 mg once daily. If necessary, the dose should be increased to losartan 100 mg and hydrochlorothiazide 25 mg once daily. Losartan HCTad 50mg/12.5mg is a suitable alternative formulation in patients who would otherwise be treated concomitantly with losartan plus hydrochlorothiazide.

**Note: Hydrochlorothiazide is not available in New Zealand*

Contraindications

Losartan HCTad is contraindicated in:

- patients who are hypersensitive to any component of this product or other sulphonamide derived medicines
- patients with anuria.

Warnings and Precautions

Losartan

➤ **Angiooedema**

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

➤ **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 prior to administration of Losartan HCTad.

➤ **Electrolyte imbalances**

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Therefore, 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 potassium - hydrochlorothiazide is not recommended (see Interactions).

➤ **Liver function impairment**

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, Losartan HCTad 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. Losartan HCTad is not recommended for patients with hepatic impairment (see Dosage and Administration).

➤ **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.

Losartan HCTad is not recommended for patients with severe renal impairment (creatinine clearance \leq 30 mL/min) (see Dosage and Administration).

➤ **Renal transplantation**

There is no experience in patients with recent kidney transplantation.

➤ **Primary hyperaldosteronism**

Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan HCTad 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 cardiomyopathy**

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

➤ **Ethnic differences**

Based on the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study, the benefits of losartan on cardiovascular morbidity and mortality compared to atenolol do not apply to Black patients with hypertension and left ventricular hypertrophy, although both treatment regimens effectively lowered blood pressure in Black patients. In the overall LIFE study population (n = 9,193), treatment with losartan resulted in a 13.0% risk reduction (p = 0.021) as compared to atenolol for patients reaching the primary composite endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction. In this study, losartan decreased the risk of cardiovascular morbidity and mortality compared to atenolol in non-Black, hypertensive patients with left ventricular hypertrophy (n = 8,660) as measured by the primary endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction (p = 0.003). In this study, however, Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with losartan (p = 0.03). In the subgroup of Black patients (n = 533; 6% of the LIFE study patients), there were 29 primary endpoints among 263 patients on atenolol (11%, 25.9 per 1,000 patient-years) and 46 primary endpoints among 270 patients (17%, 41.8 per 1,000 patient-years) on losartan.

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, hyponatraemia, hypochloaemic alkalosis, hypomagnesaemia or hypokalaemia which may occur during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

➤ **Metabolic and endocrine effects**

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see Interactions). 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 hypercalcaemia 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 hyperuricaemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricaemia.

➤ **Hepatic impairment**

Losartan HCTad is not recommended for patients with hepatic impairment (see Dosage and Administration). Thiazides may cause intrahepatic cholestasis, and minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

➤ **Hypersensitivity**

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

Excipient

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

Paediatric use

Safety and effectiveness in children and adolescents (< 18 years) have not been established. Therefore, Losartan HCTad should not be administered to children and adolescents.

Use in the elderly

In clinical studies there were no clinically significant differences in the efficacy or safety profiles of Losartan HCTad in older (≥ 65 years) and younger (< 65 years) patients.

Use in pregnancy

The use of Angiotensin II Receptor Antagonists is not recommended during pregnancy.

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 HCTad should be discontinued as soon as possible 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).

Should exposure to Losartan HCTad have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken Losartan HCTad should be closely observed for hypotension.

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 can be used.

Use in lactation

It is not known whether losartan is excreted in human milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the medicine, taking into account the importance of the medicine to the mother.

Since there is no information available regarding the use of losartan potassium - hydrochlorothiazide during breastfeeding, Losatan HCTad is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Effects on ability to drive and use machines

There are no data to suggest that Losartan HCTad affects the ability to drive and use machines. 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.

Other

Animal toxicology

Carcinogenesis

Losartan

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice.

Hydrochlorothiazide

Two-year feeding studies in mice and rats uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The studies, however, uncovered equivocal evidence for hepatocarcinogenicity in male mice.

