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

LORAM

1. Generic Name:

Losartan Potassium and Ramipril Tablets

2. Qualitative and quantitative composition:

LORAM 2.5

Each film coated tablet contains:

Losartan Potassium I.P. ….50 mg

Ramipril I.P. ..... 2.5 mg

Excipients ……q. s

Colours: Erythrosine & Titanium Dioxide I.P.

Excipients used: Microcrystalline Cellulose, Starch, Isopropyl Alcohol, Sodium Bicarbonate, Colloidal Silicon Dioxide, Crospovidone, Talc, Magnesium Stearate, Opadry OY-C-7000A, Lake of Erythrosine and Methylene Chloride.

LORAM 5

Each film coated tablet contains:

Losartan Potassium I.P. ….50 mg

Ramipril I.P. ……..…....5 mg

Excipients ……. q. s.

Colours: Indigo carmine & Titanium Dioxide I.P.

Excipients used: Microcrystalline Cellulose, Starch, Isopropyl Alcohol, Sodium Bicarbonate, Colloidal Silicon Dioxide, Crospovidone, Talc, Magnesium Stearate, Opadry OY-C-7000A, Lake of Indigo carmine and Methylene Chloride.

3. Dosage form and strength:

Dosage form: Film coated tablet

Strength: Losartan Potassium 50 mg and Ramipril 2.5/5 mg

4. Clinical particulars:

4.1 Therapeutic indication:

Treatment of mild to moderate hypertension.

4.2 Posology and method of administration:

Posology

Hypertension

The dose should be individualised according to the patient profile and blood pressure control.

Losartan Potassium and Ramipril Tablets may be used in monotherapy or in combination with other classes of antihypertensive medicinal products. The usual starting and maintenance dose of Losartan is 50 mg and Ramipril is 2.5 mg once daily for most patients. Patients with a strongly activated renin-angiotensin-aldosterone system may experience an excessive drop in blood

pressure following the initial dose. A starting dose of 1.25 mg Ramipril is recommended in such patients and the initiation of treatment should take place under medical supervision. The maximum permitted dose of Ramipril is 10 mg daily. While, some patients may receive an additional benefit by increasing the dose of Losartan to 100 mg once daily (in the morning).

The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy.

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

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. Daily dose in patients with renal impairment should be based on creatinine clearance:

- if creatinine clearance is ≥ 60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day of Ramipril); the maximal daily dose is 10 mg;

- if creatinine clearance is between 30-60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day of Ramipril); the maximal daily dose is 5 mg;

- if creatinine clearance is between 10-30 ml/min, the initial dose is 1.25 mg/day of Ramipril and the maximal daily dose is 5 mg;

- in haemodialysed hypertensive patients: Ramipril is slightly dialysable; the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg; the medicinal product should be administered few hours after haemodialysis is performed.

Use in patients with hepatic impairment:

A lower dose should be considered for patients with a history of hepatic impairment and must be initiated only under close medical supervision. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment. While, the maximum daily dose of Ramipril is 2.5 mg.

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 Potassium and Ramipril tablets 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 Potassium and Ramipril tablets is also not recommended in children with hepatic impairment.

Use in Elderly

Initial doses should be lower and subsequent dose titration should be more gradual because of greater chance of undesirable effects especially in very old and frail patients. Although consideration should be given to initiating therapy with Losartan 25 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly. A reduced initial dose of 1.25 mg Ramipril should be considered.

Method of administration

- It is recommended that it should be taken each day at the same time of the day.
- Losartan Potassium and Ramipril tablets may be administered with or without food and can be taken before, with or after meals, because food intake does not modify its bioavailability.
- Losartan Potassium and Ramipril tablets has to be swallowed with liquid/ whole with a glass of water.
- It must not be chewed or crushed.

4.3 Contraindications:

- Hypersensitivity to the active substance or to any of the excipients or any other ACE (Angiotensin Converting Enzyme) inhibitors.
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs).
- 2nd and 3rd 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).
- Concomitant use with sacubitril/valsartan therapy.
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces.
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney.
- Losartan Potassium and Ramipril must not be used in patients with hypotensive or haemodynamically unstable states.

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, potassium-containing salt substitutes, or other drugs that may increase serum potassium (e.g., trimethoprim-containing products) 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.

<u>Use in paediatric patients with renal impairment</u>
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.

Ramipril
Special populations

Pregnancy
ACE inhibitors such as Ramipril or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/AIIRAs 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 ACE inhibitors/AIIRAs should be stopped immediately, and, if

appropriate, alternative therapy should be started.

Patients at particular risk of hypotension

❖ Patients with strongly activated renin-angiotensin-aldosterone system

Patients with strongly activated renin-angiotensin-aldosterone system are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or at first dose increase.

Significant activation of renin-angiotensin-aldosterone system is to be anticipated and medical supervision including blood pressure monitoring is necessary, for example in:

- patients with severe hypertension
- patients with decompensated congestive heart failure
- patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve)
- patients with unilateral renal artery stenosis with a second functional kidney
- patients in whom fluid or salt depletion exists or may develop (including patients with diuretics)
- patients with liver cirrhosis and/or ascites
- patients undergoing major surgery or during anaesthesia with agents that produce hypotension.

Generally, it is recommended to correct dehydration, hypovolaemia or salt depletion before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed out against the risk of volume overload).

❖ 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.

❖ Transient or persistent heart failure post MI

❖ Patients at risk of cardiac or cerebral ischemia in case of acute hypotension

The initial phase of treatment requires special medical supervision.

