

Losartan

Core Safety Profile

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (see section 4.4 and 6.1).
- 2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)
- Severe hepatic impairment

4.4 Special warnings and precautions for use

Hypersensitivity

Angiooedema. Patients with a history of angiooedema (swelling of the face, lips, throat, and/ or tongue) should be closely monitored (see section 4.8).

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 (see section 4.2). This also applies to children 6 to 18 years of age.

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalemia was higher in the group treated with losartan as compared to the placebo group (see section 4.8). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a creatinine clearance between 30-50 ml/ min should be closely monitored.

The concomitant use of potassium-sparing diuretics, potassium supplements and potassium-containing salt substitutes with losartan is not recommended (see section 4.5).

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 (see sections 4.2, 4.3 and 5.2).

Losartan is not recommended in children with hepatic impairment (see section 4.2).

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 rennin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other

medicinal products that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Use in pediatric patients with renal impairment

Losartan is not recommended in children with glomerular filtration rate < 30ml/ min/ 1.73 m² as no data are available (see section 4.2).

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 (see section 4.5).

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 (see section 5.1).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

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

Excipients

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

Pregnancy

Losartan should not be initiated during pregnancy. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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.

4.5 Interaction with other medicinal products and other forms of interaction

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, baclofene, and amifostine) may increase the risk of hypotension.

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

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

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

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

Dual blockade (e.g, by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function. Some studies have shown that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, dual blockade of the renin-angiotensin-aldosterone system, is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent.

4.6 Pregnancy and lactation

Pregnancy

The use of losartan is not recommended during the first trimester of pregnancy (see section 4.4). The use of losartan is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

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 AIIA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3).

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

Infants whose mothers have taken losartan should be closely observed for hypotension (see also section 4.3 and 4.4).

Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Losartan has been evaluated in clinical studies as follows:

- in a controlled clinical trials in > 3000 adult patients 18 years of age and older for essential hypertension,
- in a controlled clinical trial in 177 hypertensive pediatric patients 6 to 16 years of age
- in a controlled clinical trial in > 9000 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy
- in a controlled clinical trial in > 7700 adult patients with chronic heart failure
- in a controlled clinical trial in > 1500 type 2 diabetic patients 31 years of age and older with proteinuria

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

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

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

Hypertension

In a controlled clinical trials in 3300 adult patients 18 years of age and older with essential hypertension, the following adverse reactions were reported:

| System organ class | Adverse reaction | Frequency |
|--|---|-----------|
| Nervous system disorders | dizziness, vertigo | common |
| | somnolence, headache, sleep disorders | uncommon |
| Cardiac disorder | palpitations, angina pectoris | uncommon |
| Vascular disorders | symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash | uncommon |
| Gastrointestinal disorders | abdominal pain, obstipation | uncommon |
| General disorders and administration site conditions | asthenia, fatigue, oedema | uncommon |
| Investigations | hyperkalemia | common |
| | increased alanine aminotransferase (ALT)* | rare |

* usually resolved upon discontinuation

Hypertensive patients with left ventricular hypertrophy

In a controlled clinical trial in 9193 hypertensive patients 55 to 80 years of age, with left ventricular hypertrophy, the following adverse reactions were reported:

| System organ class | Adverse reaction | Frequency |
|--|-------------------------|------------------|
| Nervous system disorders | dizziness | common |
| Ear and labyrinth disorders | vertigo | common |
| General disorders and administration site conditions | asthenia, fatigue | common |

Chronic heart failure

In a controlled clinical trial in patients with chronic heart failure (see ELITE I, ELITE II, and HEAAL study, section 5.1) the following adverse reactions were reported:

| System organ class | Adverse reaction | Frequency |
|--|--|------------------|
| Nervous system disorders | dizziness | common |
| | headache | uncommon |
| | paraesthesia | rare |
| Cardiac disorder | syncope, atrial fibrillation, cerebrovascular accident | rare |
| Vascular disorders | hypotension, including orthostatic hypotension | common |
| Blood and lymphatic system disorders | anaemia | common |
| Respiratory, thoracic and mediastinal disorders | dyspnoea, cough | uncommon |
| Gastrointestinal disorders | diarrhoea, nausea, vomiting | uncommon |
| Skin and subcutaneous tissue disorders | urticaria, pruritus, rash | uncommon |
| General disorders and administration site conditions | asthenia, fatigue | uncommon |
| Investigations | increase in blood urea, serum creatinine and serum potassium | common |
| Metabolism and nutrition disorders | hyperkalaemia | uncommon* |
| Renal and urinary disorders | renal impairment, renal failure | common |

* common in patients who received 150 mg losartan instead of 50 mg losartan

Hypertension and type 2 diabetes with renal disease

In a controlled clinical trial in 1513 type 2 diabetic patients 31 years of age and older, with proteinuria (RENAAL study, see section 5.1), the most common drug-related adverse reactions which were reported for losartan are as follows:

| System organ class | Adverse reaction | Frequency |
|---------------------------|-------------------------|------------------|
| Nervous system disorders | dizziness | common |

| | | |
|--|-------------------------------|--------|
| Vascular disorders | hypotension | common |
| General disorders and administration site conditions | asthenia, fatigue | common |
| Investigations | hypoglycaemia, hyperkalaemia* | common |

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

The following adverse reactions occurred more often in patients receiving losartan than placebo:

| System organ class | Adverse reaction | Frequency |
|--|--------------------------|------------------|
| Blood and lymphatic system disorders | anaemia | not known |
| Cardiac disorder | syncope, palpitations | not known |
| Vascular disorders | orthostatic hypotension | not known |
| Gastrointestinal disorders | diarrhoea | not known |
| Musculoskeletal and connective tissue disorders: | back pain | not known |
| Renal and urinary disorders | urinary tract infections | not known |
| General disorders and administration site conditions | flu-like symptoms | not known |

Post-marketing experience

The following adverse reactions have been reported in post-marketing experience:

| System organ class | Adverse reaction | Frequency |
|--------------------------------------|---|------------------|
| Blood and lymphatic system disorders | anaemia, thrombocytopenia | not known |
| Ear and labyrinth disorders | Tinnitus | not known |
| Immune system disorders | hypersensitivity: anaphylactic reactions, angiooedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angiooedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors; vasculitis, including Henoch-Schonlein | rare |

| | | |
|--|---|-----------|
| | purpura | |
| Nervous system disorders | migraine | not known |
| Respiratory, thoracic and mediastinal disorders: | Cough | not known |
| Gastrointestinal disorders | diarrhoea, pancreatitis | not known |
| General disorders and administration site conditions | malaise | not known |
| Hepatobiliary disorders | hepatitis | rare |
| | liver function abnormalities | not known |
| Skin and subcutaneous tissue disorders | urticaria, pruritus, rash, photosensitivity | not known |
| Musculoskeletal and connective tissue disorders: | myalgia, arthralgia, rhabdomyolysis | not known |
| Reproductive system and breast disorders | erectile dysfunction/impotence | not known |
| Psychiatric disorders | depression | not known |
| Investigations | hyponatraemia | not known |

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 (see section 4.4)

Paediatric population

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

4.9 Overdose

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

Treatment of intoxication

If symptomatic hypotension should occur, supportive treatment should be instituted. Measures are depending on the time of medicinal product intake and kind and severity of symptoms. Stabilisation of the cardiovascular system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary. Neither losartan nor the active metabolite can be removed by haemodialysis.