

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

LOSARDEX 100

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each caplet contains 100 mg of losartan potassium.

Each caplet contains approximately 220 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Caplets

LOSARDEX 100 are white, film-coated, biconvex caplets, scored on both sides.

The caplet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hypertension:
Losardex 100 is indicated for the treatment of hypertension.
- Heart failure:
Losardex 100 is indicated for the treatment of heart failure, usually in addition to diuretics and/or digitalis, if use of an ACE inhibitor is not appropriate.
Switching patients with heart failure who are stable on an ACE inhibitor to **Losardex 100** is not recommended.
- Renal protection in Type-2 diabetic patients with proteinuria:
Losardex 100 is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.
- Reduction in the risk of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy:
Losardex 100 is indicated to reduce the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy.
The benefit of **Losardex 100** on the primary composite endpoint was largely driven by reduction in the risk of stroke.

4.2 Posology and method of administration

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 alone or with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide) (see sections 4.3, 4.4, 4.5 and 5.1).

Renal protection in Type-2 diabetic patients with proteinuria

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 onwards after initiation of therapy. Losartan may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) (see sections 4.3, 4.4, 4.5 and 5.1) 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, 100 mg daily, up to a maximum dose of 150 mg once daily) as tolerated by the patient.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

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.

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 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.

Method of administration

LOSARDEX 100 caplets should be swallowed with a glass of water.

LOSARDEX 100 caplets may be administered with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (see 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 ($GFR < 60 \text{ ml/min/1.73 m}^2$) (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/ 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).

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, potassium-containing salt 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 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).

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.

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, total 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 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 (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.

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockage of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockage therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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 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, trimethoprim-containing products), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.

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

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

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

Grapefruit juice contains components that inhibit CYP450 enzymes and may lower the concentration 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 sections 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 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 profiles during breastfeeding are preferable, especially while nursing a new-born or preterm infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines it must be borne in mind that 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 >3,000 adult patients 18 years of age and older for essential hypertension
- in a controlled clinical trial in >9,000 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy (see LIFE Study, section 5.1)
- in a controlled clinical trial 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 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 ¹ , and vasculitis ²					rare
Psychiatric disorders					
depression					frequency not known
Nervous system disorders					
dizziness	common	common	common	common	
somnolence	uncommon				
headache	uncommon		uncommon		
sleep disorders	uncommon				
paraesthesia			rare		
migraine					frequency not known
dysgeusia					frequency not known
Ear and labyrinth disorder					
vertigo	common	common			
tinnitus					frequency not known
Cardiac disorders					
palpitations	uncommon				
angina pectoris	uncommon				
syncope			rare		
atrial fibrillation			rare		

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	
cerebrovascular accident			rare		Post-marketing experience
Vascular disorders					
(orthostatic) hypotension (including dose-related orthostatic effects) ³	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

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	
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 ⁴	common ⁵	
increased alanine aminotransferase (ALT) ⁶	rare				
increase in blood urea, serum creatinine, and serum potassium			common		
hyponatraemia					frequency not known
hypoglycaemia				common	

¹ 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

² Including Henoch-Schönlein purpura

³ Especially in patients with intravascular depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics

⁴ Common in patients who received 150 mg losartan instead of 50 mg

⁵ 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

⁶ 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)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il>

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 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.

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Angiotensin II Receptor Antagonists, plain,
ATC code: C09CA01

5.1 Pharmacodynamic properties

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

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

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

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

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

Hypertension Studies

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

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

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

LIFE-Study

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

The mean length of follow up was 4.8 years.

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

Race

In the LIFE-Study black patients treated with losartan had a higher risk of suffering the primary combined endpoint, i.e. a cardiovascular event (e.g. cardiac infarction, cardiovascular death) and especially stroke, than the black patients treated with atenolol. Therefore the results observed with losartan in comparison with atenolol in the LIFE study with regard to

cardiovascular morbidity/mortality do not apply for black patients with hypertension and left ventricular hypertrophy.

RENAAL-Study

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a controlled clinical study conducted worldwide in 1513 Type 2 diabetic patients with proteinuria, with or without hypertension. 751 patients were treated with losartan.

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

Patients with proteinuria and a serum creatinine of 1.3 – 3.0 mg/dl were randomised to receive losartan 50 mg once a day, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE-inhibitors and angiotensin II antagonists.

