SUMMARYOFPRODUCTCHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZYLTAN 50 Film-Coated Tablet 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 50mg Losartan Potassium USP

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film Coated Tablets.

White coloured oblong shaped, film coated tablets having a break line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of essential hypertension in adults and in children and adolescents 6 - 18 years of age.
- Treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment (see sections 4.3, 4.4, 4.5, and 5.1).
- Treatment of chronic heart failure in adult patients when treatment with Angiotensin-converting enzyme (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 ≤ 40% and should be clinically stable and on an established treatment regimen for chronic heart failure.
- Reduction in the risk of stroke in adult hypertensive patients with leftventricular hypertrophy documented by ECG

4.2 Posology and method of administration

Posology

Hypertension

The usual starting and maintenance dose is 50 mg once daily for most patients. Themaximal antihypertensive effect is attained 3-6 weeks after initiation of therapy.

Some patients may receive an additional benefit by increasing the dose to 100 mgonce daily (in the morning).

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

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

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mgonce daily based on blood pressure response from one month onwards after initiationof therapy. Losartan may be administered with other antihypertensive agents (e.g.diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally actingagents) (see sections 4.3, 4.4, 4.5, and 5.1) as well as with insulin and othercommonly used hypoglycaemic agents (e.g. sulfonylureas, glitazones and glucosidaseinhibitors).

Heart Failure

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

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

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

Special populations

Use in patients with intravascular volume depletion:

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

Use in patients with hepatic impairment:

A lower dose should be considered for patients with a history of hepatic impairment. There isno therapeutic experience in patients with severe hepatic impairment. Therefore, losartan iscontraindicated in patients with severe hepatic impairment.

Paediatric population

6 months – less than 6 years

The safety and efficacy of children aged 6 months to less than 6 years has not beenestablished. Currently available data are described in sections 5.1 and 5.2 but norecommendation on posology can be made.

6 years to 18 years

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

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

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

It is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m^2,as no data are available (see also section 4.4).

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

Use in Elderly

Although consideration should be given to initiating therapy with 25 mg in patients over75 years of age, dosage adjustment is not usually necessary for the elderly.

Method of administration

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

Losartan tablets may be administered with or without food.

4.3 Contraindications

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

- The concomitant use of losartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73 m^2)(see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Hypersensitivity

Angioedema. Patients with a history of angioedema (swelling of the face, lips, throat, and/ortongue) 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, mayoccur 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 toadministration of losartan, or a lower starting dose should be used (see section 4.2). This alsoapplies to children 6 to 18 years of age.

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or withoutdiabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patientswith nephropathy, the incidence of hyperkalaemia was higher in the group treated withlosartan as compared to the placebo group (see section 4.8). Therefore, the plasmaconcentrations of potassium as well as creatinine clearance values should be closelymonitored, 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, potassiumcontainingsalt substitutes, or other drugs that may increase serum potassium (e.g.,trimethoprim-containing products) with losartan is not recommended (see section 4.5).

Hepatic impairment

Based on pharmacokinetic data which demonstrate significantly increased plasmaconcentrations of losartan in cirrhotic patients, a lower dose should be considered for patientswith a history of hepatic impairment. There is no therapeutic experience with losartan inpatients with severe hepatic impairment. Therefore losartan must not be administered inpatients 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 functionincluding renal failure have been reported (in particular, in patients whose renal function isdependent on the renin- angiotensin-aldosterone system such as those with severe cardiacinsufficiency or pre-existing renal dysfunction). As with other medicinal products that affectthe renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine havealso been reported in patients with bilateral renal artery stenosis or stenosis of the artery to asolitary kidney; these changes in renal function may be reversible upon discontinuation oftherapy. Losartan should be used with caution in patients with bilateral renal artery stenosis orstenosis of the artery to a solitary kidney.

Use in paediatric patients with renal impairment

Losartan is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m2as 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 medicinalproducts acting through inhibition of the renin-angiotensin system. Therefore, the use oflosartan is not recommended.

Coronary heart disease and cerebrovascular disease

As with any antihypertensive agents, excessive blood pressure decrease in patients withischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarctionor stroke.