Surgery

It is recommended that treatment with angiotensin converting enzyme inhibitors such as Ramipril should be discontinued where possible one day before surgery.

Monitoring of renal function

Renal function should be assessed before and during treatment and dose adjusted especially in the initial weeks of treatment. Particularly careful monitoring is required in patients with renal impairment. There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after a renal transplant.

Angioedema

Angioedema has been reported in patients treated with ACE inhibitors including Ramipril. This

risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) may be increased in patients taking concomitant medications which may cause angioedema such as mTOR (mammalian target of rapamycin) inhibitors (e.g. temsirolimus, everolimus, sirolimus), vildagliptin or neprilysin (NEP) inhibitors (such as racecadotril). The combination of Ramipril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. In case of angioedema, it must be discontinued. Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours and discharged after complete resolution of the symptoms.
Intestinal angioedema has been reported in patients treated with ACE inhibitors including Losartan Potassium and Ramipril Tablets. These patients presented with abdominal pain (with or without nausea or vomiting).

Anaphylactic reactions during desensitization
The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased under ACE inhibition. A temporary discontinuation of Ramipril should be considered prior to desensitization.

Electrolyte Monitoring: Hyperkalaemia
Hyperkalaemia has been observed in some patients treated with ACE inhibitors including Ramipril. Patients at risk for development of hyperkalaemia include those with renal insufficiency, age (> 70 years), uncontrolled diabetes mellitus, or those using potassium salts, potassium retaining diuretics and other plasma potassium increasing active substances, or conditions such as dehydration, acute cardiac decompensation, metabolic acidosis. If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Electrolyte Monitoring: Hyponatraemia
Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatraemia has been observed in some patients treated with Ramipril. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatraemia.

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, as well as thrombocytopenia and anaemia, have been rarely seen and bone marrow depression has also been reported. It is recommended to monitor the white blood cell count to permit detection of a possible leucopoenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma), and all those treated with other medicinal products that can cause changes in the blood picture.

Ethnic differences
ACE inhibitors cause higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, Ramipril may be less effective in lowering blood pressure in black people than in non-black patients, possibly because of a higher prevalence of hypertension with low renin level in the black hypertensive population.

Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced

cough should be considered as part of the differential diagnosis of cough.

4.5 Drug-Interaction:

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 reported 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, trimethoprim-containing products), 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.

Ramipril

Reported clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension,

hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Contra-indicated combinations
The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema. Treatment with Ramipril must not be started until 36 hours after taking the last dose of sacubitril/valsartan. Sacubitril/valsartan must not be started until 36 hours after the last dose of Ramipril.

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions. If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Precautions for use
- Potassium salts, heparin, potassium-retaining diuretics and other plasma potassium increasing active substances (including Angiotensin II antagonists, trimethoprim and in fixed dose combination with sulfamethoxazole, tacrolimus, ciclosporin): Hyperkalaemia may occur, therefore close monitoring of serum potassium is required.
- Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anaesthetics, acute alcohol intake, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin): Potentiation of the risk of hypotension is to be anticipated.
- Vasopressor sympathomimetics and other substances (e.g. isoproterenol, dobutamine, dopamine, epinephrine) that may reduce the antihypertensive effect of Ramipril: Blood pressure monitoring is recommended.
- Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood cell count: Increased likelihood of haematological reactions.
- Lithium salts: Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium level must be monitored.
- Antidiabetic agents including insulin: Hypoglycaemic reactions may occur. Blood glucose monitoring is recommended.
- Non-steroidal anti-inflammatory drugs and acetylsalicylic acid: Reduction of the antihypertensive effect of Ramipril is to be anticipated. Furthermore, concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and to an increase in kalaemia.
- mTOR inhibitors or DPP-IV inhibitors: An increased risk of angioedema is possible in patients taking concomitant medications such as mTOR inhibitors (e.g. temsirolimus, everolimus, sirolimus) or vildagliptin. Caution should be used when starting therapy.
- Neprilysin (NEP) inhibitors: An increased risk of angioedema has been reported with concomitant use of ACE inhibitors and NEP inhibitor such as racecadotril.
- Sacubitril/valsartan: The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema.

4.6 Use in special populations

Pregnancy

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.

Reported 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 foetotoxicity (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 Potassium and Ramipril tablets should be closely observed for hypotension.

ACE inhibitor/Angiotensin II Receptor Antagonist (AIIRA) therapy exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia.

Breastfeeding

Because no information is available regarding the use of Losartan Potassium and Ramipril tablets during breastfeeding, Losartan Potassium and Ramipril tablets is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a new-born or preterm infant.

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 symptoms of a reduction in blood pressure such dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased, or when changing over from other preparations. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects:

<u>Losartan Potassium</u>

Losartan has been evaluated in reported clinical studies as follows:

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

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

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

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

• In a reported 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).

The frequency of adverse reactions identified from reported 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
thrombocytopaenia					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	

*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 reported 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.

Ramipril

Summary of safety profile
The safety profile of Ramipril includes persistent dry cough and reactions due to hypotension. Serious adverse reactions include angioedema, hyperkalaemia, renal or hepatic impairment, pancreatitis, severe skin reactions and neutropenia/agranulocytosis.

