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

LOSAR BETA

1. Generic Name

Losartan Potassium & Atenolol Tablets

2. Qualitative and quantitative composition

Each film coated tablet Contains:

Losartan Potassium I.P.….50mg

Atenolol I.P. …….50mg

Excipients …… q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Starch, Microcrystalline Cellulose, Isopropyl Alcohol, Croscarmellose Sodium, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, and Methylene Chloride.

3. Dosage form and strength

Dosage form: Film Coated Tablet

Strength: Losartan Potassium50 mg Atenolol 50mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of systemic essential hypertension in adults only.

4.2 Posology and method of administration

Posology

Dose: As directed by physician

The dose must always be adjusted to individual requirements of the patients, with the lowest possible starting dosage.

Method of administration

For administration by the oral route.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients

• 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)

• Cardiogenic shock

• Uncontrolled heart failure

• Sick sinus syndrome

• Second-or third-degree heart block

• Untreated phaeochromocytoma

• Metabolic acidosis

• Bradycardia (<45 bpm)

• Hypotension

• Severe peripheral arterial circulatory disturbances.

4.4 Special warnings and precautions for use

Losartan Potassium

Hypersensitivity

Angioedema. Patients with a history of angioedema (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 reported 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.

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.

Atenolol

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.

• 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. 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.

• 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.

• 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 cardio selective ($beta_1$) 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.

4.5 Drugs interactions

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.

Reported 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.

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 dihydropyridine, 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.)

Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have a potentiating effect on atrial-conduction time and induce 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 indometacin, 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 are best avoided.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

The use of l Losar Beta is not recommended during the first trimester of pregnancy. The use of losartan is contraindicated during the 2nd and 3rd trimester of pregnancy.

Losar Beta Contains losartan which is Angiotensin II Receptor Inhibitors, (ACE inhibitors) In 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, and hyperkalaemia).

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

Losar Beta crosses the placental barrier and appears in the cord blood. Administration of Losar Beta to pregnant women in the management of mild to moderate hypertension has been associated with intra-uterine growth retardation.

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

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.

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 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

Losartan Potassium

Losartan has been evaluated in reported 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)

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

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

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, angioedema*, 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					
urticaria			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	

9. ***Including swelling of the larynx, glottis, face, lips, pharynx, and/or tongue (causing airway obstruction); in some of these patients angioedema 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.

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).

System Organ Class	**Frequency**	**Undesirable Effect**
Blood and lymphatic system disorders	Rare	Purpura, thrombocytopenia
Psychiatric disorders	Uncommon	Sleep disturbances of the type noted with other beta-blockers
	Rare	Mood changes, nightmares, confusion, psychoses and hallucinations
Nervous system disorders	Rare	Dizziness, headache, paraesthesia
Eye disorders	Rare	Dry eyes, 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
	Rare	Dry mouth
Hepatobiliary 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
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

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 and acute cardiac insufficiency and bronchospasm.

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. 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.. 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.

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.

5.. Pharmacological properties

5.1. Mechanism of Action

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.

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.

Atenolol

Atenolol is a beta-blocker which is $beta_1$-selective, (i.e. acts preferentially on $beta_1$-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.

5.2. Pharmacodynamics properties

Losartan Potassium

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

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 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' 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 reported 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

In the reported 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.

In reported study 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 Reported study, 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

The reported 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 pharmacodynamics 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

In the reported study 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≤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.

Atenolol

Pharmacotherapeutic group: Beta-blocking agents, plain, selective, ATC code: CO7A B03**.**

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.

5.3 Pharmacokinetic Properties

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

In the reported study 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.

Atenolol

Absorption

Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40–50%) with peak plasma concentrations occurring 2–4 hours after dosing. The atenolol blood levels are consistent and subject to little variability. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered.

Distribution

Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is low (approximately 3%).

Elimination

The plasma half-life is about 6 hours but this may rise in severe renal impairment since the kidney is the major route of elimination.

6 Nonclinical properties

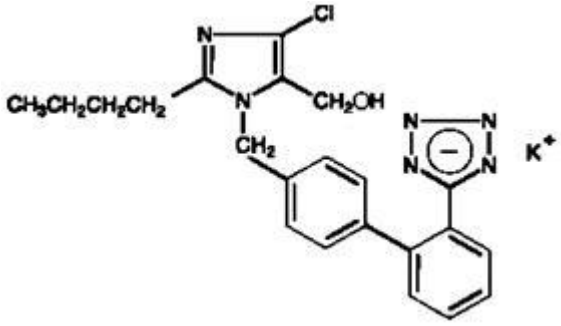
6.1. Animal Toxicology or Pharmacology

In reported Preclinical study 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

