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

LOSAR - CH

1. Generic Name

Chlorthalidone & Losartan Potassium Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LOSAR – CH 6.25

Each film coated tablet contains:
Chlorthalidone I.P. ……..……6.25 mg
Losartan Potassium I.P. …….50 mg
Excipients……. q.s.
Colour: Sunset Yellow
The excipients used are Microcrystalline cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Starch, Aerosil, Sodium Starch Glycolate, Talc, Croscarmellose Sodium, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose E15, Methylene Dichloride, Sunset Yellow, Polyethylene Glycol 6000 & Castor oil.

LOSAR – CH 12.5

Each film coated tablet contains:
Chlorthalidone I.P. ……..……12.5 mg
Losartan Potassium I.P. …….50 mg
Excipients……. q.s.
Colour: Titanium Dioxide I.P.
The excipients used are Microcrystalline cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Starch, Aerosil, Sodium Starch Glycolate, Talc, Croscarmellose Sodium, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose E15, Methylene Dichloride, Titanium Dioxide, Polyethylene Glycol 6000 & Castor oil.

3. DOSAGE FORM AND STRENGTH

Dosage Form: Film Coated Tablet
Strength: Chlorthalidone 6.25mg/12.5mg & Losartan Potassium 50mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

For the treatment of mild to moderate hypertension in adult patients whose blood pressure is not adequately controlled by monotherapy.

4.2 Posology and Method Of Administration

Dosage: As directed by the Physician

Chlorthalidone

The dosage of Chlortalidone should be individually titrated to give the lowest effective dose; this is particularly important in the elderly. Chlortalidone should be taken orally, preferably as a single daily dose at breakfast time.

Adults:

Hypertension

The recommended starting dose is 25mg/day. This is sufficient to produce the maximum hypotensive effect in most patients. If the decrease in blood pressure proves inadequate with 25mg/day, then the dose can be increased to 50mg/day. If a further reduction in blood pressure is required, additional hypertensive therapy may be added to the dosage regime.

Stable, chronic heart failure (NYHA: functional class II /III):

The recommended starting dose is 25 to 50mg/day, in severe cases it may be increased up to 100 to 200mg/day. The usual maintenance dose is the lowest effective dose, eg 25 to 50mg/day either daily or every other day. If the response proves inadequate, digitalis or an ACE inhibitor, or both, may be added. (See "Special warnings and precautions for use").

Oedema of specific origin ("Therapeutic indications")

The lowest effective dose is to be identified by titration and administered over limited periods only. It is recommended that doses should not exceed 50mg/day.

Diabetes insipidus:

Initially 100mg twice daily but reducing where possible to a daily maintenance dose of 50mg.

Children:

The lowest effective dose should also be used in children. For example, an initial dose of 0.5 to 1mg/kg/48hours and a maximum dose of 1.7mg/kg/48hours have been used.

Elderly patients and patients with renal impairment:

The lowest effective dose of Chlortalidone is also recommended for patients with mild renal insufficiency and for elderly patients (see "Pharmacokinetic properties").

In elderly patients, the elimination of chlortalidone is slower than in healthy young adults, although absorption is the same. Therefore, a reduction in the recommended adult dosage may be needed. Close medical observation is indicated when treating patients of advanced age with chlortalidone.

Chlortalidone and the thiazide diuretics lose their diuretic effect when the creatinine clearance is <30ml/min.

Losartan Potassium

Posology

Hypertension

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning).

Losartan may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

Hypertensive type II diabetic patients with proteinuria ≥ 0.5 g/day

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month onwards after initiation of therapy. Losartan may be administered with other antihypertensive agents (e.g. diuretics, calcium channel

blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Heart Failure

The usual initial dose of losartan in patients with heart failure is 12.5 mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5 mg daily, 25 mg daily, 50 mg daily, 100 mg daily, up to a maximum dose of 150 mg once daily) as tolerated by the patient.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG

The usual starting dose is 50 mg of losartan once daily. A low dose of hydrochlorothiazide should be added and/or the dose of losartan should be increased to 100 mg once daily based on blood pressure response.

Special populations

Use in patients with intravascular volume depletion:

For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered.

Use in patients with renal impairment and haemodialysis patients:

No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

Use in patients with hepatic impairment:

A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment.

Paediatric population

6 months – less than 6 years

The safety and efficacy of children aged 6 months to less than 6 years has not been established.

6 years to 18 years

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients >20 to <50 kg. (In exceptional cases the dose can be increased to a maximum of 50 mg once daily). Dosage should be adjusted according to blood pressure response.

In patients >50 kg, the usual dose is 50 mg once daily. In exceptional cases the dose can be adjusted to a maximum of 100 mg once daily. Doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied in paediatric patients.

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.

It is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m^2, as no data are available .

Losartan is also not recommended in children with hepatic impairment.

Use in Elderly

Although consideration should be given to initiating therapy with 25 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.

Method of administration

Losartan tablets should be swallowed whole with a glass of water.

Losartan tablets may be administered with or without food.

4.3 Contraindications

•Known hypersensitivity to chlortalidone or any of the excipients.

•Anuria, severe hepatic or renal failure (creatinine clearance <30ml/min), hypersensitivity to chlortalidone and other sulphonamide derivatives, refractory hypokalaemia, hyponatraemia and hypercalcaemia, symptomatic hyperuricaemia (history of gout or uric acid calculi), hypertension during pregnancy, untreated Addison's disease and concomitant lithium therapy.

• 2^{nd} and 3^{rd} trimester of pregnancy

• Severe hepatic impairment.

• The concomitant use of losartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

4.4 Special Warnings And Precautions For Use

Chlorthalidone

Warnings:

Chlortalidone should be used with caution in patients with impaired hepatic function or progressive liver disease since minor changes in the fluid and electrolyte balance due to thiazide diuretics may precipitate hepatic coma, especially in patients with liver cirrhosis (see "Contra-indications").

Chlortalidone should also be used with caution in patients with severe renal disease. Thiazides may precipitate azotaemia in such patients, and the effects of repeated administration may be cumulative.