Heart failure

In patients with heart failure, with or without renal impairment, there is - as with othermedicinal products acting on the renin-angiotensin system - a risk of severe arterialhypotension, and (often acute) renal impairment.

There is no sufficient therapeutic experience with losartan in patients with heart failure andconcomitant 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 oflosartan 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 ormitral stenosis, or obstructive hypertrophic cardiomyopathy.

Excipients

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

Pregnancy

Losartan should not be initiated during pregnancy. Unless continued losartan therapy isconsidered essential, patients planning pregnancy should be changed to alternativeanti-hypertensive treatments which have an established safety profile for use in pregnancy.When pregnancy is diagnosed, treatment with losartan should be stopped immediately, and, ifappropriate, 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 angiotensinantagonists are apparently less effective in lowering blood pressure in black people than innon-blacks, possibly because of higher prevalence of low-renin states in the blackhypertensive population.

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

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

If dual blockade therapy is considered absolutely necessary, this should only occur underspecialist supervision and subject to frequent close monitoring of renal function, electrolytesand blood pressure.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the activecarboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor ofCYP2C9) decreases the exposure to the active metabolite by approximately 50%. It wasfound that concomitant treatment of losartan with rifampicin (inducer of metabolismenzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinicalrelevance of this effect is unknown. No difference in exposure was found with concomitanttreatment with fluvastatin (weak inhibitor of CYP2C9).

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

Reversible increases in serum lithium concentrations and toxicity have been reportedduring concomitant administration of lithium with ACE inhibitors. Very rare cases havealso been reported with angiotensin II receptor antagonists. Co-administration of lithiumand losartan should be undertaken with caution. If this combination proves essential, serumlithium 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 andnon-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitantuse of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk ofworsening of renal function, including possible acute renal failure, and

an increase inserum potassium, especially in patients with poor pre-existing renal function. Thecombination should be administered with caution, especially in the elderly. Patients shouldbe adequately hydrated and consideration should be given to monitoring renal functionafter initiation of concomitant therapy, and periodically thereafter.

Clinical trial data have shown that dual blockade of the renin-angiotensin-aldosterone system(RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers oraliskiren is associated with a higher frequency of adverse events such as hypotension,hyperkalaemia, and decreased renal function (including acute renal failure) compared to theuse of a single RAAS-acting agent (see sections 4.3, 4.4, and 5.1).

Grapefruit juice contains components that inhibit CYP450 enzymes and may lower theconcentration of the active metabolite of losartan which may reduce the therapeutic effect.

Consumption of grapefruit juice should be avoided while taking losartan tablets.

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 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) (see also section 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 sections 4.3 and 4.4).

Breastfeeding

Because no information is available regarding the use of losartan during breastfeeding,losartan is not recommended and alternative treatments with better established safety profilesduring 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 thatdizziness or drowsiness may occasionally occur when taking antihypertensive therapy, inparticular 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 > 3,000 adult patients 18 years of age and olderfor essential hypertension
- In a controlled clinical trial in 177 hypertensive paediatric patients 6 to 16years of age
- In a controlled clinical trial in > 9,000 hypertensive patients 55 to 80 years ofage with left ventricular hypertrophy (see LIFE Study, section 5.1)
- In controlled clinical trials in > 7,700 adult patients with chronic heart failure(see ELITE I, ELITE II, and HEAAL study, section 5.1)
- In a controlled clinical trial in > 1,500 type 2 diabetic patients 31 years of ageand 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 (≥ 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 theavailable 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 patientswith left-ventricular hypertrophy	Chronic Heart Failure	Hypertension and type 2 diabeteswith renal disease	Post-marketing experience
Blood and lymphatic system disorders					
anaemia			common		frequencynot known
thrombocytopaenia					Frequencynot 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					frequencynot known
dysgeusia					frequencynot known
Ear and labyrinth disorders					
vertigo	common	common			frequency not known
tinnitus					
Cardiac disorders					
palpitations	uncommon				
angina pectoris	uncommon				
syncope			rare		
atrial fibrillation			rare		
cerebrovascular accident			rare		
Vascular disorders					
(orthostatic) hypotension	uncommon		common	common	