Tabulated list of adverse reactions
Adverse reactions frequency 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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

	Common	Uncommon	Rare	Very rare	Not known

Blood and lymphatic system disorders		Eosinophilia	White blood cell count decreased (including neutropenia or agranulocytosis), red blood cell count decreased, haemoglobin decreased, platelet count decreased		Bone marrow failure, pancytopenia, haemolytic anaemia
Immune system disorders					Anaphylactic or anaphylactoid reactions, antinuclear antibody increased
Endocrine disorders					Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Blood potassium increased	Anorexia, decreased appetite,			Blood sodium decreased
Psychiatric disorders		Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence	Confusional state		Disturbance in attention
Nervous system disorders	Headache, dizziness	Vertigo, paraesthesia, ageusia, dysgeusia,	Tremor, balance disorder		Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning

					sensation, parosmia
Eye disorders		Visual disturbance including blurred vision	Conjunctivitis		
Ear and labyrinth disorders			Hearing impaired, tinnitus		
Cardiac disorders		Myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral			
Vascular disorders	Hypotension, orthostatic blood pressure decreased, syncope	Flushing	Vascular stenosis, hypoperfusion, vasculitis		Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	Bronchospasm including asthma aggravated, nasal congestion			
Gastrointestinal disorders	Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth	Glossitis		Aphtous stomatitis

Hepatobiliary disorders		Hepatic enzymes and/or bilirubin conjugated increased,	Jaundice cholestatic, hepatocellular damage		Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional).
Skin and subcutaneous tissue disorders	Rash in particular maculo-papular	Angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; pruritus, hyperhidrosis	Exfoliative dermatitis, urticaria, onycholysis,	Photosensitivity reaction	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia
Musculoskeletal and connective tissue disorders	Muscle spasms, myalgia	Arthralgia			
Renal and urinary disorders		Renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increased			
Reproductive system and		Transient erectile impotence, libido decreased			Gynaecomastia

breast disorders					
General disorders and administration site conditions	Chest pain, fatigue	Pyrexia	Asthenia		

Paediatric population

The safety of Ramipril was monitored in 325 children and adolescents, aged 2-16 years old, during 2 clinical trials. Whilst the nature and severity of the adverse events are similar to that of the adults, the frequency of the following is higher in the children:
Tachycardia, nasal congestion and rhinitis, "common" (i.e. ≥ 1/100 to < 1/10) in paediatric, and "uncommon" (i.e. ≥ 1/1,000 to < 1/100) in adult population.
Conjunctivitis "common" (i.e. ≥ 1/100 to < 1/10) in paediatric and "rare" (i.e. ≥ 1/10,000 to < 1/1,000) in adult population.
Tremor and urticaria "uncommon" (i.e. ≥ 1/1,000 to < 1/100) in paediatric population and "rare" (i.e. ≥ 1/10,000 to < 1/1,000) in adult population.
The overall safety profile for Ramipril in paediatric patients does not differ significantly from the safety profile 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.

4.9 Overdose:

Symptoms

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.

Symptoms associated with overdose of ACE inhibitors may include excessive peripheral vasodilation (with marked hypotension, shock), bradycardia, electrolyte disturbances and renal failure.

Management

The patient should be closely monitored and 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.

Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore haemodynamic stability, including, administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration. Ramiprilat, the active metabolite of Ramipril is poorly removed from the general circulation by haemodialysis.

5. Pharmacological properties:

5.1 Mechanism of Action:

Losartan Potassium

Losartan is a synthetic oral angiotensin-II receptor (type AT1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation. Losartan selectively blocks the AT1 receptor. In vitro and in vivo losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.

Ramipril

Ramiprilat, the active metabolite of the prodrug Ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.

Since angiotensin II also stimulates the release of aldosterone, Ramiprilat causes a reduction in aldosterone secretion. The average response to ACE inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.

5.2 Pharmacodynamic properties:

Losartan Potassium

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 principle active metabolite have a far greater affinity for the AT1-receptor than for the AT2-receptor. The active metabolite is 10- to 40- times more active than losartan on a weight for weight basis.

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. Measurements of blood pressure 24 hours post-dose relative to 5 – 6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood pressure reduction at the end of the dosing interval was 70 – 80% of the effect seen 5-6 hours 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 effects on heart rate.

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

LIFE-Study

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

The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95% confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001, 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

<u>Race</u>

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 antihypertensives) 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 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 m2. 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/1.73m^2.

An open label, dose-ranging reported 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.

Ramipril

Antihypertensive properties:

Administration of Ramipril causes a marked reduction in peripheral arterial resistance. Generally, there are no major changes in renal plasma flow and glomerular filtration rate. Administration of Ramipril to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.

In most patients the onset of the antihypertensive effect of a single dose becomes apparent 1 to 2 hours after oral administration. The peak effect of a single dose is usually reached 3 to 6 hours after oral administration. The antihypertensive effect of a single dose usually lasts for 24 hours.

The maximum antihypertensive effect of continued treatment with Ramipril is generally apparent after 3 to 4 weeks. It has been shown that the antihypertensive effect is sustained under long term therapy lasting 2 years.

Abrupt discontinuation of Ramipril does not produce a rapid and excessive rebound increase in blood pressure.

Heart failure:

In addition to conventional therapy with diuretics and optional cardiac glycosides, Ramipril has been shown to be effective in patients with functional classes II-IV of the New-York Heart Association. The drug had beneficial effects on cardiac haemodynamics (decreased left and right ventricular filling pressures, reduced total peripheral vascular resistance, increased cardiac output and improved cardiac index). It also reduced neuroendocrine activation.

Clinical efficacy and safety

Cardiovascular prevention/Nephroprotection;

A reported preventive placebo-controlled study (the HOPE-study), was done in which Ramipril was added to standard therapy in more than 9,200 patients. Patients with increased risk of cardiovascular disease following either atherothrombotic cardiovascular disease (history of coronary heart disease, stroke or peripheral vascular disease) or diabetes mellitus with at least one additional risk factor (documented microalbuminuria, hypertension, elevated total cholesterol level, low high-density lipoprotein cholesterol level or cigarette smoking) were included in the study.

