For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

LOSAR BETA-H

1. Generic Name

Losartan Potassium, Atenolol and Hydrochlorothiazide Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Losartan Potassium I.P. …… 50 mg

Atenolol I.P. ……..50 mg

Hydrochlorothiazide I.P..…..12.5 mg

Colour: Ferric Oxide Red NF

The excipients used are Starch, Lactose, Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Talc, Croscarmellose Sodium, Sodium Lauryl Sulphate, Crospovidone, Magnesium Stearate, Hydroxyl Propyl Methyl Cellulose, Dichloromethane, Titanium Dioxide, Polyethylene Glycol, Castor oil and Ferric Oxide Red.

3. Dosage form and strength

Dosage Form: Film Coated Tablet

Strength: Losartan Potassium 50 mg, Atenolol 50 mg, Hydrochlorothiazide 12.5 mg.

4. Clinical particulars

4.1 Therapeutic Indication

For the treatment of hypertension.

4.2 Posology and Method of Administration

As directed by the Physician.

4.3 Contraindications

- Hypersensitivity to losartan, sulphonamide-derived substances (as hydrochlorothiazide), active substance, to any of the excipients or any other ACE (Angiotensin Converting Enzyme) inhibitors or to any of the excipients.
- Therapy resistant hypokalaemia or hypercalcaemia.
- Severe hepatic impairment; cholestasis and biliary obstructive disorders.
- Refractory hyponatraemia.
- Symptomatic hyperuricaemia/gout.
- 2^{nd} and 3^{rd} trimester of pregnancy.
- Severe renal impairment (i.e. creatinine clearance <30 ml/min).
- Anuria
- The concomitant use of Losartan Potassium, Atenolol and Hydrochlorothiazide Tablets with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).
- Cardiogenic shock
- Uncontrolled heart failure
- Sick sinus syndrome (including sino-atrial block)

- Second-or third-degree heart block
- Untreated phaeochromocytoma
- Metabolic acidosis
- Bradycardia (< 50 bpm before treatment initiation)
- Hypotension
- Severe peripheral arterial circulatory disturbances.
- Severe asthma and severe chronic obstructive pulmonary disorders, such as airway obstructions.
- The intravenous application of calcium channel blockers (verapamil / diltiazem type) is contraindicated in patients who use atenolol (except in intensive care unit).

4.4 Special Warnings and Precautions for Use

Losartan

Angioedema

Patients with a history of angioedema (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 before the administration of Losartan Potassium, Atenolol and Hydrochlorothiazide tablets.

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, atenolol and hydrochlorothiazide is not recommended.

Liver function impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, Losartan Potassium, atenolol and 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, atenolol and Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment.

Renal function impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), 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 medicinal products 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 medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan Potassium, atenolol and Hydrochlorothiazide tablets 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 medicinal products acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

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

Ethnic differences

As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, 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.

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.

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.

Atenolol as with other beta-blockers:

- Should not be withdrawn abruptly. The dosage should be withdrawn gradually over a period of 7–14 days, to facilitate a reduction in beta-blocker dosage. Patients should be followed during withdrawal, especially those with ischaemic heart disease. Furthermore, there is a risk on myocardial infarction and sudden death.
- When a patient is scheduled for surgery, and a decision is made to discontinue beta-blocker therapy, this should be done at least 24 hours prior to the procedure. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypotension may be increased as well. The risk-benefit assessment of stopping beta-blockade should be made for each patient. If treatment is continued, an anaesthetic with little negative inotropic activity should be selected to minimise the risk of myocardial depression. The patient may be protected against vagal reactions by intravenous administration of atropine.
- Although contraindicated in uncontrolled heart failure, may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.
- May increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Atenolol is a $beta_1$-selective beta-blocker; consequently, its use may be considered although utmost caution must be exercised.
- Although contraindicated in severe peripheral arterial circulatory disturbances, may also aggravate less severe peripheral arterial circulatory disturbances (Raynaud's disease or syndrome, intermittent claudication).
- Due to its negative effect on conduction time, caution must be exercised if it is given to patients with first-degree heart block.
- May mask the symptoms of hypoglycaemia, in particular, tachycardia. Insulin sensitivity may be reduced in patients treated with atenolol.
- May mask the signs of thyrotoxicosis.
- Will reduce heart rate as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms, which may be attributable to a slow heart rate and the pulse rate drops to less than 50–55 bpm at rest, the dose should be reduced.
- May cause a more severe reaction to a variety of allergens when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline (epinephrine) used to treat the allergic reactions.
- May cause a hypersensitivity reaction including angioedema and urticaria.
- Should be used with caution in the elderly, starting with a lesser dose.
- Since Atenolol is excreted via the kidneys, dosage should be reduced in patients with a creatinine clearance of below 35 ml/min/1.73 m^2.
- Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with reversible obstructive airways disease, unless there are compelling clinical reasons for their use. Where such reasons exist, Atenolol may be used with caution. Occasionally, some increase in airways resistance may occur in asthmatic patients however, and this may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline. The label and patient information leaflet for this product state the following warning: “If you have ever had asthma or wheezing, you should not take this medicine unless you have discussed these symptoms with the prescribing doctor”.