Mutagenesis

Losartan - Hydrochlorothiazide

Losartan potassium - hydrochlorothiazide was negative in the Ames microbial mutagenesis assay and the V-79 Chinese hamster lung cell mutagenesis assay. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution assay

in rat hepatocytes and *in vitro* chromosomal aberration assay in Chinese hamster ovary cells at noncytotoxic concentrations.

Losartan

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution and *in vitro* chromosomal aberration assays at concentrations that were approximately 1,700 times greater than the maximum plasma level achieved in man at the recommended therapeutic dosage level. Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of toxic oral doses of up to 1,500 mg/kg (4,500 mg/m²) (750 times the maximum recommended daily human dose). In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Hydrochlorothiazide

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1,300 µg/ml, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Reproduction

Losartan - Hydrochlorothiazide

Losartan potassium - hydrochlorothiazide administration had no effect on the reproductive performance or fertility in male rats at dosage levels of up to 135 mg/kg/day of losartan in combination with 33.75 mg/kg/day of hydrochlorothiazide. These dosage levels provided respective plasma concentrations (AUC) for losartan, the active metabolite and hydrochlorothiazide that were approximately 260-, 120-, and 50- fold greater than those achieved in man with 50 mg of losartan potassium in combination with 12.5 mg hydrochlorothiazide. In female rats, however, the co-administration of losartan potassium/hydrochlorothiazide (10/2.5 mg/kg/day) induced a slight but statistically significant decrease in fecundity and fertility indices. Compared to plasma concentrations in man (see above), these dosage levels provided respective increases in plasma concentration (AUC) for losartan, the active metabolite, and hydrochlorothiazide of approximately 15-, 4-, and 5-fold.

Losartan

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the recommended daily dose.

Hydrochlorothiazide

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Development

Losartan - Hydrochlorothiazide

There was no evidence of teratogenicity in rats or rabbits treated with losartan potassium - hydrochlorothiazide. 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 decreased body weight and renal toxicity, also occurred when pregnant rats were treated with losartan potassium - hydrochlorothiazide during late gestation and/or lactation.

Losartan

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates. The effects include decreased body weight, mortality and/or renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to medicine exposure in late gestation and during lactation.

Hydrochlorothiazide

Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the maximum human dose) showed no evidence of external abnormalities of the foetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4-5.6 mg/kg/day (approximately 2-3 times the maximum recommended human dose) did not impair fertility or produce birth abnormalities in the offspring.

Adverse Effects

In clinical trials with losartan potassium - hydrochlorothiazide, no adverse experiences peculiar to this combination medicine have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo. The percentage of discontinuations of therapy was also comparable to placebo.

In general, treatment with losartan potassium - hydrochlorothiazide was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as medicine related that occurred with an incidence greater than placebo in one percent or more of patients treated with losartan potassium - hydrochlorothiazide.

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy, losartan, often in combination with hydrochlorothiazide, was generally well tolerated. The most common medicine-related side effects were dizziness, asthenia/fatigue, and vertigo.

Laboratory test findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan potassium - hydrochlorothiazide.

Hyperkalaemia (serum potassium > 5.5 mEq/L) occurred in 0.7% of patients, but in these trials, discontinuation of losartan potassium - hydrochlorothiazide due to hyperkalaemia was not necessary. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

Post-marketing experience

The following additional adverse reactions have been reported in post-marketing experience with losartan potassium - hydrochlorothiazide and/or in clinical trials or post-marketing use with the individual components:

Blood and the lymphatic system disorders: Thrombocytopenia, anaemia, purpura, Henoch-Schoenlein purpura, ecchymosis, aplastic anaemia, haemolytic anaemia, leukopenia, agranulocytosis.