The study showed that Ramipril statistically significantly decreases the incidence of myocardial infarction, death from cardiovascular causes and stroke, alone and combined (primary combined events).

The HOPE Study: Main Results;

	Ramipril **%**	Placebo **%**	relative risk (95% confidence interval)	p-value
All patients	**n=4,645**	**N=4,652**		
Primary combined events	**14.0**	**17.8**	**0.78 (0.70-0.86)**	**<0.001**
Myocardial infarction	*9.9*	*12.3*	*0.80 (0.70-0.90)*	*<0.001*
Death from cardiovascular causes	*6.1*	*8.1*	*0.74 (0.64-0.87)*	*<0.001*
Stroke	*3.4*	*4.9*	*0.68 (0.56-0.84)*	*<0.001*
Secondary endpoints				
Death from any cause	*10.4*	*12.2*	*0.84 (0.75-0.95)*	*0.005*
Need for Revascularisation	*16.0*	*18.3*	*0.85 (0.77-0.94)*	*0.002*
Hospitalisation for unstable angina	*12.1*	*12.3*	*0.98 (0.87-1.10)*	*NS*
Hospitalisation for heart failure	*3.2*	*3.5*	*0.88 (0.70-1.10)*	*0.25*
Complications related to diabetes	*6.4*	*7.6*	*0.84 (0.72-0.98)*	*0.03*

The MICRO-HOPE study, a predefined substudy from HOPE, investigated the effect of the addition of Ramipril 10 mg to the current medical regimen versus placebo in 3,577 patients at least ≥ 55 years old (with no upper limit of age), with a majority of type 2 diabetes (and at least another CV risk factor), normotensive or hypertensive.

The primary analysis showed that 117 (6.5 %) participants on Ramipril and 149 (8.4 %) on placebo developed overt nephropathy, which corresponds to a RRR 24 %; 95 % CI [3-40], p = 0.027.

The REIN study, a multicenter randomized, double-blind parallel group, placebo-controlled study reported aimed at assessing the effect of treatment with Ramipril on the rate of decline of glomerular function rate (GFR) in 352 normotensive or hypertensive patients (18-70 years old) suffering from mild (i.e. mean urinary protein excretion > 1 and < 3 g/24 h) or severe proteinuria

(≥ 3 g/24 h) due to chronic non-diabetic nephropathy. Both subpopulations were prospectively stratified.

The main analysis of patients with the most severe proteinuria (stratum prematurely disrupted due to benefit in Ramipril group) showed that the mean rate of GFR decline per month was lower with Ramipril than with placebo; -0.54 (0.66) vs. -0.88 (1.03) ml/min/month, p = 0.038. The intergroup difference was thus 0.34 [0.03-0.65] per month, and around 4 ml/min/year; 23.1 % of the patients in the Ramipril group reached the combined secondary endpoint of doubling of baseline serum creatinine concentration and/or end-stage renal disease (ESRD) (need for dialysis or renal transplantation) vs. 45.5 % in the placebo group (p = 0.02).

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.

Secondary prevention after acute myocardial infarction

The AIRE study included more than 2,000 patients with transient/persistent clinical signs of heart failure after documented myocardial infarction. The Ramipril treatment was started 3 to 10 days after the acute myocardial infarction. The study showed that after an average follow-up time of 15 months the mortality in Ramipril-treated patients was 16.9 % and in the placebo treated patients was 22.6 %. This means an absolute mortality reduction of 5.7 % and a relative risk reduction of 27 % (95 % CI [11-40 %]).

Paediatric Population

In a reported randomized, double-blind, placebo-controlled clinical study involving 244 paediatric patients with hypertension (73% primary hypertension), aged 6-16 years, patients received either low dose, medium dose or high dose of Ramipril to achieve plasma concentrations of Ramiprilat corresponding to the adult dose range of 1.25mg, 5mg and 20mg

on the basis of body weight. At the end of 4 weeks, Ramipril was ineffective in the endpoint of lowering systolic blood pressure but lowered diastolic blood pressure at the highest dose. Both medium and high doses of Ramipril showed significant reduction of both systolic and diastolic blood pressure in children with confirmed hypertension.

This effect was not seen in a 4 week dose-escalation, randomized, double-blind withdrawal study in 218 paediatric patients aged 6-16 years (75% primary hypertension), where both diastolic and systolic blood pressures demonstrated a modest rebound but not a statistically significant return to the baseline, in all three dose levels tested [low dose (0.625mg – 2.5mg), medium dose (2.5mg – 10mg) or high dose (5mg – 20mg)] Ramipril based on weight. Ramipril did not have a linear dose response in the paediatric population studied.

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 14C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

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

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 14C-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.

Ramipril

Absorption

Following oral administration Ramipril is rapidly absorbed from the gastrointestinal tract: peak plasma concentrations of Ramipril are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56 % and is not significantly influenced by the presence of food in the gastrointestinal tract. The bioavailability of the active metabolite Ramiprilat after oral administration of 2.5 mg and 5 mg Ramipril is 45 %.

Peak plasma concentrations of Ramiprilat, the sole active metabolite of Ramipril are reached 2-4 hours after Ramipril intake. Steady state plasma concentrations of Ramiprilat after once daily dosing with the usual doses of Ramipril are reached by about the fourth day of treatment.

Distribution

The serum protein binding of Ramipril is about 73 % and that of Ramiprilat about 56 %.

Biotransformation

Ramipril is almost completely metabolised to Ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of Ramipril and Ramiprilat.