- As with other beta-blockers, in patients with a phaeochromocytoma, an alpha-blocker should be given concomitantly.
- Patients with anamnestically known psoriasis should take atenolol only after careful consideration.

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. Dose adjustment of antidiabetic agents, including insulin, may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

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

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

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

Hepatic impairment

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, atenolol and Hydrochlorothiazide is contraindicated for patients with severe hepatic impairment.

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 exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide 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 hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC.

Other

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

Special warnings regarding excipients

Losartan Potassium, Atenolol and Hydrochlorothiazide contains lactose.

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

4.5 Drugs Interactions

Losartan

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

As with other medicinal products that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.

As with other medicinal products which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

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

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory medicinal products, 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.

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

Atenolol

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects, e.g. verapamil and diltiazem, can lead to an exaggeration of these effects particularly

in patients with impaired ventricular function and/or sinoatrial or atrioventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridines, e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Digitalis glycosides, in association with beta-blockers, may increase atrioventricular conduction time.

Beta-blockers may exacerbate the rebound hypertension, which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped. (See also prescribing information for clonidine.)

Caution must be exercised when prescribing a beta-blocker with Class I antiarrhythmic agents such as disopyramide, and quinidine which may have potentiating effect on atrial-conduction time and induce a negative inotropic effect.

Concomitant use of sympathomimetic agents, e.g. adrenaline (epinephrine), may counteract the effect of beta-blockers.

Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs. Symptoms of hypoglycaemia, particularly tachycardia, may be masked.

Concomitant use of prostaglandin synthetase-inhibiting drugs, e.g. ibuprofen and indomethacin, may decrease the hypotensive effects of beta-blockers.

Caution must be exercised when using anaesthetic agents with Atenolol. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression such as cyclopropane and trichlorethylene, lidocaine, procainamide and beta-adrenoceptor stimulants such as noradrenaline (norepinephrine) are best avoided.

Not recommended association with monoamineoxidase inhibitors (except MAO-B inhibitors)

Not recommended association with Baclofen: Causes an increased antihypertensive activity.

Not recommended association with contrast media, iodinated: Atenolol may impede the compensatory cardiovascular reactions associated with hypotension or shock induced by iodinated contrast products.

Amiodarone: Combination with atenolol may result in additive depressant effects on conduction and negative inotropic effects, especially in patients with underlying sinus node dysfunction or atrioventricular node dysfunction.

Ampicillin: May reduce the bioavailability of atenolol. Therefore, the physician should watch for evidence of altered atenolol response especially when large doses of ampicillin are administered concomitantly.

Peripheral muscle relaxants (e.g. Suxamethonium halogenide, Tubocurarine): concomitant use of atenolol could increase and extent the relaxative effect of muscle relaxants.

Hydrochlorothiazide

When given concurrently, the following medicinal products may interact with thiazide diuretics:

Alcohol, barbiturates, narcotics or antidepressants:

Potentiation of orthostatic hypotension may occur.

Antidiabetic medicinal products (oral agents and insulin):

The treatment with a thiazide may influence the glucose tolerance. Dose adjustment of the antidiabetic medicinal product 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 medicinal products:

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, non-depolarizing (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):

Dose adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dose 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 to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

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

Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Salicylates:

In case of high doses of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa:

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

Cyclosporin:

Concomitant treatment with cyclosporin 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, atenolol and 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 antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)

- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)

- Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

Calcium salts:

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

Laboratory Test Interactions:

Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function.

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 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

Losartan

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs):

The use of AIIRAs is not recommended during the first trimester of pregnancy. The use of AIIRAs is contra-indicated during the 2nd and 3rd trimester of 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 medicinal products. Unless continued AIIRA 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 AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

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

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

Infants whose mothers have taken AIIRAs should be closely observed for hypotension.