Precautions:

Electrolytes:

Treatment with thiazide diuretics has been associated with electrolyte disturbances such as hypokalaemia, hypomagnesaemia, hyperglycaemia and hyponatraemia. Since the excretion of electrolytes is increased, a very strict low-salt diet should be avoided.

Hypokalaemia can sensitise the heart or exaggerate its response to the toxic effects of digitalis.

Like all thiazide diuretics, kaluresis induced by Chlortalidone is dose dependent and varies in extent from one subject to another. With 25 to 50mg/day, the decrease in serum potassium concentrations averages 0.5mmol/l. Periodic serum electrolyte determinations should be carried out, particularly in digitalised patients.

If necessary, Chlortalidone may be combined with oral potassium supplements or a potassium-sparing diuretic (eg triamterene).

If hypokalaemia is accompanied by clinical signs (eg muscular weakness, paresis and ECG alteration), Chlortalidone should be discontinued.

Combined treatment consisting of Chlortalidone and a potassium salt or a potassium-sparing diuretic should be avoided in patients also receiving ACE inhibitors.

Monitoring of serum electrolytes is particularly indicated in the elderly, in patients with ascites due to liver cirrhosis, and in patients with oedema due to nephrotic syndrome. There have been isolated reports of hyponatraemia with neurological symptoms (eg nausea, debility, progressive disorientation and apathy) following thiazide treatment.

For nephrotic syndrome, Chlortalidone should be used only under close control in normokalaemic patients with no signs of volume depletion.

Metabolic effects:

Chlortalidone may raise the serum uric acid level, but attacks of gout are uncommon during chronic treatment.

As with the use of other thiazide diuretics, glucose intolerance may occur; this is manifest as hyperglycaemia and glycosuria. Chlortalidone may very seldom aggravate or precipitate diabetes mellitus; this is usually reversible on stopping therapy.

Small and partly reversible increases in plasma concentrations of total cholesterol, triglycerides, or low-density lipoprotein cholesterol were reported in patients during long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is a matter for debate.

Chlortalidone should not be used as a first-line drug for long-term treatment in patients with overt diabetes mellitus or in subjects receiving therapy for hypercholesterolaemia (diet or combined).

As with all antihypertensive agents, a cautious dosage schedule is indicated in patients with severe coronary or cerebral arteriosclerosis.

Other effects:

The antihypertensive effect of ACE inhibitors is potentiated by agents that increase plasma renin activity (diuretics). It is recommended that the diuretic be reduced in dosage or withdrawn for 2 to 3 days and/or that the ACE inhibitor therapy be started with a low initial dose of the ACE inhibitor. Patients should be monitored for several hours after the first dose.

Losartan Potassium

Hypersensitivity

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

Hypotension and Electrolyte/Fluid Imbalance

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

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group . Therefore, the plasma concentrations of potassium as well as

creatinine clearance values should be closely monitored, especially patients with heart failure and a creatinine clearance between 30-50 ml/min should be closely monitored.

The concomitant use of potassium-sparing diuretics, potassium supplements and potassium-containing salt substitutes with losartan is not recommended.

Hepatic impairment

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

Losartan is not recommended in children with hepatic impairment .

Renal impairment

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

Use in paediatric patients with renal impairment

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

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

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

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 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.

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

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

Excipients

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

Pregnancy

Losartan should not be initiated during pregnancy. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately, and, if appropriate, alternative therapy should be started.

Other warnings and precautions

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

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

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

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.

4.5 Drugs Interactions

Chlorthalidone

Diuretics potentiate the action of curare derivatives and antihypertensive drugs (e.g. guanethidine, methyldopa, β-blockers, vasodilators, calcium antagonists and ACE inhibitors).

The hypokalaemic effect of diuretics may be potentiated by corticosteroids, ACTH, ß2 – agonists, amphotericin and carbenoxolone.

It may prove necessary to adjust the dosage of insulin and oral anti-diabetic agents.

Thiazide-induced hypokalaemia or hypomagnesaemia may favour the occurrence of digitalis-induced cardiac arrhythmias (see"Special warnings and precautions for use").

Concomitant administration of certain non-steroidal anti-inflammatory drugs (e.g. indometacin) may reduce the diuretic and antihypertensive activity of Chlortalidone; there have been isolated reports of a deterioration in renal function in predisposed patients.

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (eg atropine, biperiden), apparently due to a decrease in gastrointestinal motility and stomach-emptying rate.

Absorption of thiazide diuretics is impaired in the presence of anionic exchange resins such as colestyramine. A decrease in the pharmacological effect may be expected.

Concurrent administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, increase the risk of adverse effects caused by amantadine, enhance the hyperglycaemic effect of diazoxide, and reduce renal excretion of cytotoxic agents (eg cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

The pharmacological effects of both calcium salts and vitamin D may be increased to clinically significant levels if given with thiazide diuretics. The resultant hypercalcaemia is usually transient but may be persistent and symptomatic (weakness, fatigue, anorexia) in patients with hyperparathyroidism.

Concomitant treatment with cyclosporin may increase the risk of hyperuricaemia and gout-type complications.

Thiazide and related diuretics can cause a rapid rise in serum lithium levels as the renal clearance of lithium is reduced by these compounds.

Losartan Potassium

Other antihypertensive agents may increase the hypotensive action of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan with rifampicin (inducer of metabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).

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

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

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.

Clinical trial data have 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

4.6 Use In Special Populations (Such As Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue the product as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Chlorthalidone

Diuretics are best avoided for the management of oedema or hypertension in pregnancy as their use may be associated with hypovolaemia, increased blood viscosity and reduced placental perfusion. There have been reports of foetal bone marrow depression, thrombocytopenia, and foetal and neonatal jaundice associated with the use of thiazide diuretics.

Chlortalidone passes into the breast milk; mothers taking Chlortalidone should refrain from breast-feeding their infants.

Losartan Potassium

Pregnancy

The use of losartan is not recommended during the first trimester of pregnancy. The use of losartan is contraindicated 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 anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

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

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

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

Breastfeeding

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

4.7 Effects On Ability To Drive And Use Machines

Chlorthalidone

Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness.

Losartan Potassium

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8 Undesirable Effects

Chlorthalidone

Frequency estimate: very rare <0.01%, rare ≤0.01% to ≤0.1%;uncommon ≤0.1% to <1%; common ≤1% to <10%; very common ≥10%.