Elimination

Excretion of the metabolites is primarily renal.

Plasma concentrations of Ramiprilat decline in a polyphasic manner. Because of its potent, saturable binding to ACE and slow dissociation from the enzyme, Ramiprilat shows a prolonged terminal elimination phase at very low plasma concentrations.

After multiple once-daily doses of Ramipril, the effective half-life of Ramiprilat concentrations was 13-17 hours for the 5-10 mg doses and longer for the lower 1.25-2.5 mg doses. This difference is related to the saturable capacity of the enzyme to bind Ramiprilat.

Patients with renal impairment

Renal excretion of Ramiprilat is reduced in patients with impaired renal function, and renal Ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of Ramiprilat, which decrease more slowly than in subjects with normal renal function.

Patients with hepatic impairment

In patients with impaired liver function, the metabolism of Ramipril to Ramiprilat was delayed, due to diminished activity of hepatic esterases, and plasma Ramipril levels in these patients were increased. Peak concentrations of Ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function.

Lactation

A single oral dose of Ramipril produced an undetectable level of Ramipril and its metabolite in breast milk. However, the effect of multiple doses is not known.

Paediatric Population

The pharmacokinetic profile of Ramipril was studied in 30 paediatric hypertensive patients, aged 2-16 years, weighing $\geq$ 10kg. After doses of 0.05 to 0.2mg/kg, Ramipril was rapidly and extensively metabolized to Ramiprilat. Peak plasma concentrations of Ramiprilat occurred within 2-3 hours. Ramiprilat clearance highly correlated with the log of body weight ($p<0.01$) as

well as dose ($p<0.001$). Clearance and volume of distribution increased with increasing children age for each dose group. The dose of 0.05mg/kg in children achieved exposure levels comparable to those in adults treated with Ramipril 5mg. The dose of 0.2mg/kg in children resulted in exposure levels higher than the maximum recommended dose of 10mg per day in adults.

6. Nonclinical properties:

Losartan Potassium

Reported 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.

Ramipril

Oral administration of Ramipril has been found to be devoid of acute toxicity in rodents and dogs. Studies involving chronic oral administration have been conducted in rats, dogs and monkeys. Indications of plasma electrolyte shifts and changes in blood picture have been found in the three species. As an expression of the pharmacodynamic activity of Ramipril, pronounced enlargement of the juxtaglomerular apparatus has been noted in the dog and monkey from daily doses of 250 mg/kg/d. Rats, dogs and monkeys tolerated daily doses of 2, 2.5 and 8 mg/kg/d respectively without harmful effects.

Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties.

Fertility was not impaired either in male or in female rats. The administration of Ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight or higher.

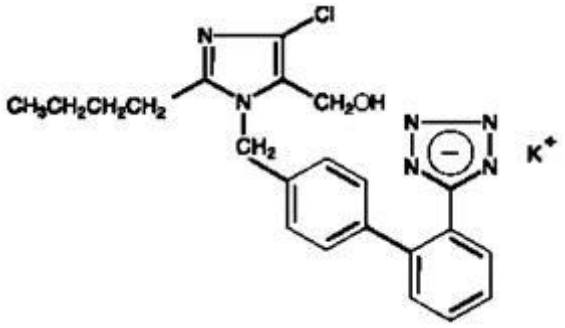
Extensive mutagenicity testing using several test systems has yielded no indication that Ramipril possesses mutagenic or genotoxic properties.

Irreversible kidney damage has been observed in very young rats given a single dose of Ramipril.

7. Description:

Losartan Potassium

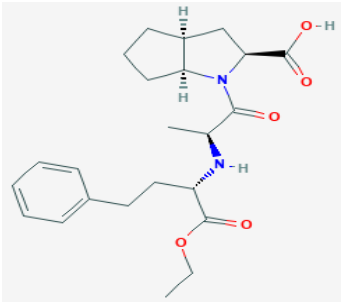
Losartan potassium is an angiotensin II receptor blocker acting on the AT_1 receptor subtype. Losartan potassium, a non-peptide molecule, is chemically described as monopotasium salt of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5 methanol. Its empirical formula 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 and slightly soluble in acetonitrile.

Ramipril

Ramipril is chemically *(2S,3aS,6aS)*-1-[(*2S)*-2-[[(*2S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-3,3a,4,5,6,6a-hexahydro-2H-cyclopenta[b]pyrrole-2-carboxylic acid having molecular weight of 416.5g/mol and molecular formula is $C_{23}H_{32}N_2O_5$ and its structural formula is:



Ramipril is a white to almost white crystalline powder. It is freely soluble in methanol and sparingly soluble in water.

Product Description:

LORAM 2.5

Losartan Potassium and Ramipril Tablets are pink coloured, biconvex, round, film coated tablet with score line on one side. The excipients used are Microcrystalline Cellulose, Starch, Isopropyl Alcohol, Sodium Bicarbonate, Colloidal Silicon Dioxide, Crospovidone, Talc, Magnesium Stearate, Opadry OY-C-7000A, Lake of Erythrosine and Methylene Chloride.

LORAM 5

Losartan Potassium and Ramipril Tablets are Blue coloured, biconvex, round, film coated tablet with score line on one side. The excipients used are Microcrystalline Cellulose, Starch, Isopropyl Alcohol, Sodium Bicarbonate, Colloidal Silicon Dioxide, Crospovidone, Talc, Magnesium Stearate, Opadry OY-C-7000A, Lake of Indigo carmine and Methylene Chloride.

8. Pharmaceutical particulars:

8.1 Incompatibilities:

None stated.