Atenolol

Caution should be exercised when Atenolol tablets is administered during pregnancy or to a woman who is breast-feeding.

Pregnancy

Atenolol crosses the placental barrier and appears in the cord blood. No studies have been performed on the use of Atenolol in the first trimester and the possibility of foetal injury cannot be excluded. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of Atenolol to pregnant women in the management of mild to moderate hypertension has been associated with intra-uterine growth retardation.

The use of Atenolol in women who are, or may become, pregnant requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters, since beta-blockers, in general, have been associated with a decrease in placental perfusion which may result in intra-uterine deaths, immature and premature deliveries.

Breast-feeding

There is significant accumulation of Atenolol in breast milk.

Neonates born to mothers who are receiving Atenolol at parturition or breast-feeding may be at risk of hypoglycaemia and bradycardia.

Hydrochlorothiazide

Pregnancy

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

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

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

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

Breast-feeding

Angiotensin II Receptor Antagonists (AIIRAs):

Because no information is available regarding the use of Losartan Potassium, atenolol and Hydrochlorothiazide during breastfeeding, Losartan Potassium, atenolol and Hydrochlorothiazide is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide:

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production.

The use of Losartan Potassium, atenolol and Hydrochlorothiazide during breast feeding is not recommended. If Losartan Potassium, atenolol and Hydrochlorothiazide is used during breast feeding, doses should be kept as low as possible.

4.7 Effects on Ability to Drive and Use Machines

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

However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness or fatigue 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 reported 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 salt, atenolol and/or hydrochlorothiazide.

In controlled clinical trials for 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

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

Losartan

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
	thrombocytopenia	not known
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, obstipation	uncommon
	pancreatitis	not known
General disorders and administration site conditions	asthenia, fatigue, chest pain	common
	facial oedema, oedema, fever	uncommon
	flu-like symptoms, malaise	not known

System organ class	Adverse reaction	Frequency
Hepatobiliary disorders	liver function abnormalities	not known
Immune system disorders	hypersensitivity: anaphylactic reactions, angiooedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angiooedema had been reported in the past in connection with the administration of other medicinal products, including ACE inhibitors;	rare
Metabolism and nutrition disorders	anorexia, gout	uncommon
Musculoskeletal and connective tissue disorders	muscle cramp, back pain, leg pain, myalgia	common
	arm 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
	dysgeusia	not known
Psychiatric disorders	insomnia	common
	anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment	uncommon
Renal and urinary disorders	renal impairment, renal failure	common
	nocturia, urinary frequency, urinary tract infection	uncommon
Reproductive system and breast disorders	decreased libido, erectile dysfunction/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
	dose-related orthostatic effects	not known
Investigations	hyperkalaemia, mild reduction of haematocrit and haemoglobin, hypoglycaemia	common
	mild increase in urea and creatinine serum levels	uncommon
	increase in hepatic enzymes and bilirubin	very rare

System organ class	Adverse reaction	Frequency
	hyponatraemia	non known

Atenolol

Atenolol is well tolerated. In clinical studies, the undesired events reported are usually attributable to the pharmacological actions of atenolol.

The following undesired events, listed by body system, have been reported with the following frequencies: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) including isolated reports, not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:

Rare: Purpura, thrombocytopenia, leucopenia.

Psychiatric disorders:

Uncommon: Sleep disturbances of the type noted with other beta-blockers.

Rare: Mood changes, depression, anxiety, nightmares, confusion, psychoses and hallucinations.

Nervous system disorders:

Rare: Dizziness, headache, paraesthesia of extremities.

Eye disorders:

Rare: Dry eyes, impaired vision, visual disturbances.

Cardiac disorders:

Common: Bradycardia.

Rare: Heart failure deterioration, precipitation of heart block.

Vascular disorders:

Common: Cold extremities.

Rare: Postural hypotension, which may be associated with syncope, intermittent claudication, may be increased if already present, in susceptible patients Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders:

Rare: Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

Gastrointestinal disorders:

Common: Gastrointestinal disturbances, constipation.

Rare: Dry mouth.

Hepato-biliary disorders:

Uncommon: Elevations of transaminase levels.

Rare: Hepatic toxicity including intrahepatic cholestasis.

Skin and subcutaneous tissue disorders:

Rare: Alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.

Not known: Hypersensitivity reactions, including angioedema and urticaria.

Musculoskeletal and connective tissue disorders:

Not known: Lupus like syndrome

Reproductive system and breast disorders:

Rare: Impotence.

General disorders and administration site conditions:

Common: Fatigue, sweating.