Adverse reaction	Frequency of adverse reaction by indication				Other
	Hypertension	**Hypertensive patientswith left-ventricular hypertrophy**	**Chronic Heart Failure**	**Hypertension and type 2 diabeteswith renal disease**	**Post-marketing experience**
(including doserelated orthostatic effects)[1]					
Respiratory, thoracic and mediastinal disorders					
dyspnoea			uncommon		
cough			uncommon		frequency not known
Gastrointestinal disorders					
abdominal pain	uncommon				
obstipation	uncommon				
diarrhoea			uncommon		
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					
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		

Adverse reaction	Frequency of adverse reaction by indication				Other
	Hypertension	**Hypertensive patientswith left-ventricular hypertrophy**	**Chronic Heart Failure**	**Hypertension and type 2 diabeteswith renal disease**	**Post-marketing experience**
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 thesepatients angioedema had been reported in the past in connection with the administration of other medicines, including ACEinhibitors

**Including Henoch-Schönlein purpura

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

†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 tabletsdeveloped 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 renalfunction including renal failure have been reported in patients at risk; these changes in renalfunction 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 inadult 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 manifestationof overdose would be hypotension and tachycardia. Bradycardia could occur fromparasympathetic (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 ofsymptoms. Stabilisation of the cardiovascular system should be given priority. After oralintake, the administration of a sufficient dose of activated charcoal is indicated. Afterwards,close monitoring of the vital parameters should be performed. Vital parameters should becorrected 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:** C09CA01

Losartan is a synthetic oral angiotensin-II receptor (type AT1) antagonist. Angiotensin II, apotent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and animportant determinant of the pathophysiology of hypertension. Angiotensin II binds to theAT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys andthe heart) and elicits several important biological actions, including vasoconstriction and therelease of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

Losartan selectively blocks the AT1 receptor. In vitro and in vivo losartan and itspharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevantactions of angiotensin II, regardless of the source or route of its synthesis.

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

During administration of losartan, removal of the angiotensin II negative feedback on reninsecretion leads to increased plasma renin activity (PRA). Increase in the PRA leads to anincrease in angiotensin II in plasma. Despite these increases, antihypertensive activity andsuppression of plasma aldosterone concentration are maintained, indicating effectiveangiotensin II receptor blockade. After discontinuation of losartan, PRA and angiotensin IIvalues fell within three days to the baseline values.

Both losartan and its principal active metabolite have a far greater affinity for theAT1-receptor than for the AT2-receptor. The active metabolite is 10- to 40- times more activethan losartan on a weight for weight basis.

Hypertension Studies

In controlled clinical studies, once-daily administration of losartan to patients with mild tomoderate essential hypertension produced statistically significant reductions in systolic anddiastolic 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 diurnalrhythm 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 bloodpressure (rebound). Despite the marked decrease in blood pressure, losartan had no clinicallysignificant 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 arandomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to80 years with ECG-documented left-ventricular hypertrophy. Patients were randomised toonce daily losartan 50 mg or once daily atenolol 50 mg. If goal blood pressure (< 140/90mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, thedose 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 addedif 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 asmeasured by a reduction in the combined incidence of cardiovascular death, stroke andmyocardial infarction. Blood pressure was significantly lowered to similar levels in the twogroups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95% confidenceinterval 0.77-0.98) compared with atenolol for patients reaching the primary compositeendpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatmentwith losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001, 95% confidenceinterval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were notsignificantly different between the treatment groups.

Race

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

<u>RENAAL Study</u>

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan

RENAAL study was a controlled clinical study conducted worldwide in 1,513 Type 2 diabeticpatients with proteinuria, with or without hypertension. 751 patients were treated withlosartan.