Immune system disorders: Anaphylactic reactions; angioedema (including swelling of the larynx and glottis causing airway obstruction and/or face, lips, pharynx and/or tongue) has been reported rarely in patients treated with losartan, some of these patients previously experienced angioedema with other medicines including ACE inhibitors; urticaria.

Metabolism and nutrition disorders: Anorexia, hyperglycaemia, hyperuricaemia/gout, electrolyte imbalance including hyponatraemia and hypokalaemia.

Psychiatric disorders: Insomnia, restlessness, anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment.

Nervous system disorders: Dysgeusia, headache, migraine, paraesthesia, dizziness, nervousness, peripheral neuropathy, tremor, vertigo, migraine, syncope, cephalgia.

Eye disorders: Xanthopsia, transient blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity, transient failures of vision.

Ear and labyrinth disorders: Vertigo, tinnitus.

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).

Vascular disorders: Dose-related orthostatic effects, necrotising angiitis (vasculitis) (cutaneous vasculitis).

Respiratory, thoracic and mediastinal disorders: Cough, nasal congestion, pharyngitis, sinus disorder, upper respiratory infection, respiratory distress (including pneumonitis and pulmonary oedema), sinusitis, pharyngeal discomfort, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion.

Gastrointestinal disorders: Dyspepsia, abdominal pain, gastric irritation, cramping, diarrhoea, constipation, nausea, vomiting, pancreatitis, sialoadenitis, dental pain, dry mouth, flatulence, gastritis, vomiting, spasms.

Hepato-biliary disorders: Hepatitis, jaundice (intrahepatic cholestatic jaundice), liver function abnormalities, pancreatitis.

Skin and subcutaneous tissue disorders: Rash, pruritus, purpura (including Henoch-Schoenlein purpura), toxic epidermal necrolysis, urticaria, erythroderma, photosensitivity, cutaneous lupus erythematosus, alopecia, dermatitis, dry skin, erythema, flushing, sweating.

Musculoskeletal and connective tissue disorders: Back pain, muscle cramps, muscle spasm, myalgia, arthralgia, leg pain, arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthritis, coxalgia, fibromyalgia, muscle weakness.

Renal and urinary disorders: Glycosuria, renal dysfunction, interstitial nephritis, renal failure, nocturia, urinary frequency, urinary tract infection.

Reproductive system and breast disorders: Erectile dysfunction/impotence, decreased libido.

General disorders and administration site conditions: Chest pain, oedema/swelling, malaise, fever, asthenia, fatigue, facial oedema, dizziness.

Investigations: Liver function abnormalities, hyperkalaemia, mild reduction of haematocrit and haemoglobin, mild increase in urea and creatinine serum levels, increase in hepatic enzymes and bilirubin.

Interactions

Pharmacokinetic interactions

Losartan

In clinical pharmacokinetic trials, no medicine interactions of clinical significance have been identified with **hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital** (see Hydrochlorothiazide - *Alcohol, barbiturates, or narcotics* below), **ketoconazole and erythromycin**. **Rifampicin and fluconazole** have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

Potassium - As with other medicines 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.

Lithium - 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.

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 medicines may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics - potentiation of orthostatic hypotension may occur.

Antidiabetic medicines (oral agents and insulin) - the treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic medicine 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 medicines - 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 or glycyrrhizin (found in liquorice) - 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. Refer to the package insert for lithium preparations before use of such preparations.

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. Co-administration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden) - increase of the bioavailability of 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 effects of 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 antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- class III antiarrhythmics (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, halofantrine, mizolastine, 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.

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 administration.

Amphotericin B (parenteral), corticosteroids, ACTH or stimulant laxatives - hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

Medicine/laboratory test interactions - Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see Warnings and Precautions).

Losartan - Hydrochlorothiazide

Non-steroidal anti-inflammatory medicines (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) - these medicines may reduce the effect of diuretics and other antihypertensive medicines. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

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 (e.g. elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result

in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

Overdose

No specific information is available on the treatment of overdosage with Losartan HCTad. Treatment is symptomatic and supportive. Therapy with Losartan HCTad 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.