Losartan potassium

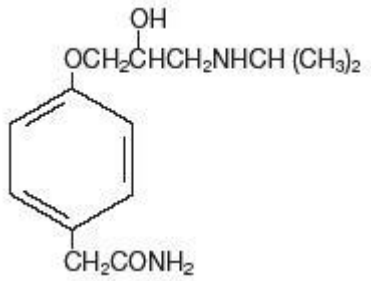
Losartan potassium is a monopotassium salt of 2-butyl-4-chloro-1-[[2´-(1H-tetrazol-5-yl)[1,1´-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol. Its empirical formula is $C_{22}H_{22}ClKN_6O$ having molecular weight of 461.0, and its structural formula is:



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.

Losartan Potassium & Atenolol Tablets are white coloured, circular, biconvex, film coated tablet with a "LB" debossed on one side and plain on other side. The excipients used are Starch, Microcrystalline Cellulose, Isopropyl Alcohol, Croscarmellose Sodium, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, and Methylene Chloride.

8. Pharmaceutical particular

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Losar Beta is available in blister strip of 15 tablets.

8.4 Storage and handing instructions

Store in a cool & dry place, protected from light. Keep all medicines out of reach of Children.

9. Patient Counselling Information

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

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

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

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

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.1.What Losar Beta is and what it is used for.

Losar Beta is combination of Losartan potassium and Atenolol.

Losartan potassium (belongs to a group of medicines known as angiotensin-II receptor antagonists.

Angiotensin-II is a substance produced in the body which binds to receptors in blood vessels, causing them to tighten. This results in an increase in blood pressure.) Losartan potassium prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax which in turn lowers the blood pressure. Losartan potassium slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes.

Losar Beta also contains a medicine called atenolol. This belongs to a group of medicines called beta-blockers.

Losar Beta is used for the treatment of systemic essential hypertension in adults only.

9.2 What you need to know before you use Losar Beta

Do not take Losar Beta:

If you are allergic to Losartan potassium and atenolol or to any of the other ingredients of this medicine,

If you are more than 3 months pregnant (It is also better to avoid LOSAR BETA in early pregnancy - see Pregnancy),

If your liver function is severely impaired,

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

If you have ever had any of the following heart problems:

Heart failure which is not under control (this usually makes you breathless and causes your ankles to swell) Second- or third-degree heart block (a condition which may be treated by a pacemaker) Very slow or very uneven heart beats, very low blood pressure or very poor circulation.

If you have a tumour called phaeochromocytoma that is not being treated. This is usually near your kidney and can cause high blood pressure. If you are being treated for phaeochromocytoma, your doctor will give you another medicine, called an alpha-blocker, to take as well as Losar Beta.

If you have been told that you have higher than normal levels of acid in your blood (metabolic acidosis).

Do not take Losar Beta if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Losar Beta.

Warnings and precautions

Talk to your doctor, pharmacist, or nurse before taking Losar Beta.

You must tell your doctor if you think you are (or might become) pregnant. Losar Beta 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 Beta:

You have asthma, wheezing or any other similar breathing problems, or you get allergic reactions, for example to insect stings. If you have ever had asthma or wheezing, do not take this medicine without first checking with your doctor.

If you have had a history of angioedema (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),

You have poor blood circulation or controlled heart failure.

You have first-degree heart block.

You have diabetes. Your medicine may change how you respond to having low blood sugar. You may feel your heart beating faster.

You have thyrotoxicosis (a condition caused by an overactive thyroid gland). Your medicine may hide the symptoms of thyrotoxicosis.

You have problems with your kidneys. You may need to have some check-ups during your treatment.

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.

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 “

Children and adolescents

Losar Beta has been studied in children. For more information, talk to your doctor. This medicine must not be given to children.

Other medicines and. Losar Beta

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. Take particular care if you are taking the following medicines while under treatment with. Losar Beta:

Other blood pressure lowering medicines as they may additionally reduce your blood pressure.E.g Verapamil, diltiazem and nifedipine (for high blood pressure or chest pain).

Blood pressure may also be lowered by one of the following drugs/ class of drugs: tricyclic antidepressants, antipsychotics, baclofen, amifostine, Medicines which retain potassium or may increase potassium levels (e.g. Potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines such as certain diuretics [amiloride, triamterene, spironolactone] or heparin),

Non-steroidal anti-inflammatory drugs such as indomethacin, including cox-2-inhibitors (medicines that reduce inflammation, and can be used to help relieve pain) as they may reduce the blood pressure lowering effect of Losartan potassium.