Investigators were instructed to titrate the study medication to 100 mg daily as appropriate; 72% of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed up for up to 4.6 years (3.4 years on average). The primary endpoint of the study was a composite endpoint of doubling of the serum creatinine, end-stage renal failure (need for dialysis or transplantation) or death.

The results showed that the treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1 % risk reduction ($p = 0.022$) in the number of patients reaching the primary composite endpoint. For the following individual and combined components of the primary endpoint, the results showed a significant risk reduction in the group treated with losartan: 25.3 % risk reduction for doubling of the serum creatinine ($p = 0.006$); 28.6 % risk reduction for end-stage renal failure ($p = 0.002$); 19.9 % risk reduction for end-stage renal failure or death ($p = 0.009$); 21.0 % risk reduction for doubling of serum creatinine or end-stage renal failure ($p = 0.01$).

All-cause mortality rate was not significantly different between the two treatment groups. In this study losartan was generally well tolerated, as shown by a therapy discontinuation rate on account of adverse reactions that was comparable to the placebo group.

HEAAL Study

The Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEAAL) study was a controlled clinical study conducted worldwide in 3834 patients aged 18 to 98 years with heart failure (NYHA Class II-IV) who were intolerant of ACE inhibitor treatment. Patients were randomised to receive losartan 50 mg once a day or losartan 150 mg, on a background of conventional therapy excluding ACE-inhibitors.

Patients were followed for over 4 years (median 4.7 years). The primary endpoint of the study was a composite endpoint of all cause death or hospitalisation for heart failure.

The results showed that treatment with 150 mg losartan (828 events) as compared with 50 mg losartan (889 events) resulted in a 10.1% risk reduction ($p=0.027$ 95% confidence interval 0.82-0.99) in the number of patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of hospitalisation for heart failure.

Treatment with 150 mg losartan reduced the risk of hospitalisation for heart failure by 13.5% relative to 50 mg losartan ($p=0.025$ 95% confidence interval 0.76-0.98). The rate of all cause death was not significantly different between the treatment groups.

Renal impairment, hypotension, and hyperkalaemia were more common in the 150 mg group than in the 50 mg group, but these adverse events did not lead to significantly more treatment discontinuations in the 150 mg group.

ELITE I and ELITE II Study

In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between the patients treated with losartan and those treated with captopril with regard to the primary endpoint of a long-term change in renal function. The observation of the ELITE I Study, that, compared with captopril, losartan reduced the mortality risk, was not confirmed in the subsequent ELITE II Study, which is described in the following.

In the ELITE II Study losartan 50 mg once daily (starting dose 12.5 mg, increased to 25 mg, then 50 mg once daily) was compared with captopril 50 mg three times daily (starting dose 12.5 mg, increased to 25 mg and then to 50 mg three times daily). The primary endpoint of this prospective study was the all-cause mortality.

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

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

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

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

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

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE- inhibitors and angiotensin II receptor blockers.

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

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

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 potassium 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 $\geq 99\%$ bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Biotransformation

About 14% of an intravenously or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C -labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

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

Elimination

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of ^{14}C -labelled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58% / 50% in the faeces.

Characteristics in patients

In elderly hypertensive patients the plasma concentrations of losartan and its active metabolite do not differ essentially from those found in young hypertensive patients.

In female hypertensive patients the plasma levels of losartan were up to twice as high as in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women.

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

Plasma concentrations of losartan are not altered in patients with a creatinine clearance above 10 ml/minute. Compared to patients with normal renal function, the AUC for losartan is about 2-times higher in haemodialysis patients.

The plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients.

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

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

Cellulose microcrystalline

Lactose monohydrate

Starch pregelatinized

Hypromellose

Silica colloidal anhydrous

Magnesium stearate

Titanium dioxide (E-171)

Macrogol 400

Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store in the original package, in a dark, dry and cool place. Do not store above 25°C.

6.5 Nature and contents of container

Blister.

Pack sizes: 2, 10, 14, 20, 28, 30 caplets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Dexcel Pharma Technologies Ltd., 21 Nahum Haftzadi Street, Jerusalem 9548402, Israel

8. MARKETING AUTHORIZATION NUMBER

138-20-31492

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