

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Losartan Teva 12.5mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 12.5 mg of losartan potassium, equivalent to 11.44 mg of losartan.

Excipients:

Each tablet contains 2.250 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, round, slightly arched film-coated tablets, debossed "L" on one side, plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension

Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment

Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction $\leq 40\%$ and should be stabilised under the treatment of the chronic heart failure.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

4.2 Posology and method of administration

Method of administration

Losartan tablets should be swallowed with a glass of water
Losartan tablets may be administered with or without food.

Posology

Hypertension

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning). Losartan may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

Pediatric hypertension

There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 years old for the treatment of hypertension (see 5.1: Pharmacodynamic properties). Limited pharmacokinetic data are available in hypertensive children above one month of age (see 5.2 : Pharmacokinetic properties).

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 pediatric patients.

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

It is not recommended in children with glomerular filtration rate < 30 ml/ min / 1.73 m², as no data are available (see also section 4.4).

Losartan is also not recommended in children with hepatic impairment (see also section 4.4).

Hypertensive type II diabetic patients with proteinuria \geq 0.5 g/day

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month after initiation of therapy onwards. Losartan may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Heart Failure

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

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

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

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 (see section 4.4).

Use in patients with renal impairment and haemodialysis patients:

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

Use in patients with hepatic impairment

A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Use in Elderly

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

4.3 Contraindications

Hypersensitivity to losartan 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 hyperkalaemia 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 also 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 renin angiotensin aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other medicinal products that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Use in paediatric patients with renal impairment

Losartan is not recommended in children with glomerular filtration rate < 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, baclofen and amifostine) may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 in 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 Fertility, 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 contraindicated 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 antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (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 sections 4.3 and 4.4).

Breast-feeding

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 machinery 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 trial in > 3000 adult patients 18 years of age and older for essential hypertension,
- in a controlled clinical trial in 177 hypertensive paediatric patients 6 to 16 years of age
- in a controlled clinical trial in > 9000 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy (see LIFE Study, section 5.1)

- in a controlled clinical trial in > 7700 adult patients with chronic heart failure (see ELITE I, ELITE II, and HEAAL study, section 5.1)
- in a controlled clinical trial in > 1500 type 2 diabetic patients 31 years of age and older with proteinuria (see RENAAL study, section 5.1)

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 ($\geq 1/10$); 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).

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

Adverse reaction	Frequency of adverse reaction by indication				Other
	Hypertension	Hypertensive patients with left-ventricular hypertrophy	Chronic Heart Failure	Hypertension and type 2 diabetes with renal disease	Post-marketing experience
Blood and lymphatic system disorders					
anaemia			common		frequency not known
thrombocytopenia					frequency not known
Immune system disorders					
Hypersensitivity reactions, anaphylactic reactions, angioedema*, and vasculitis**					rare
hyperkalaemia					
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 disorder					
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 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			common		

potassium					
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 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 (see section 4.4)

Paediatric population

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

4.9 Overdose

Symptoms of intoxication

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

Treatment of intoxications

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain

ATC code: C09C A01

Mechanism of action

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*, both losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of its source or route of synthesis.

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

During administration of losartan, removal of angiotensin II negative feedback on renin secretion leads to increased plasma-renin activity (PRA). Increases in PRA lead to increases 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 baseline values.

Both losartan and its principal active metabolite have a far greater affinity for the AT₁ receptor than for the AT₂ receptor. The active metabolite is 10 to 40 times more effective than losartan on a weight for weight basis.

Clinical efficacy and safety

Hypertension studies

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

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

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

LIFE Study

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or 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.

Race

In the LIFE study the black patients treated with losartan had a higher risk of suffering the primary composite endpoint, i.e. a cardiovascular event (e.g. myocardial 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 the nephroprotective effect of losartan potassium over and above the benefit of a lowering of blood pressure.

Patients with proteinuria and a serum creatinine of 1.3-3.0 mg/dl were randomised to receive losartan 50 mg once daily, 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 once daily as appropriate; 72% of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensives (diuretic agents, calcium antagonists, alpha and beta receptor blockers and centrally active antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed for up to 4.6 years (3.4 years on average).

The primary endpoint of the study was a composite endpoint of doubling of serum creatinine, end-stage renal failure (need for dialysis or transplantation) or death.

The results showed that 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 also showed a significant risk reduction in the group treated with losartan: 25.3% risk reduction for doubling of 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 events that was comparable to the placebo group.

ELITE-I and ELITE-II Study

In the ELITE study carried out over 48 weeks in 722 patients with heart failure (NYHA class II-IV) no difference between the patients treated with losartan and those treated with captopril was observed with regard to the primary endpoint of a long-term change in renal function. The observation of the ELITE 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, 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 showed no statistically significant difference between losartan and captopril in reducing all-cause mortality.

In both comparator-controlled (not placebo-controlled) clinical studies in 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 events 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.

Pediatric Hypertension

The antihypertensive effect of Losartan was established in a clinical study involving 177 hypertensive pediatric 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 >20kg 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 randomized 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.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. Peak plasma 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 $\geq 99\%$ bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Biotransformation

Approximately 14% of an intravenously or orally administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C -labelled losartan, circulating plasma radioactivity is attributed primarily 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 oncedaily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of ^{14}C -labeled 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 (see section 4.2 and 4.4).

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/minute. Compared to patients with normal renal function, the AUC for losartan is approximately two times greater in haemodialysis patients.

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.

5.3 Preclinical safety data

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 effects on the late foetal development, resulting in foetal death and malformations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Lactose monohydrate

Cellulose, microcrystalline (E 460a)

Starch, pregelatinized (maize)

Magnesium stearate (E 572)

Coating – white Opadry:

Polyvinyl alcohol (partially hydrolysed)

Titanium dioxide (E 171)

Macrogol 3350

Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

PVC/PVdC/Al blisters or PVC/PE/PVdC/ Al blisters:
Do not store above 25°C.

OPA/Alu/PVC/ Al blisters:
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Pack sizes: 1, 7, 21, 28, 30, 56 and 98 film-coated tablets, hospital packs of 210 (10 x 21) film-coated tablets in white opaque PVC/PVdC/Al blisters or in white opaque PVC/PE/PVdC/Al blisters or in OPA/Alu/PVC/ Al blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/90/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First authorisation: 20th June 2008

10 DATE OF REVISION OF THE TEXT

March 2013