Electrolytes and metabolic disorders:

Very common: mainly at higher doses, hypokalaemia, hyperuricaemia, and rise in blood lipids.

Common: hyponatraemia, hypomagnesaemia and hyperglycaemia.

Uncommon: gout.

Rare: hypercalcaemia, glycosuria, worsening of diabetic metabolic state.

Very rare: hypochloraemic alkalosis.

Skin:

Common: urticaria and other forms of skin rash.

Rare: photosensitisation.

Liver:

Rare: intrahepatic cholestasis or jaundice.

Cardiovascular system:

Common: postural hypotension.

Rare: cardiac arrhythmias.

Central nervous system:

Common: Dizziness.

Rare: paraesthesia, headache.

Gastro-intestinal tract:

Common: loss of appetite and minor gastrointestinal distress.

Rare: mild nausea and vomiting, gastric pain, constipation and diarrhoea.

Very rare: pancreatitis.

Blood:

Rare: Thrombocytopenia, leucopenia, agranulocytosis and eosinophilia.

Other effects:

Common: impotence

Rare: Idiosyncratic pulmonary oedema (respiratory disorders), allergic interstitial nephritis.

Losartan Potassium

Losartan has been evaluated in clinical studies as follows:

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

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

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

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

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

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

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

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

Table 1. The frequency of adverse reactions identified from placebo-controlled clinical studies and post marketing experience

Adverse reaction	**Frequency of adverse reaction by indication**				**Other**
	Hypertension	**Hypertensive patients with left-ventricular hypertrophy**	**Chronic Heart Failure**	**Hypertension and type 2 diabetes with renal disease**	**Post-marketing experience**
Blood and lymphatic system disorders					
Anaemia			common		frequency not known

thrombocytopenia					frequency not known
Immune system disorders					
hypersensitivity reactions, anaphylactic reactions, angiooedema*, and vasculitis**					rare
Psychiatric disorders					
Depression					frequency not known
Nervous system disorders					
Dizziness	common	common	common	common	
Somnolence	uncommon				
Headache	uncommon		uncommon		
sleep disorders	uncommon				
Paraesthesia			rare		
Migraine					frequency not known
Dysgeusia					frequency not known
Ear and labyrinth disorders					
Vertigo	common	common			
Tinnitus					frequency not known
Cardiac disorders					
Palpitations	uncommon				
angina pectoris	uncommon				
Syncope			rare		
atrial fibrillation			rare		
cerebrovascular accident			rare		
Vascular disorders					
(orthostatic) hypotension (including dose-related orthostatic effects)‖	uncommon		common	common	
Respiratory, thoracic and mediastinal disorders					
Dyspnoea			uncommon		
Cough			uncommon		frequency not known

Gastrointestinal disorders					
abdominal pain	uncommon				
Obstipation	uncommon				
Diarrhoea			uncommon		frequency not known
Nausea			uncommon		
Vomiting			uncommon		
Hepatobiliary disorders					
Pancreatitis					frequency not known
Hepatitis					rare
liver function abnormalities					frequency not known
Skin and subcutaneous tissue disorders					
urticarial			uncommon		frequency not known
Pruritus			uncommon		frequency not known
Rash	uncommon		uncommon		frequency not known
photosensitivity					frequency not known
Musculoskeletal and connective tissue disorders					
Myalgia					frequency not known
Arthralgia					frequency not known
rhabdomyolysis					frequency not known
Renal and urinary disorders					
renal impairment			common		
renal failure			common		
Reproductive system and breast disorders					
erectile dysfunction / impotence					frequency not known
General disorders and administration site conditions					
Asthenia	uncommon	common	uncommon	common	
Fatigue	uncommon	common	uncommon	common	
Oedema	uncommon				
Malaise					frequency not known
Investigations					

Hyperkalaemia	common		uncommon†	common‡	
increased alanine aminotransferase (ALT) §	rare				
increase in blood urea, serum creatinine, and serum potassium			common		
Hyponatraemia					frequency not known
hypoglycaemia				common	

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

**Including Henoch-Schönlein purpura

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

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

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

§Usually resolved upon discontinuation

The following additional adverse reactions occurred more frequently in patients who received losartan than placebo (frequencies not known): back pain, urinary tract infection, and flu-like symptoms.

Renal and urinary disorders:

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

Paediatric population

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

4.9 Overdose

Chlorthalidone

Signs and symptoms: In poisoning due to an overdosage the following signs and symptoms may occur: dizziness, nausea, somnolence, hypovolaemia, hypotension and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Treatment: There is no specific antidote to Chlortalidone. Gastric lavage, emesis or activated charcoal should be employed to reduce absorption. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken. Intravenous fluid and electrolyte replacement may be indicated.

Losartan Potassium

Symptoms of intoxication

Limited data are available with regard to overdose in humans. The most likely manifestation of overdose would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.

Treatment of intoxication

If symptomatic hypotension should occur, supportive treatment should be instituted.

Measures are depending on the time of medicinal product intake and kind and severity of symptoms. Stabilisation of the cardiovascular system should be given priority. After oral intake, the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism Of Action

Chlorthalidone

Chlortalidone is a benzothiadiazine (thiazide)-related diuretic with a long duration of action.

Thiazide and thiazide-like diuretics act primarily on the distal renal tubule (early convoluted part), inhibiting $NaCl^-$ reabsorption (by antagonising the $Na+Cl^-$ cotransporter) and promoting Ca++ reabsorption (by an unknown mechanism). The enhanced delivery of Na+ and water to the cortical collection tubule and/or the increased flow rate leads to increased secretion and excretion of K+ and H+.

Losartan Potassium

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

5.2 Pharmacodynamic Properties

Chlorthalidone

In persons with normal renal function, diuresis is induced after the administration of 12.5mg Chlortalidone. The resulting increase in urinary excretion of sodium and chloride and the less prominent increase in urinary potassium are dose dependent and occur both in normal and in oedematous patients. The diuretic effect sets in after 2 to 3 hours, reaches its maximum after 4 to 24 hours, and may persist for 2 to 3 days.