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

Patients with proteinuria and a serum creatinine of 1.3 – 3.0 mg/dl were randomised toreceive losartan 50 mg once a day, titrated if necessary, to achieve blood pressure response, orto placebo, on a background of conventional antihypertensive therapy excludingACE-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. Otherantihypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers andalso centrally acting antihypertensives) were permitted as supplementary treatment dependingon the requirement in both groups. Patients were followed up for up to 4.6 years (3.4 years onaverage). The primary endpoint of the

study was a composite endpoint of doubling of theserum 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 renalfailure or death (p = 0.009); 21.0% risk reduction for doubling of serum creatinine orend-stage renal failure (p = 0.01). All-cause mortality rate was not significantly differentbetween the two treatment groups. In this study losartan was generally well tolerated, asshown by a therapy discontinuation rate on account of adverse reactions that was comparableto 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 98years 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 abackground of conventional therapy excluding ACE-inhibitors.

Patients were followed for over 4 years (median 4.7 years). The primary endpoint of the studywas 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 mglosartan (889 events) resulted in a 10.1% risk reduction (p=0.027, 95% confidence interval0.82-0.99) in the number of patients reaching the primary composite endpoint. This wasmainly 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 causedeath 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 mggroup, but these adverse events did not lead to significantly more treatment discontinuationsin 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 ClassII-IV), no difference was observed between the patients treated with losartan and those treatedwith 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 themortality risk, was not confirmed in the subsequent ELITE II Study, which is described in thefollowing.

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 dose12.5 mg, increased to 25 mg and then to 50 mg three times daily). The primary endpoint ofthis prospective study was the all-cause mortality.

In this study, 3,152 patients with heart failure (NYHA Class II-IV) were followed for almosttwo years (median: 1.5 years) in order to determine whether losartan is superior to captopril inreducing all-cause mortality. The primary endpoint did not show any statistically significantdifference between losartan and captopril in reducing all-cause mortality.

In both comparator-controlled (not placebo-controlled) clinical studies on patients with heartfailure the tolerability of losartan was superior to that of captopril, measured on the basis of asignificantly lower rate of discontinuations of therapy on account of adverse reactions and asignificantly lower frequency of cough.

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

<u>Dual Blockade of the renin-angiotensin-aldosterone system (RAAS)</u>

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

ONTARGET was a study conducted in patients with a history of cardiovascular orcerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organdamage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabeticnephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascularoutcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/orhypotension as compared to monotherapy was observed. Given

their similarpharmacodynamic properties, these results are also relevant for other ACE-inhibitors andangiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be usedconcomitantly inpatients with diabetic nephropathy.

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

Paediatric Population

Paediatric Hypertension

The antihypertensive effect of losartan was established in a clinical study involving 177hypertensive paediatric patients 6 to 16 years of age with a body weight > 20 kg and aglomerular filtrationrate > 30 ml/min/1.73 m2. Patients who weighed > 20 kg to < 50 kg received either 2.5, 25 or50 mg of losartan daily and patients who weighed > 50 kg received either 5, 50 or 100 mg oflosartan daily. At the end of three weeks, losartan administration once daily lowered troughblood pressure in adose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious inthe low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65mmHg), 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 consistentantihypertensive efficacy.

These results were confirmed during period II of the study where patients were randomised tocontinue losartan or placebo, after three weeks of treatment. The difference in blood pressureincrease as compared to placebo was largest in the middle dose group (6.70 mmHg middledose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same inpatients 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 antihypertensiveeffect.

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

In hypertensive (N=60) and normotensive (N=246) children with proteinuria, the effect oflosartan 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 eitherlosartan (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 atdoses of 0.7 mg/kg to 1.4 mg/kg (up to maximum dose of 100 mg per day). Amlodipine wasgiven 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 statisticallysignificant reduction from baseline in proteinuria of 36% versus 1% increase inplacebo/amlodipine group (p≤0.001). Hypertensive patients receiving losartan experienced areduction 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 diastolicblood pressure was greater in the losartan group (-5.5/-3.8 mmHg) versus the amlodipinegroup (-0.1/+0.8 mmHg). In normotensive children a small decrease in blood pressure wasobserved in the losartan group (-3.7/-3.4 mmHg) compared to placebo. No significantcorrelation between the decline in proteinuria and blood pressure was noted, however it ispossible that the decline in blood pressure was responsible, in part, for the decline inproteinuria in the losartan treated group.