Clonidine (for high blood pressure or migraine). If you are taking clonidine and Losar Beta together, do not stop taking clonidine unless your doctor tells you to do so. If you have to stop taking clonidine, your doctor will give you careful instructions about how to do it.

Disopyramide, quinidine.

Digoxin (for heart problems).

Adrenaline, also known as epinephrine (a medicine that stimulates the heart).

Insulin or medicines that you take by mouth for diabetes.

Medicines to treat nose or sinus congestion or other cold remedies (including those you can buy in the pharmacy).

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

If you are taking an ACE-inhibitor or aliskiren (see also information under the headings

“**Do not take Losar Beta” and “Warnings and precautions**”

If your kidney function is impaired, the concomitant use of these medicines may lead to a worsening of the kidney function.

Lithium containing medicines should not be taken in combination with Losartan potassium without close supervision by your doctor. Special precautionary measures (e.g. blood tests) may be appropriate.

Operations

If you go into hospital to have an operation, tell the anaesthetist or medical staff that you are taking Losar Beta. This is because you can get low blood pressure (hypotension) if you are given certain anaesthetics while you are taking Losar Beta.

Pregnancy, breast-feeding and fertility

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

Driving and using machines

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

Losar Beta is unlikely to affect your ability to drive or use machines. However, as with many other medicines used to treat high blood pressure, LOSAR BETA may cause dizziness or drowsiness in some people. If you experience dizziness or drowsiness, you should consult your doctor before attempting such activities.

9.3 How to use Losar Beta

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

Dose: As directed by physician

Elderly

If you are an elderly person, your doctor may decide to give you a lower dose, particularly if you have problems with your kidneys.

People with severe kidney problems

If you have severe kidney problems your doctor may decide to give you a lower dose.

Use in children and adolescents

This medicine must not be given to children.

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 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 BETA is not recommended in patients with severe hepatic impairment until your doctor tells you otherwise.

If you take more LOSAR BETA than you should

If you take more Tenormin than prescribed by your doctor, talk to a doctor or go to a hospital

Straight away. Take the medicine pack with you so that the tablets can be identified. .

If you forget to take LOSAR BETA

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

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

If you experience the following, stop taking Losar Beta tablets and tell your doctor immediately or go to the casualty department of your nearest hospital:

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

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

The following side effects have been reported with Losar Beta:

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

• Dizziness,

• 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),

• dose-related orthostatic effects such as lowering of blood pressure appearing when rising from a lying or sitting position,

• Debility,

• 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.

• You may notice that your pulse rate becomes slower while you are taking the tablets. This is normal, but if you are concerned please tell your doctor about it.

• Cold hands and feet.

• Diarrhoea.

• Feeling sick (nausea).

• Feeling tired.

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

• 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 (may affect up to 1 in 1,000 people):

• Hypersensitivity,

• Angioedema,

• Inflammation of blood vessels (vasculitis including Henoch-Schönlein purpura),

• 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.

• Heart block (which can cause dizziness, abnormal heart beat, tiredness or fainting).

• Numbness and spasm in your fingers which is followed by warmth and pain (Raynaud's disease).

• Mood changes.

• Nightmares.

• Feeling confused.

• Changes in personality (psychoses) or hallucinations.

• Headache.

• Dizziness (particularly when standing up).

• Tingling of your hands.

• Being unable to get an erection (impotence).

• Dry mouth.

• Dry eyes.

• Disturbances of vision.

• Thinning of your hair.

• Skin rash.

• Reduced numbers of platelets in your blood (this may make you bruise more easily).

• Purplish marks on your skin.

• Jaundice (causing yellowing of your skin or the whites of your eyes).

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

• Changes to some of the cells or other parts of your blood. Your doctor may take blood samples every so often to check whether Losar Beta has had any effect on your blood.

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).

• Lupus-like syndrome (a disease where the immune system produces antibodies that attacks mainly skin and joints).

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

- **Reporting of side effects**

  If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

  By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store Losar Beta

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

9.6 Contents of the pack and other information

Each film coated tablet of Losar Beta Contains Losartan Potassium I.P 50mg and Atenolol I.P 50mg as active ingredients.

The excipients used are Starch, Microcrystalline Cellulose, Isopropyl Alcohol, Croscarmellose Sodium, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, and Methylene Chloride.

LOSAR BETA is available in blister strip of 15 tablets.

10. Details of manufacturer

Torrent Pharmaceuticals Ltd.

32 No. Middle Camp, NH-10, East District, Gangtok. Sikkim-737 135

11. Details of Permission or Licence Number with Date

Mfg Licence No.: M/563/2010 issued on 15.11.2017

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN/ Losar Beta 50, 50 mg/OCT-19/01/PI