8.2 Shelf-life:

Do not use later than the date of expiry.

8.3 Packaging information:

LORAM is available in strip of 10 tablets each.

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

Package leaflet: Information for the user

LORAM

Losartan Potassium and Ramipril Tablets

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

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

What is in this leaflet?

9.1. What LORAM is and what it is used for

LORAM contains Losartan Potassium and Ramipril. Losartan 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 prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax which in turn lowers the blood pressure. Losartan slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes. Ramipril belongs to a group of medicines called ACE inhibitors (Angiotensin Converting Enzyme Inhibitors) and it works by: Decreasing your body's production of substances that could raise your blood pressure, Making your blood vessels relax and widen, Making it easier for your heart to pump blood around your body.

LORAM is used

- to treat patients with high blood pressure (hypertension) in adults and in children and adolescents 6 - 18 years of age.
- in patients with high blood pressure and a thickening of the left ventricle, LORAM has been shown to decrease the risk of stroke ("LIFE indication").
- to reduce the risk of you having a heart attack or stroke.
- to treat your heart when it cannot pump enough blood to the rest of your body (heart failure).
- as treatment following heart attack (myocardial infarction) complicated with heart failure.
- to treat patients with chronic heart failure when therapy with specific medicines called angiotensin-converting-enzyme inhibitors (ACE inhibitors, medicine used to lower high

blood pressure) is not considered suitable by your doctor. If your heart failure has been stabilised with an ACE inhibitor you should not be switched to losartan.
- to reduce the risk or delay the worsening of kidney problems (whether or not you have diabetes).
- to protect the kidney in hypertensive type 2 diabetic patients with laboratory evidence of impaired renal function and proteinuria ≥ 0.5 g per day (a condition in which urine contains an abnormal amount of protein).

9.2. What you need to know before you take LORAM

Do not take LORAM

If you are allergic to LORAM or any other ACE inhibitor medicine or any of the other ingredients of this medicine.

- If you are more than 3 months pregnant (It is also better to avoid LORAM in early 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.
- Signs of an allergic reaction may include a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- If you have ever had a serious allergic reaction called "angioedema"? The signs include itching, hives (urticaria), red marks on the hands, feet and throat, swelling of the throat and tongue, swelling around the eyes and lips, difficulty breathing and swallowing
- If you have taken or are currently taking sacubitril/valsartan, a medicine used to treat a type of longterm (chronic) heart failure in adults.
- If you are having dialysis or any other type of blood filtration. Depending on the machine that is used, LORAM may not be suitable for you.
- If you have kidney problems where the blood supply to your kidney is reduced (renal artery stenosis).
- During the last 6 months of pregnancy, (see section below on "Pregnancy and breast-feeding").
- If your blood pressure is abnormally low or unstable. Your doctor will need to make this assessment
- Do not take LORAM if any of the above apply to you.
- If you are not sure, talk to your doctor before taking LORAM.

Warnings and precautions

Talk to your doctor, pharmacist, or nurse before taking LORAM.

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

- 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, sweating more than usual leading to an extreme loss of fluid and/or salt in your body or being on a low salt diet, taking diuretics (water tablets) for a long time or having had dialysis
- 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 (see "Do not take LORAM" and "Dosage in special patient groups"),
- 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, sodium) in your blood especially if you are elderly, at regular intervals.

See also information under the heading "Do not take LORAM".

- if you are taking other medications that may increase serum potassium (see section "Other medicines and LORAM").
- if you have heart, liver or kidney problems.
- if you are going to have treatment to reduce your allergy to bee or wasp stings (desensitization).
- if you are going to receive an anaesthetic. This may be given for an operation or any dental work.
- you may need to stop your LORAM treatment one day beforehand; ask your doctor for advice
- if you have high amounts of potassium in your blood (shown in blood test results).
- if you are taking medicines or have conditions which may decrease sodium levels in your blood.
- if you are taking medicines that may increase the risk of angioedema, a serious allergic reaction, such as mTOR inhibitors (e.g. temsirolimus, everolimus, sirolimus), vildagliptin, neprilysin (NEP) inhibitors (such as racecadontril) or sacubitril/valsartan. For sacubitril/valsartan, see "Do not take LORAM".
- if you have collagen vascular disease such as scleroderma or systemic lupus erythematosus,
- you must tell your doctor if you think that you are (or might become) pregnant. LORAM is not recommended in the first 3 months of pregnancy and may cause serious harm to your baby after 3 months of pregnancy (see section below on "Pregnancy and breast-feeding").
- if you are taking any of the following medicines used to treat high blood pressure:
  - an angiotensin II receptor blocker (ARBs) (also known as sartans-for example valsartan, telmisartan, irbesartan), in particular if you have diabetes-related kidney problems.
  - aliskiren

Children and adolescents

LORAM is not recommended in children and adolescents below 18 years of age, because the safety and efficacy of LORAM in children has not yet been established. *For more information,*

talk to your doctor.

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

If any of the above apply to you (or you are not sure), talk to your doctor before taking LORAM.

Other medicines and LORAM

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This is because LORAM can affect the way some other medicines work. Also some medicines can affect the way LORAM works.

Tell your doctor if you are taking any of the following medicines. They can make LORAM work less well: Medicines used to relieve pain and inflammation (e.g. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or indometacin and aspirin), Medicines used for the treatment of low blood pressure, shock, cardiac failure, asthma or allergies such as ephedrine, noradrenaline or adrenaline. Your doctor will need to check your blood pressure. Potassium supplements, potassium-containing salt substitutes, potassium-sparing medicines such as certain diuretics (amiloride, triamteren, spironolactone), or other medicines that may increase serum potassium (e.g., heparin, trimethoprim-containing medicines), as the combination with LORAM is not advisable.