Further Information

Actions

Pharmacotherapeutic group

Angiotensin II Receptor Antagonists and diuretics. ATC codes: *C09CA01*

Mechanism of action (Losartan – Hydrochlorothiazide)

The components of Losartan HCTad 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.

Losartan and hydrochlorothiazide, when used in combination are additive in their antihypertensive efficacy.

The antihypertensive effect of Losartan HCTad 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.

In a study comparing the combination of losartan 50 mg/hydrochlorothiazide 12.5 mg with the combination captopril 50 mg/hydrochlorothiazide 25 mg in young (< 65 years) and elderly (\geq 65 years) hypertensive patients, the antihypertensive responses were similar between the two treatments and by age groups. Overall, there were statistically significantly fewer medicine-related clinical adverse experiences and discontinuations due to clinical adverse events with losartan 50 mg/hydrochlorothiazide 12.5 mg than with captopril 50mg/hydrochlorothiazide 25 mg.

A study with 131 patients with severe hypertension showed the utility of losartan potassium - hydrochlorothiazide administered as initial therapy and in a regimen with other antihypertensive agents after 12 weeks of therapy.

Losartan HCTad is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (< 65 years) and older (\geq 65 years) patients and is effective in all degrees of hypertension.

Pharmacokinetics

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 medicine 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.

Metabolism

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-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 excretions contribute to the elimination of losartan and its metabolites. Following an oral dose of ¹⁴C-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. Neither losartan nor the active metabolite can be removed by haemodialysis.

Other

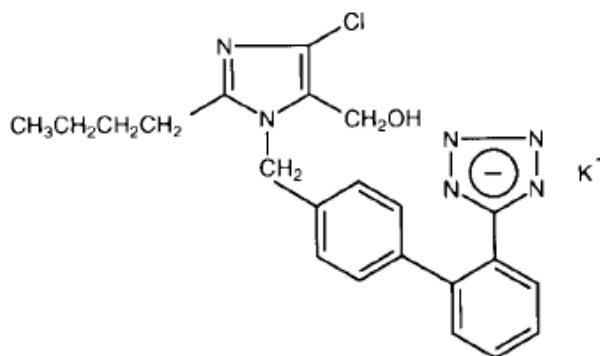
Chemistry

Losartan potassium

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-methanol monopotassium salt.

Empirical formula: C₂₂H₂₂ClKN₆O

Structural formula:



Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

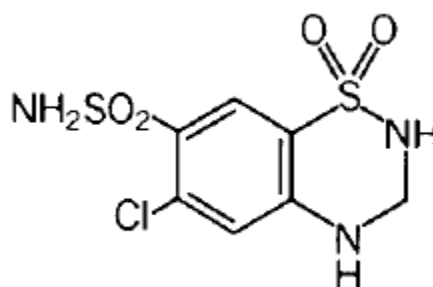
Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

Hydrochlorothiazide

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Empirical formula: C₇H₈ClN₃O₄S₂

Structural formula:



It is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Excipients

The excipients of Losartan HCTad 50mg/12.5mg are starch – pregelatinised, cellulose – microcrystalline, lactose monohydrate, magnesium stearate, hypromellose, macrogol 4000, quinoline yellow, titanium dioxide, talc - purified.

Losartan HCTad 50mg/12.5mg contains 4.24 mg (0.108 mEq) of potassium.

Contains lactose.

Pharmaceutical Precautions

Instructions for handling

Nil

Incompatibilities

Nil

Shelf-life

5 years

Special precautions for storage

Store below 30°C. Store in the original package to protect from moisture.

Package Quantities

Blister packs of 98 tablets.

Medicine Schedule

Prescription Only Medicine.

Sponsor Details

BNM Group
39 Anzac Road
Browns Bay
Auckland 0753

Ph: 0800 565 633

Date of Preparation

18 August 2011