Thiazide-induced diuresis initially leads to decreases in plasma volume, cardiac output, and systemic blood pressure. The renin-angiotensin-aldosterone system may possibly become activated.

In hypertensive individuals, chlortalidone gently reduces blood pressure. On continued administration, the hypotensive effect is maintained, probably due to the fall in peripheral resistance; cardiac output returns to pretreatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated.

On chronic administration, the antihypertensive effect of Chlortalidone is dose dependent between 12.5 and 50mg/day. Raising the dose above 50mg increases metabolic complications and is rarely of therapeutic benefit.

As with other diuretics, when Chlortalidone is given as monotherapy, blood pressure control is achieved in about half of patients with mild to moderate hypertension. In general, elderly and black patients are found to respond well to diuretics given as primary therapy. Randomised clinical trials in the elderly have shown that treatment of hypertension or predominant systolic hypertension in older persons with low-dose thiazide diuretics, including chlortalidone, reduces cerebrovascular (stroke), coronary heart and total cardiovascular morbidity and mortality.

Combined treatment with other antihypertensive potentiates the blood-pressure lowering effects. In the large proportion of patients failing to respond adequately to monotherapy, a further decrease in blood pressure can thus be achieved.

In renal diabetes insipidus, Chlortalidone paradoxically reduces polyuria. The mechanism of action has not been elucidated.

Losartan Potassium

Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA01

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

Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.

During administration of losartan, 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 plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, PRA and angiotensin II values fell within three days to the baseline values.

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

Hypertension Studies

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

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

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

LIFE-Study

The Losartan Intervention For Endpoint Reduction in Hypertension [LIFE] study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left-ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or once daily atenolol 50 mg. If goal blood pressure (< 140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensive, 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.

Race

In the LIFE-Study black patients treated with losartan had a higher risk of suffering the primary combined endpoint, i.e. a cardiovascular event (e.g. cardiac infarction, cardiovascular death) and especially stroke, than the black patients treated with atenolol. Therefore the results observed with losartan in comparison with atenolol in the LIFE study with regard to cardiovascular morbidity/mortality do not apply for black patients with hypertension and left ventricular hypertrophy.

RENAAL Study

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan RENAAL study was a controlled clinical study conducted worldwide in 1513 Type 2 diabetic patients with proteinuria, with or without hypertension. 751 patients were treated with losartan.

The objective of the study was to demonstrate a nephroprotective effect of losartan potassium over and above the benefit of lowering blood pressure.

Patients with proteinuria and a serum creatinine of 1.3 – 3.0 mg/dl were randomised to receive losartan 50 mg once a day, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE-inhibitors and angiotensin II antagonists.

Investigators were instructed to titrate the study medication to 100 mg daily as appropriate; 72% of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting antihypertensive) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed up for up to 4.6 years (3.4 years on average). The primary endpoint of the study was a composite endpoint of doubling of the serum creatinine end-stage renal failure (need for dialysis or transplantation) or death.

The results showed that the treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p = 0.022) in the number of patients reaching the primary composite endpoint. For the following individual and combined components of the primary endpoint, the results showed a significant risk reduction in the group treated with losartan: 25.3% risk reduction for doubling of the serum creatinine (p = 0.006); 28.6% risk reduction for end-stage renal failure (p = 0.002); 19.9% risk reduction for end-stage renal failure or death (p = 0.009); 21.0% risk reduction for doubling of serum creatinine or end-stage renal failure (p = 0.01). All-cause mortality rate was not significantly different between the two treatment groups. In this study losartan was generally well tolerated, as shown by a therapy discontinuation rate on account of adverse reactions that was comparable to the placebo group.

HEAAL Study

The Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEAAL) study was a controlled clinical study conducted worldwide in 3834 patients aged 18 to 98 years with heart failure (NYHA Class II-IV) who were intolerant of ACE inhibitor treatment. Patients were randomised to receive losartan 50 mg once a day or losartan 150 mg, on a background of conventional therapy excluding ACE-inhibitors.

Patients were followed for over 4 years (median 4.7 years). The primary endpoint of the study was a composite endpoint of all-cause death or hospitalisation for heart failure.

The results showed that treatment with 150 mg losartan (828 events) as compared with 50 mg losartan (889 events) resulted in a 10.1% risk reduction (p=0.027, 95% confidence interval 0.82-0.99) in the number of patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of hospitalisation for heart failure. Treatment with 150 mg losartan reduced the risk of hospitalisation for heart failure by 13.5% relative to 50 mg losartan (p=0.025, 95% confidence interval 0.76-0.98). The rate of all cause death was not significantly different between the treatment groups. Renal impairment, hypotension, and hyperkalaemia were more common in the 150 mg group than in the 50 mg group, but these adverse events did not lead to significantly more treatment discontinuations in the 150 mg group.

ELITE I and ELITE II Studies

In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between the patients treated with losartan and those treated with captopril was observed with regard to the primary endpoint of a long-term change in renal function. The observation of the ELITE I Study, that compared with captopril, losartan reduced the mortality risk, was not confirmed in the subsequent ELITE II Study, which is described in the following.

In the ELITE II Study losartan 50 mg once daily (starting dose 12.5 mg, increased to 25 mg, then 50 mg once daily) was compared with captopril 50 mg three times daily (starting dose 12.5 mg, increased to 25 mg and then to 50 mg three times daily). The primary endpoint of this prospective study was the all-cause mortality.

In this study, 3152 patients with heart failure (NYHA Class II-IV) were followed for almost two years (median: 1.5 years) in order to determine whether losartan is superior to captopril in reducing all-cause mortality. The primary endpoint did not show any statistically significant difference between losartan and captopril in reducing all-cause mortality.

In both comparator-controlled (not placebo-controlled) clinical studies on patients with heart failure the tolerability of losartan was superior to that of captopril, measured on the basis of a

significantly lower rate of discontinuations of therapy on account of adverse reactions and a significantly lower frequency of cough.

An increased mortality was observed in ELITE II in the small subgroup (22% of all HF patients) taking beta-blockers at baseline.

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

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

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

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

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

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

Paediatric Population

Paediatric Hypertension

The antihypertensive effect of losartan was established in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age with a body weight > 20 kg and a glomerular filtration rate > 30 ml/min/1.73 m^2. Patients who weighed > 20 kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious in the low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg), but was attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/ kg, did not appear to offer consistent antihypertensive efficacy.