Take particular care if you are taking the following medicines while under treatment with LORAM:

- other blood pressure lowering medicines as they may additionally reduce your blood pressure. Blood pressure may also be lowered by one of the following drugs/ class of drugs: tricyclic antidepressants, antipsychotics, baclofen, amifostine.
- 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.
- Sacubitril/valsartan – used for treating a type of long term (chronic) heart failure in adults (see section 'Do not take LORAM')
- Medicines used to relieve pain and inflammation (e.g. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or indometacin and aspirin)
- Medicines for cancer (chemotherapy)
- Medicines to stop the rejection of organs after a transplant such as ciclosporin
- Diuretics (water tablets) such as furosemide
- Medicines which can increase the amount of potassium in your blood such as spironolactone, triamterene, amiloride, potassium salts, trimethoprim alone or in combination with sulfamethoxazole (for infections) and heparin (for thinning blood)
- Steroid medicines for inflammation such as prednisolone
- Allopurinol (used to lower the uric acid in your blood)
- Procainamide (for heart rhythm problems)
- Temsirolimus (for cancer)
- Sirolimus, everolimus (for prevention of graft rejection)
- Vildagliptin (used for treating type 2 diabetes)
- Racecadotril (used against diarrhoea)
- Your doctor may need to change your dose and/ or to take other precautions if you are taking an angiotensin II receptor blocker (ARB) or aliskiren (see also information under the headings "Do not take LORAM" and "Warnings and precautions").

- Tell your doctor if you are taking any of the following medicines. They may be affected by LORAM:
- Medicines for diabetes such as oral glucose lowering medicines and insulin. LORAM may lower your blood sugar amounts. Check your blood sugar amounts closely while taking LORAM
- Lithium (for mental health problems). LORAM may increase the amount of lithium in your blood. Your lithium amount will need to be closely checked by your doctor.
- If any of the above apply to you (or you are not sure), talk to your doctor before taking LORAM

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 LORAM" 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 without close supervision by your doctor. Special precautionary measures (e.g. blood tests) may be appropriate.

LORAM with food and drink

LORAM may be taken with or without food.

Drinking alcohol with LORAM may make you feel dizzy or light-headed. If you are concerned about how much you can drink while you are taking LORAM, discuss this with your doctor as medicines used to reduce blood pressure and alcohol can have additive effects.

Pregnancy and breast-feeding

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking LORAM before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of LORAM. LORAM is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy. If you become pregnant while on LORAM, tell your doctor immediately. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. LORAM is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is a new-born, or born prematurely.

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.

LORAM is unlikely to affect your ability to drive or use machines. However, as with many other medicines used to treat high blood pressure, LORAM may cause dizziness or drowsiness in some people. If you experience dizziness or drowsiness, you should consult your doctor before attempting such activities. If this happens, do not drive or use any tools or machines.

9.3. How to take LORAM

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 LORAM, depending on your condition and whether you are taking other medicines. It is important to continue taking LORAM for as long as your doctor prescribes it in order to maintain smooth control of your blood pressure.

Adult patients with High Blood Pressure

Treatment usually starts with 50 mg losartan (one tablet LORAM 50 mg) and Ramipril 1.25 mg or 2.5 mg once a day. 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 losartan (two tablets LORAM 50 mg or one tablet of LORAM 100 mg) and Ramipril 10 mg once daily.

If you have the impression that the effect of losartan is too strong or too weak, please talk to your doctor or pharmacist. Your doctor will adjust the amount you take until your blood pressure is controlled.

If you are already taking diuretics (water tablets), your doctor may stop or reduce the amount of the diuretic you take before beginning treatment with LORAM.

Use in children and adolescents

Children below 6 years of age

LORAM is not recommended for use in children under 6 years old, as it has not been shown to work in this age group.

Children aged 6 - 18 years old

The recommended starting dose in patients who weigh between 20 and 50 kg is 0.7 mg of losartan per kg of body weight administered once a day (up to 25 mg of LORAM). The doctor may increase the dose if blood pressure is not controlled.

Other form(s) of this medicine may be more suitable for children; ask your doctor or pharmacist.

Adult patients with high blood pressure and Type 2 diabetes

Treatment usually starts with 50 mg losartan (one tablet LORAM 50 mg) once a day. The dose may later be increased to 100 mg losartan (two tablets LORAM 50 mg or one tablet of LORAM 100 mg) once daily depending on your blood pressure response.

Losartan may be administered with other blood pressure lowering medicines (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used medicines that decrease the level of glucose in the blood (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Adult patients with Heart Failure

Treatment usually starts with 12.5 mg losartan (one tablet LORAM 12.5 mg) once a day. Generally, the dose should be increased weekly step-by-step (i.e., 12.5 mg daily during the first week, 25 mg daily during the second week, 50 mg daily during the third week, 100 mg daily during the fourth week, 150 mg daily during the fifth week) up to the maintenance dose as determined by your physician. A maximum dose of 150 mg losartan (for example, three tablets of LORAM 50 mg or one tablet each of LORAM 100 mg and LORAM 50 mg) once daily may be used.

In the treatment of heart failure, losartan is usually combined with a diuretic (medicine that increases the amount of water that you pass out through your kidneys) and/or digitalis (medicine that helps to make the heart stronger and more efficient) and/or a beta-blocker.

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 losartan is not recommended in patients with severe hepatic impairment (see section "Do not take LORAM ").