Investigations:

Very rare: An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear.

Discontinuance of the drug should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions.

Hydrochlorothiazide

System organ class	Adverse reaction	Frequency
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
Vascular disorders	Necrotizing angiitis (vasculitis, cutaneous vasculitis)	uncommon
Respiratory, thoracic and mediastinal disorders	Respiratory distress including pneumonitis and pulmonary oedema	uncommon
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
	cutaneous lupus erythematosus	not known
Musculoskeletal and connective tissue disorders	Muscle cramps	uncommon
Renal and urinary disorders	Glycosuria, interstitial nephritis, renal dysfunction, renal failure	uncommon

System organ class	Adverse reaction	Frequency
General disorders and administration site conditions	Fever, dizziness	uncommon

Description of Selected Adverse Reaction:

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose dependent association between hydrochlorothiazide and NMSC has been observed.

Reporting of 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. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com

4.9 Overdose

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

Losartan

Limited data are available in regard to overdose in humans. The most likely manifestation of overdose would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

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

Atenolol

The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision; treatment in an intensive care ward; the use of gastric lavage; activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract; the use of plasma or plasma substitutes to treat hypotension and shock. The possible uses of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can be countered with atropine 1–2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1–10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blocker blockade if a large overdose has been taken. The dose of dobutamine should

therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm can usually be reversed by bronchodilators.

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 Mechanism of Action

Losartan

Losartan is a synthetically produced oral angiotensin-II receptor (type AT1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the 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.

Atenolol

Atenolol is a beta-blocker, which is beta1-selective, (i.e. acts preferentially on beta1-adrenergic receptors in the heart). Selectivity decreases with increasing dose.

Atenolol is without intrinsic sympathomimetic and membrane-stabilising activities and as with other beta-blockers, has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure).

As with other beta-blockers, the mode of action of atenolol in the treatment of hypertension is unclear. It is probably the action of atenolol in reducing cardiac rate and contractility, which makes it effective in eliminating, or reducing the symptoms of patients with angina.

It is unlikely that any additional ancillary properties possessed by S (-) atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

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.

5.3 Pharmacodynamic Properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; Angiotensin II antagonists, Beta-blocking agents, plain, selective and diuretics:

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/hydrochlorothiazde is sustained for a 24-hour period. In reported 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/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/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 does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is thus no increase in bradykinin-mediated undesirable effects.

During the administration of losartan, the removal of the angiotensin II negative feedback on renin secretion leads to increased plasma-renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of the plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After the discontinuation of losartan, PRA and angiotensin II values fell within 3 days to the baseline values.

Both losartan and its principal active metabolite have a far greater affinity for the 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 reported 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 non-diabetic 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 reported controlled clinical studies, once-daily administration of losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurement of blood pressure 24 hours' post-dose relative to 5 – 6 hours' post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood pressure reduction at the end of the dosing interval was 70 – 80 % of the effect seen 5-6 hours 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 effect on heart rate.

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

LIFE Study

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

The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke.

Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

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

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

ONTARGET was a reported 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 reported 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.

Atenolol

Clinical efficacy and safety

Atenolol is effective and well tolerated in most ethnic populations although the response may be less in black patients.

Atenolol is effective for at least 24 hours after a single oral dose. The drug facilitates compliance by its acceptability to patients and simplicity of dosing. The narrow dose range and early patient response ensure that the effect of the drug in individual patients is quickly demonstrated. Atenolol is compatible with diuretics, other hypotensive agents and antianginals. Since it acts preferentially on beta-receptors in the heart, Atenolol may, with care, be used successfully in the treatment of patients with respiratory disease, who cannot tolerate non-selective beta-blockers.

Early intervention with Atenolol in acute myocardial infarction reduces infarct size and decreases morbidity and mortality. Fewer patients with a threatened infarction progress to frank infarction; the incidence of ventricular arrhythmias is decreased and marked pain relief may result in reduced need of opiate analgesics. Early mortality is decreased. Atenolol is an additional treatment to standard coronary care.

Hydrochlorothiazide

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 hydrochlorothiazide 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 hydrochlorothiazide 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 hydrochlorothiazide: 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).

5.3 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 active substance was administered with a standardized meal.

Atenolol

Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40–50%) with peak plasma concentrations occurring 2–4 hours after dosing. The bioavailability is decreased by 20% when taken with food. There is a linear relationship between dosage and plasma concentration. The inter-subject variability in AUC and Cmax is about 30-40%. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered.