These results were confirmed during period II of the study where patients were randomised to continue losartan or placebo, after three weeks of treatment. The difference in blood pressure

increase as compared to placebo was largest in the middle dose group (6.70 mmHg middle dose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

Long-term effects of losartan on growth, puberty and general development have not been studied. The long-term efficacy of antihypertensive therapy with losartan in childhood to reduce cardiovascular morbidity and mortality has also not been established.

In hypertensive (N=60) and normotensive (N=246) children with proteinuria, the effect of losartan on proteinuria was evaluated in a 12-week placebo- and active-controlled (amlodipine) clinical study. Proteinuria was defined as urinary protein/creatinine ratio of ≥0.3. The hypertensive patients (ages 6 through 18 years) were randomised to receive either losartan (n=30) or amlodipine (n=30). The normotensive patients (ages 1 through 18 years) were randomised to receive either losartan (n=122) or placebo (n=124). Losartan was given at doses of 0.7 mg/kg to 1.4 mg/kg (up to maximum dose of 100 mg per day). Amlodipine was given at doses of 0.05 mg/kg to 0.2 mg/kg (up to a maximum dose of 5 mg per day).

Overall, after 12 weeks of treatment, patients receiving losartan experienced a statistically significant reduction from baseline in proteinuria of 36% versus 1% increase in placebo/amlodipine group ($p \leq 0.001$). Hypertensive patients receiving losartan experienced a reduction from baseline proteinuria of -41.5% (95% CI -29.9;-51.1) versus +2.4% (95% CI -22.2; 14.1) in the amlodipine group. The decline in both systolic blood pressure and diastolic blood pressure was greater in the losartan group (-5.5/-3.8 mmHg) versus the amlodipine group (-0.1/+0.8 mmHg). In normotensive children a small decrease in blood pressure was observed in the losartan group (-3.7/-3.4 mmHg) compared to placebo. No significant correlation between the decline in proteinuria and blood pressure was noted, however it is possible that the decline in blood pressure was responsible, in part, for the decline in proteinuria in the losartan treated group.

Long-term effects of losartan in children with proteinuria were studied for up to 3 years in the open-label safety extension phase of the same study, in which all patients completing the 12-week base study were invited to participate. A total of 268 patients entered the open-label extension phase and were re-randomized to losartan (N=134) or enalapril (N=134) and 109 patients had ≥3 years of follow-up (pre-specified termination point of ≥100 patients completing 3 years of follow-up in the extension period). The dose ranges of losartan and enalapril, given according to investigator discretion, were 0.30 to 4.42 mg/kg/day and 0.02 to 1.13 mg/kg/day, respectively. The maximum daily doses of 50 mg for <50 kg body weight and 100 mg>50 kg were not exceeded for most patients during the extension phase of the study.

In summary, the results of the safety extension show that losartan was well-tolerated and led to sustained decreases in proteinuria with no appreciable change in glomerular filtration rate (GFR) over 3 years. For normotensive patients (n=205), enalapril had a numerically greater effect compared to losartan on proteinuria (-33.0% (95%CI -47.2;-15.0) vs -16.6% (95%CI -34.9; 6.8)) and on GFR (9.4 (95%CI 0.4; 18.4) vs -4.0 (95%CI -13.1; 5.0) ml/min/1.73m2)). For hypertensive patients (n=49), losartan had a numerically greater effect on proteinuria (-44.5% (95%CI -64.8; -12.4) vs -39.5% (95%CI -62.5; -2.2)) and GFR (18.9 (95%CI 5.2; 32.5) vs -13.4 (95%CI -27.3; 0.6)) ml/min/1.73m2.

An open label, dose-ranging clinical trial was conducted to study the safety and efficacy of losartan in paediatric patients aged 6 months to 6 years with hypertension. A total of 101 patients were randomized to one of three different starting doses of open-label losartan: a low dose of 0.1 mg/kg/day (N=33), a medium dose of 0.3 mg/kg/day (N=34), or a high dose of 0.7

mg/kg/day (N=34). Of these, 27 were infants which were defined as children aged 6 months to 23 months. Study medication was titrated to the next dose level at Weeks 3, 6, and 9 for patients that were not at blood pressure goal and not yet on the maximal dose (1.4 mg/kg/day, not to exceed 100 mg/day) of losartan.

Of the 99 patients treated with study medication, 90 (90.9%) patients continued to the extension study with follow up visits every 3 months. The mean duration of therapy was 264 days.

In summary, the mean blood pressure decrease from baseline was similar across all treatment groups (change from baseline to Week 3 in SBP was -7.3, -7.6, and -6.7 mmHg for the low-, medium-, and high-dose groups, respectively; the reduction from baseline to Week 3 in DBP was -8.2, -5.1, and -6.7 mmHg for the low-, medium-, and high-dose groups.); however, there was no statistically significant dose-dependent response effect for SBP and DBP.

Losartan, at doses as high as 1.4 mg/kg, was generally well tolerated in hypertensive children aged 6 months to 6 years after 12 weeks of treatment. The overall safety profile appeared comparable between treatment groups.

5.3 Pharmacokinetic Properties
Chlorthalidone

Absorption and plasma concentration

The bioavailability of an oral dose of 50mg Chlortalidone is approximately 64%, peak blood concentrations being attained after 8 to 12 hours. For doses of 25 and 50mg, Cmax values average 1.5µg/ml (4.4µmol/L) and 3.2µg/ml (9.4µmol/L) respectively. For doses up to 100mg there is a proportional increase in AUC. On repeated daily doses of 50mg, mean steady-state blood concentrations of 7.2µg/ml (21.2µmol/L), measured at the end of the 24 hour dosage interval, are reached after 1 to 2 weeks.

Distribution

In blood, only a small fraction of chlortalidone is free, due to extensive accumulation in erythrocytes and binding to plasma proteins. Owing to the large degree of high affinity binding to the carbonic anhydrase of erythrocytes, only some 1.4% of the total amount of chlortalidone in whole blood was found in plasma at steady state during treatment with 50mg doses. In vitro, plasma protein binding of chlortalidone is about 76% and the major binding protein is albumin.