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. Do not crush or chew the tablets/capsules. It is important that you continue to take LORAM until your doctor tells you otherwise.

If you take more LORAM than you should

If you accidentally take too many tablets, contact your doctor immediately. Tell a doctor or go to the nearest hospital casualty department straight away. Do not drive to the hospital, get somebody else to take you or call for an ambulance. Take the medicine pack with you. This is so the doctor knows what you have taken. Symptoms of overdose are low blood pressure, increased heartbeat, possibly decreased heartbeat.

If you forget to take LORAM

If you accidentally miss a daily dose, just take the next dose as normal when it is next due. 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 LORAM 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).

Tell your doctor immediately if you experience:

- Faster heart rate, uneven or forceful heartbeat (palpitations), chest pain, tightness in your chest or more serious problems including heart attack and stroke.
- Shortness of breath or a cough. These could be signs of lung problems.
- Bruising more easily, bleeding for longer than normal, any sign of bleeding (e.g. bleeding from the gums), purple spots, blotching on the skin or getting infections more easily than usual, sore throat and fever, feeling tired, faint, dizzy or having pale skin. These can be signs of blood or bone marrow problems.
- Severe stomach pain which may reach through to your back. This could be a sign of pancreatitis (inflammation of the pancreas).
- Fever, chills, tiredness, loss of appetite, stomachpain, feeling sick, yellowing of your skin or eyes (jaundice). These can be signs of liver problems such as hepatitis (inflammation of the liver) or liver damage.

Other side effects include:
Tell your doctor if any of the following gets serious or lasts longer than a few days.

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 LORAM:

Common (may affect up to 1 in 10 people):
- dizziness, this is more likely to happen when you start taking LORAM or start taking a higher dose,
- 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,
- 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,
- headache or feeling tired,
- dry tickly cough, inflammation of your sinuses (sinusitis) or bronchitis, shortness of breath,
- stomach or gut pain, diarrhoea, indigestion, feeling or being sick.

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.
- balance problems (vertigo)
- itching and unusual skin sensations such as numbness, tingling, pricking, burning or creeping on your skin (paraesthesia),
- loss or change in the way things taste,
- sleep problems,

- feeling depressed, anxious, more nervous than usual or restless,
- blocked nose, difficulty breathing or worsening of asthma
- a swelling in your gut called "intestinal angioedema" presenting with symptoms like abdominal pain, vomiting and diarrhoea,
- heartburn, constipation or dry mouth,
- passing more water (urine) than usual over the day,
- sweating more than usual,
- loss or decrease of appetite (anorexia),
- increased or irregular heartbeats,
- swollen arms and legs. This may be a sign of your body holding onto more water than usual Flushing,
- blurred vision,
- pain in your joints,
- fever,
- sexual inability in men, reduced sexual desire in men or women,
- an increased number of certain white blood cells (eosinophilia) found during a blood test,
- blood tests showing changes in the way your liver,
- pancreas or kidneys are working.

Rare (may affect up to 1 in 1,000 people):
- hypersensitivity,
- angioedema,
- 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,
- feeling shaky or confused,
- red and swollen tongue,
- severe flaking or peeling of the skin, itchy, lumpy rash,
- nail problems (e.g. loosening or separation of a nail from its bed),
- skin rash or bruising,
- blotches on your skin and cold extremities,
- red, itchy, swollen or watery eyes,
- disturbed hearing and ringing in your ears,
- feeling weak,
- blood tests showing a decrease in the number of red blood cells, white blood cells or platelets or in the amount of haemoglobin.

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

- Being more sensitive to the sun than usual.

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),
- difficulty concentrating,
- swollen mouth,
- blood tests showing too few blood cells in your blood,
- blood tests showing less sodium than usual in your blood,
- concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits which may be due to inappropriate ADH (anti-diuretic hormone) secretion. If you have these symptoms contact your doctor as soon as possible,
- fingers and toes changing colour when you are cold and then tingling or feeling painful when you warm up (Raynaud's phenomenon),
- breast enlargement in men,
- slowed or impaired reactions,
- burning sensation,
- change in the way things smell,
- hair loss.

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.

9.5. How to store LORAM

- Keep this medicine out of the sight and reach of children.
- Store in a cool & dry place, protected from light.
- Do not use this medicine after the expiry date, which is stated on the carton and bottle after expiry. The expiry date refers to the last day of that month.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

9.6. Contents of the pack and other information

What LORAM contains

The active substance is Losartan Potassium and Ramipril, film-coated tablet, comes in two strengths containing Losartan Potassium 50 mg and Ramipril 2.5 mg or 5 mg.

LORAM 2.5

The other ingredients are Microcrystalline Cellulose, Starch, Isopropyl Alcohol, Sodium Bicarbonate, Colloidal Silicon Dioxide, Crospovidone, Talc, Magnesium Stearate, Opadry OY-C-7000A, Lake of Erythrosine and Methylene Chloride.

Colours: Erythrosine & Titanium Dioxide I.P.

LORAM 5

The other ingredients are Microcrystalline Cellulose, Starch, Isopropyl Alcohol, Sodium Bicarbonate, Colloidal Silicon Dioxide, Crospovidone, Talc, Magnesium Stearate, Opadry OY-C-7000A, Lake of Indigo carmine and Methylene Chloride.

Colours: Indigo carmine & Titanium Dioxide I.P.

LORAM is packed in strip of 10 tablets each.

10. Details of manufacturer

Manufactured in India by:
Manufactured by:
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 Lic No. M/563/2010 issued on 20.11.2017.

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/LORAM 50, 2.5, 5 mg/DEC-20/01/PI