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 blood brain barrier poorly, if at all.

Atenolol

Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. The volume of distribution is 50 to 75 L. The protein binding is low (approximately 3%). Most of an absorbed dose (85-100%) is excreted unchanged via the urine.

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-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

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

Elimination

Losartan

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

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

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

Atenolol

The clearance is about 6l/h and the half-life is about 6 to 9 hours. In elderly patients, clearance is decreased and elimination half-life increased. The clearance is correlated to renal function and the elimination is prolonged in patients with renal impairment. Impaired liver function does not influence the pharmacokinetics of atenolol.

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.

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

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

6. Nonclinical properties

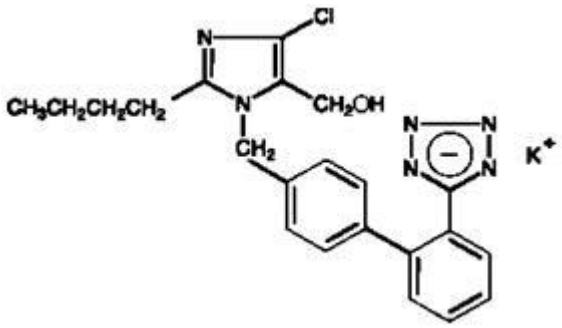
6.1 Animal Toxicology or Pharmacology

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, and 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 rats were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

7. Description

Losartan Potassium

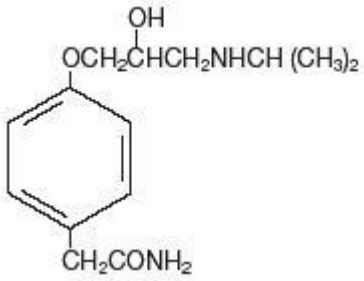
Losartan potassium is a monopotassium salt of 2-butyl-4-chloro-1-[[2´-(1H-tetrazol-5-yl)[1,1´-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol. Its empirical formula is $C_{22}H_{22}ClKN_6O$ having molecular weight of 461.0, and its structural formula is:



Losartan potassium is a white to off-white crystalline powder. It is freely soluble in water; sparingly soluble in isopropyl alcohol; slightly soluble in acetonitrile.

Atenolol

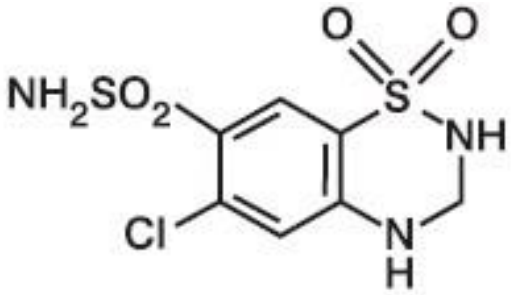
Atenolol is (RS)-4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide. Atenolol has a molecular weight of 266.34 and its empirical formula is $C_{14}H_{22}N_2O_3$. The chemical structure is:



Atenolol is a white or almost white powder, soluble in ethanol; sparingly soluble in water; slightly soluble in dichloromethane; practically insoluble in ether.

Hydrochlorothiazide

Hydrochlorothiazide is a white or almost white, crystalline powder; odourless with a molecular weight of 297.74. It is soluble in acetone; sparingly soluble in ethanol (95%); very slightly soluble in water. It dissolves in dilute solutions of alkali hydroxides. Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$, and its structural formula is:



Losartan Potassium, Atenolol and Hydrochlorothiazide Tablets are brown coloured, circular shaped slightly biconvex film coated tablets having plain on both sides. The excipients used are Starch, Lactose, Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Talc, Croscarmellose Sodium, Sodium Lauryl Sulphate, Crospovidone, Magnesium Stearate, Hydroxyl Propyl Methyl Cellulose, Dichloromethane, Titanium Dioxide, Polyethylene Glycol, Castor oil and Ferric Oxide Red.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

LOSAR BETA-H is available in Blister pack of 10 Tablets.

8.4 Storage and Handing Instructions

Store in a cool & dry place. Protect from light. Keep all medicines out of reach of children.

9. Patient counselling information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Manufactured in India by:

GKM New Pharma,

Spl Type No. 5, 6, 7 & 8,

PIPDIC Electronic Park, Thirubuvanai, Puducherry – 605107.

11. Details of permission or licence number with date

Mfg Lic No. 09 13 2634 issued on 15.06.2015.

12. Date of revision

Feb-26

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/LOSAR BETA-H 50, 50, 12.5 mg /FEB-26/02/PI