Chlortalidone crosses the placental barrier and passes into the breast milk. In mothers treated with 50mg chlortalidone daily before and after delivery, chlortalidone levels in fetal whole blood are about 15% of those found in maternal blood. Chlortalidone concentrations in amniotic fluid and in the maternal milk are approximately 4% of the corresponding maternal blood level.

Metabolism

Metabolism and hepatic excretion into bile constitute a minor pathway of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and the faeces, mainly in unchanged form.

Elimination

Chlortalidone is eliminated from whole blood and plasma with an elimination half-life averaging 50 hours. The elimination half-life is unaltered after chronic administration. The major part of an absorbed dose of chlortalidone is excreted by the kidneys, with a mean renal clearance of 60ml/min.

Special patient groups

Renal dysfunction does not alter the pharmacokinetics of chlortalidone, the rate-limiting factor in the elimination of the drug from blood or plasma being most probably the affinity of the drug to the carbonic anhydrase of erythrocytes.

No dosage adjustment is needed in patients with impaired renal function.

In elderly patients, the elimination of chlortalidone is slower than in healthy young adults, although absorption is the same. Therefore, close medical observation is indicated when treating patients of advanced age with chlortalidone.

Losartan Potassium

Absorption

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.

Distribution

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

Biotransformation

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

In addition to the active metabolite, inactive metabolites are formed.

Elimination

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/intravenous administration of ^{14}C-labelled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58%/ 50% in the faeces.

Characteristics in patients

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

In female hypertensive patients the plasma levels of losartan were up to twice as high as in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women. In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma levels of losartan and its active metabolite after oral administration were respectively 5 and 1.7 times higher than in young male volunteers.

Plasma concentrations of losartan are not altered in patients with a creatinine clearance above 10 ml/minute. Compared to patients with normal renal function, the AUC for losartan is about 2-times higher in haemodialysis patients. The plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients.

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

Pharmacokinetics in paediatric patients

The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/ kg of losartan (mean doses).

The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughly similar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/ toddlers was comparatively high.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology Or Pharmacology

Chlorthalidone

There are no pre-clinical data of relevance to the prescriber.

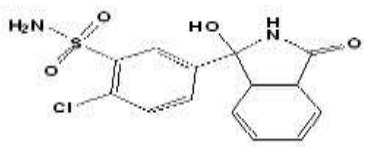
Losartan Potassium

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse reactions on the late foetal development, resulting in foetal death and malformations.

7. DESCRIPTION

Chlorthalidone

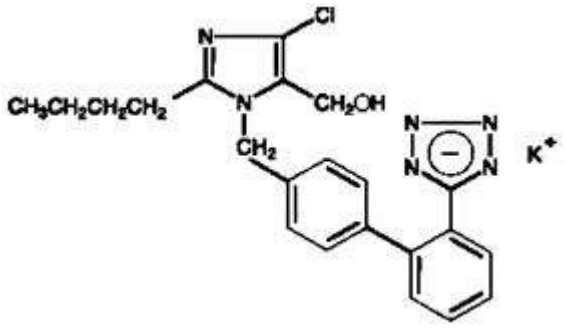
Chlorthalidone is chemically described as (RS)-2-chloro-5-(1-hydroxy-3-oxoisoindolin-1-yl)benzenesulphonamide. Its empirical formula is $C_{14}H_{11}ClN_2O_4S$ with a molecular weight of 338.76. The structural formula for chlorthalidone is:



Chlorthalidone is a white to yellowish-white, crystalline powder which is soluble in methanol; slightly soluble in ethanol (95%); practically insoluble in water, in ether and in chloroform.

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.

LOSAR – CH 6.25

Chlorthalidone & Losartan Potassium Tablets are an orange colour, circular shaped slightly biconvex, film coated tablets having plain on both sides. The excipients used are Microcrystalline cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Starch, Aerosil, Sodium Starch Glycolate, Talc, Croscarmellose Sodium, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose E15, Methylene Dichloride, Sunset Yellow, Polyethylene Glycol 6000 & Castor oil.

LOSAR – CH 12.5

Chlorthalidone & Losartan Potassium Tablets are a white colour, circular shaped slightly biconvex, film coated tablets having plain on both sides. The excipients used are Microcrystalline cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Starch, Aerosil, Sodium Starch Glycolate, Talc, Croscarmellose Sodium, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose E15, Methylene Dichloride, Titanium Dioxide, Polyethylene Glycol 6000 & Castor oil.

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 – CH is available in blister strip of 10 tablets.

8.4 Storage and Handing Instructions

Store in a cool and dry place. Protect from light and moisture.

Keep all medicines out of reach of children.

9. PATIENT COUNSELLING INFORMATION

LOSAR – CH

Read all of this leaflet carefully before you start taking this medicine

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet please tell your doctor or pharmacist.

The information in this leaflet has been divided into the following sections:

9.1 **What LOSAR – CH and what it is taken for**

9.2 **Check before you take LOSAR – CH**

9.3 **How to take LOSAR – CH**

9.4 **Possible side effects**

9.5 **How to store LOSAR – CH**

9.6 **Contents of the pack and other information**

9.1 **What LOSAR – CH is and what it is taken for**

LOSAR – CH is combination of LOSAR – CH belongs to a group of medicines called thiazide diuretics. Thiazide diuretics help to reduce the amount of water in your body. They do this by increasing the amount of water that you pass as urine. They are sometimes called 'water tablets'.
LOSAR – CH is used to:
For the treatment of mild to moderate hypertension in adult patients whose blood pressure is not adequately controlled by monotherapy.

9.2 **Check before you take LOSAR – CH**

Do not take LOSAR – CH :

- if you are allergic (hypersensitive) to chlortalidone, sulphonamides such as sulfamethoxazole
- or any of the ingredients of LOSAR – CH
- if you are not passing any urine at all
- if you have severe kidney or liver problems
- if you have low blood levels of potassium which can cause muscle weakness, muscle
- twitching or abnormal heartbeat
- if you have low blood levels of sodium which can cause tiredness, confusion, muscle
- twitching, fits or coma
- if you have high blood levels of calcium which can cause loss of appetite, tiredness or muscle
- weakness
- if you have ever had gout or kidney stones
- if you have Addison's disease (which is a condition where your adrenal gland is not producing enough steroids)
- if you are taking lithium.
- If any of the above applies to you, or if you are not sure, speak to your doctor or pharmacist before you take LOSAR – CH.

- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren

Warnings and precautions

Talk to your doctor, pharmacist, or nurse before taking LOSAR – CH

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

It is important to tell your doctor before taking LOSAR – CH:

• if you have had a history of angiooedema (swelling of the face, lips, throat, and/or tongue),

- if you suffer from excessive vomiting or diarrhoea leading to an extreme loss of fluid and/or salt in your body,
- if you receive diuretics (medicines that increase the amount of water that you pass out through your kidneys) or are under dietary salt restriction leading to an extreme loss of fluid and salt in your body,
- if you are known to have narrowing or blockage of the blood vessels leading to your kidneys or if you have received a kidney transplant recently,
- if your liver function is impaired,
- if you suffer from heart failure with or without renal impairment or concomitant severe life threatening cardiac arrhythmias. Special caution is necessary when you are treated with a ß-blocker concomitantly,
- if you have problems with your heart valves or heart muscle,
- if you suffer from coronary heart disease (caused by a reduced blood flow in the blood vessels of the heart) or from cerebrovascular disease (caused by a reduced blood circulation in the brain),
- if you suffer from primary hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldosterone by the adrenal gland, caused by an abnormality within the gland),
- if you are taking any of the following medicines used to treat high blood pressure:
  - An ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
  - aliskiren

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

See also information under the heading "

Do not take LOSAR – CH".

Children and adolescents

LOSAR – CH has been studied in children. For more information, talk to your doctor.

LOSAR – CH is not recommended for use in children suffering from kidney or liver problems, as limited data are available in these patient groups. LOSAR – CH is not recommended for use in children under 6 years old, as it has not been shown to work in this age group.

Take special care with LOSAR – CH

Before you take LOSAR – CH tell your doctor if:

- you suffer from any other liver or kidney problems
- you are on a low-salt diet
- you suffer from diabetes mellitus (increased levels of sugar in the blood)
- you have high cholesterol levels
- if you have recently had an anaesthetic

- you are elderly.

If any of the above applies to you, or if you are not sure, speak to your doctor or pharmacist before you take LOSAR – CH .

Taking other medicines

Tell your doctor or pharmacist if you are taking or have recently taken any of the following medicines as they may interfere with LOSAR – CH : □other treatments for high blood pressure or heart problems such as: - ACE inhibitors (for example, lisinopril) - beta blockers (for example propranolol hydrochloride) - methyldopa - vasodilators (for example baseman) - calcium channel blockers (for example amlodipine) - guanethidine	□adrenocorticotropic hormone (ACTH) - used to treat a number of different conditions, including ulcerative colitis, Crohn's disease and rheumatoid arthritis
corticosteroids such as prednisolone or betamethasone - used to treat allergic and inflammatory diseases and immune reactions	□anticholinergics such as atropine sulphate or hyoscine butyl bromide - for abdominal or stomach spasms or cramps
□□cytotoxic agents such as cyclophosphamide or methotrexate - used to treat cancer	□□colestyramine - used to reduce cholesterol levels and prevent heart disease
□□asthma treatments such as salbutamol or formoterol	□□amantadine - used to treat Parkinson’s disease or viral infections
□□amphotericin - used to treat infections	□□allopurinol - used to treat gout
□□carbenoxolone - used to treat ulcers	□□calcium salts or vitamin D - used for replacement therapy
□□insulin and other treatments for diabetes such as chlorpropamide or glibenclamide	□□non-steroidal anti-inflammatories (NSAIDs) such as aspirin or indometacin - used for pain relief or rheumatism
□□digoxin - for an irregular heartbeat	□□ciclosporin - used to treat rheumatic disease or skin complaints or after a transplant
□□lithium - used to treat mental illness	

Driving and using machines
If you feel dizzy when you start taking these tablets, do not drive or work with machinery until these effects have worn off.

9.3 **How to take LOSAR – CH**

Always take LOSAR – CH exactly as your doctor has told you to.

It is important to take your tablets at the right time. You should check with your doctor or pharmacist if you are not sure.

Your doctor will choose a suitable starting dose for your particular condition and monitor your progress. If necessary, this dose can be increased or reduced.

Whilst you are taking LOSAR – CH , your doctor may want to carry out a number of tests from time to time. This is quite usual and nothing to worry about. It is best to take LOSAR – CH in the morning with food. Swallow your tablets whole with a drink of water.

Adults

The usual doses for adults are as follows:

• High blood pressure:

The starting dose is 25 mg (half a tablet) a day. Your doctor may increase this to 50 mg (one tablet) a day if necessary of LOSAR – CH and. 50 mg LOSAR – CH

• Heart failure:

The starting dose is 25mg (half a tablet) a day. Your doctor may increase this up to 200 mg (four tablets) a day if necessary. The maximal blood pressure lowering effect should be reached 3-6 weeks after beginning treatment. In some patients the dose may later be increased to 100 mg LOSAR – CH (two tablets) • Fluid retention associated with kidney or liver disease:

Up to 50 mg (one tablet) a day.

• Diabetes insipidus (a disease in which an individual produces large amounts of dilute urine and is constantly thirsty):

The starting dose is 100mg (two tablets) twice a day. Your doctor may reduce your dose to 50mg (one tablet) a day.

Children: Your doctor will choose a suitable dose based on your child's age and weight.

Elderly patients or those with kidney problems

Your doctor may give you a lower dose because your body may not get rid of LOSAR – CH as quickly as normal.

If you are not sure how many tablets to take, ask your doctor or pharmacist. Do not stop taking your tablets suddenly. Ask your doctor first.

Dosage in special patient groups

The doctor may advise a lower dose, especially when starting treatment in certain patients such as those treated with diuretics in high doses, in patients with liver impairment, or in patients over the age of 75 years. The use of LOSAR – CH is not recommended in patients with severe hepatic impairment.