Long-term effects of losartan in children with proteinuria were studied for up to 3 years in theopen-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-labelextension phase and were re-randomised to losartan (N=134) or enalapril (N=134) and 109patients had ≥3 years of follow-up (pre-specified termination point of ≥100 patientscompleting 3 years of follow-up in the extension period). The dose ranges of losartan andenalapril, given according to investigator discretion, were 0.30 to 4.42 mg/kg/day and 0.02 to1.13 mg/kg/day, respectively. The maximum daily doses of 50 mg for <50 kg body weightand 100 mg>50 kg were not exceeded for most patients during the extension phase of thestudy.

In summary, the results of the safety extension show that losartan was well-tolerated and ledto sustained decreases in proteinuria with no appreciable change in glomerular filtration rate(GFR) over3 years. For normotensive patients (n=205), enalapril had a numerically greater effectcompared 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/1.73 m2)). Forhypertensive 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/1.73 m^2.

An open label, dose-ranging clinical trial was conducted to study the safety and efficacy oflosartan in paediatric patients aged 6 months to 6 years with hypertension. A total of 101patients were randomised to one of three different starting doses of open-label losartan: a lowdose of 0.1 mg/kg/day (N=33), a medium dose of 0.3 mg/kg/day (N=34), or a high dose of 0.7mg/kg/day (N=34). Of these, 27 were infants which were defined as children aged 6 monthsto 23 months. Study medication was titrated to the next dose level at Weeks 3, 6, and 9 forpatients 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 theextension study with follow up visits every 3 months. The mean duration of therapy was 264days.

In summary, the mean blood pressure decrease from baseline was similar across all treatmentgroups (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 DBPwas -8.2, -5.1, and -6.7 mmHg for the low-, medium-, and high-dose groups.); however, therewas 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 childrenaged 6 months to 6 years after 12 weeks of treatment. The overall safety profile appearedcomparable between treatment groups.

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. 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, primarilyalbumin. The volume of distribution of losartan is 34 litres.

Biotransformation

About 14% of an intravenously- or orally-administered dose of losartan is converted to itsactive metabolite. Following oral and intravenous administration of 14C-labelled losartanpotassium, circulating plasma radioactivity primarily is attributed to losartan and its activemetabolite. Minimal conversion of losartan to its active metabolite was seen in about onepercent 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 isexcreted unchanged in the urine, and about 6% of the dose is excreted in the urine as activemetabolite. The pharmacokinetics of losartan and its active metabolite are linear with orallosartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolitedecline 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 metaboliteaccumulates 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 metabolitedo 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 inmale hypertensive patients, while the plasma levels of the active metabolite did not differbetween men and women.

In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma levels oflosartan and its active metabolite after oral administration were respectively 5 and 1.7 timeshigher than in young male volunteers (see sections 4.2 and 4.4).

Plasma concentrations of losartan are not altered in patients with a creatinine clearance above10 ml/minute. Compared to patients with normal renal function, the AUC for losartan is about2-times higher in haemodialysis patients. The plasma concentrations of the active metaboliteare 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 paediatricpatients > 1 month to < 16 years of age following once daily oral administration ofapproximately 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. Theresults showed roughly similar pharmacokinetic parameters of losartan following oraladministration in infants and toddlers, preschool children, school age children andadolescents. The pharmacokinetic parameters for the metabolite differed to a greater extentbetween the age groups. When comparing preschool children with adolescents thesedifferences became statistically significant. Exposure in infants/ toddlers was comparativelyhigh.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Microcrystalline Cellulose (DC)
Sodium Starch Glycollate
Cros carmellose Sodium
Colloidal Silocon Dioxide
Talc
Magnesium Stearate

Film-Coat
Ethyl Cellulose
Hydroxypropyl methylcellulose (E15)
Propylene Glycol
Titanium Dioxide
Isopropyl Alcohol
Methylene Chloride

6.2 Incompatibilities

Not Known

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Alu Alu Blister pack

6.6 Special precautions for disposal

Anyunused medicinal product or waste material should be disposed of in accordancewith local requirements.

7. MARKETING AUTHORISATION HOLDER

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- Date of renewal : 05 October 2017

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