Administration
The tablets should be swallowed whole with a glass of water. You should try to take your daily dose at about the same time each day. It is important that you continue to take LOSAR – CH until your doctor tells you otherwise.
What to do if you take more LOSAR – CH than you should
If you accidentally take too many tablets, or someone else takes any of your medicine, you should tell your doctor immediately or contact your nearest accident and emergency department because you may need urgent treatment. Show any left-over medicines or the empty packet to the doctor. Symptoms of overdose are low blood pressure, increased heartbeat, possibly decreased heartbeat.
If you forget to take LOSAR – CH
If you accidentally miss a daily dose, just take the next dose as normal. Do not take a double dose to make up for a forgotten tablet. If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

9.4 **. Possible side effects**
Do not worry. Like all medicines, LOSAR – CH can cause side effects, although not everyone gets them.
If you get any of the following tell your doctor or pharmacist immediately as they may tell you to stop taking LOSAR – CH:
• Muscles feel weak or will not work properly
• Irregular heartbeat.
A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing).
Very common side effects (that affect more than 1 person in 10)
• low blood levels of potassium which can cause muscle weakness, muscle twitching or abnormal heartbeat This is a serious but rare side effect, which affects more than 1 out of 10,000 patients but fewer than 1 out of 1,000 patients. You may need urgent medical attention or hospitalisation.
The following side effects have been reported with LOSAR – CH
• increased blood levels of uric acid
• increased blood levels of cholesterol.
Common side effects (that affect less than 1 person in 10)
- low levels of sodium which can cause tiredness, confusion, muscle twitching, fits or coma
- low levels of magnesium
- high blood sugar levels which can cause tiredness, weakness or feeling thirsty
- nettle rash
- skin rash
- low blood pressure (especially after excessive loss of water from the body within blood vessels e.g. in patients with severe heart failure or under treatment with high dose diuretics),
- dizziness
- loss of appetite
- upset stomach
- impotence in men.
- debility,
- fatigue
- too little sugar in the blood (hypoglycaemia),
- too much potassium in the blood (hyperkalaemia),
- changes in kidney function including kidney failure,

- reduced number of red blood cells (anaemia),
- increase in blood urea, serum creatinine and serum potassium in patients with heart failure.

Uncommon side effects (that affect less than 1 person in 100)
- gout which causes pain and swelling in the joints.
- somnolence,
- headache,
- sleep disorders,
- feeling of increased heart rate (palpitations),
- severe chest pain (angina pectoris),
- shortness of breath (dyspnoea),
- abdominal pain,
- obstipation,
- diarrhoea,
- nausea,
- vomiting,
- hives (urticaria),
- itching (pruritus),
- rash,
- localised swelling (oedema),
- cough.

Rare side effects (that affect less than 1 person in 1000)
- increased calcium in the blood which can cause agitation, sore eyes, abdominal pain
- sugar in the urine (this would show up when your doctor or nurse tests your urine)
- worsening of diabetes
- yellowing of the skin or eyes caused by liver or blood problems (jaundice)
- increased sensitivity of your skin to sunlight
- abnormal heartbeat the symptoms of which include palpitations and fainting
- pins and needles
- headache
- feeling or being sick
- stomach pain
- constipation
- diarrhoea
- reduction in blood platelets which increases the risk of bruising or bleeding
- severe reduction in the number of white blood cells which makes infection more likely
- an abnormally high amount of eosinophils (type of white blood cell) in the blood
- breathing problems
- problems with your kidneys.
- hypersensitivity,
- angiooedema,
- inflammation of blood vessels (vasculitis including Henoch-Schönlein purpura),
- numbness or tingling sensation (paraesthesia),
- fainting (syncope),
- very rapid and irregular heartbeat (atrial fibrillation),
- brain attack (stroke),
- inflammation of the liver (hepatitis),

- elevated blood alanine aminotransferase (ALT) levels, usually resolved upon discontinuation of treatment.
- *Not known (frequency cannot be estimated from the available data):*
- reduced number of thrombocytes,
- migraine,
- liver function abnormalities,
- muscle and joint pain,
- flu-like symptoms,
- back pain and urinary tract infection,
- increased sensitivity to the sun (photosensitivity),
- unexplained muscle pain with dark (tea-coloured) urine (rhabdomyolysis),
- impotence,
- inflammation of the pancreas (pancreatitis),
- low levels of sodium in the blood (hyponatraemia),
- depression,
- generally feeling unwell (malaise),
- ringing, buzzing, roaring, or clicking in the ears (tinnitus),
- disturbed taste (dysgeusia).

Side effects in children are similar to those seen in adults.

Very rare side effects (that affect less than 1 person in 10 000)
• Low levels of chloride in the blood, symptoms include dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, restlessness, seizures, confusion, headache, muscle pains or cramps, hypotension
• Inflammation of the pancreas which causes severe stomach and back pain.

If any of the side effects gets worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

9.5 **How to store LOSAR – CH**
Store in a cool and dry place. Protect from light and moisture.
Keep all medicines out of reach of children

9.6 Contents of the pack and other information

<u>LOSAR – CH 6.25</u>
Each film coated tablet contains:
Chlorthalidone 6.25 mg and Losartan Potassium 50 mg
The excipients used are Microcrystalline cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Starch, Aerosil, Sodium Starch Glycolate, Talc, Croscarmellose Sodium, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose E15, Methylene Dichloride, Sunset Yellow, Polyethylene Glycol 6000 & Castor oil. Colour: Sunset Yellow

LOSAR – CH 12.5

Each film coated tablet contains:
Chlorthalidone I.P. 12.5 mg and Losartan Potassium I.P 50 mg
Colour: Titanium Dioxide I.P.
The excipients used are Microcrystalline cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Starch, Aerosil, Sodium Starch Glycolate, Talc, Croscarmellose Sodium, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose E15, Methylene Dichloride, Titanium Dioxide, Polyethylene Glycol 6000 & Castor oil.

What LOSAR – CH looks like and contents of the pack

LOSAR – CH is available in blister strip of 10 tablets.

10. Details of manufacturer

Manufactured in India by:
GKM New Pharma
Spl Type Plot 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 17.12.2020

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ LOSAR – CH 6.25/12.5, 50mg/ Feb-21/01/PI