Losartan Hexal
Film-coated Tablets 50 mg/100 mg

1. NAME OF THE MEDICINAL PRODUCT
Losartan Hexal 50 mg Film-Coated Tablets
Losartan Hexal 100 mg Film-Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Losartan Hexal 50 mg Film-Coated Tablets
Each tablet contains 50 mg of losartan potassium equivalent to losartan 45.76 mg.
Each tablet contains 4.24 (0.108 mEq) of Potassium.

Losartan Hexal 100 mg Film-Coated Tablets
Each tablet contains 100 mg of losartan potassium equivalent to losartan 91.52 mg.
Each tablet contains 8.48 (0.216 mEq) of Potassium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
Losartan Hexal 50mg: White, oval-shaped, film-coated tablet marked '3' on one side and 1 score line on both sides.
Losartan Hexal 100mg: White, oblong-shaped, film-coated tablet marked '5' on one side 3 score lines on both sides.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
- Losartan is indicated for the treatment of hypertension.
- Losartan is indicated for the reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy (see section 5.1 Pharmacodynamic properties, LIFE study).
- Losartan is indicated for the treatment of renal disease in patients with type 2 diabetes with proteinuria and hypertension, as part of the anti-hypertensive therapy (see section 5.1 Pharmacodynamic properties).

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.

Losartan may be administered with other antihypertensive agents especially with diuretics (e.g. hydrochlorothiazide) (see sections 4.3, 4.4, 4.5 and 5.1).

Renal Disease in Type 2 Diabetic Patients with Proteinuria and Hypertension
The usual starting dose is 50 mg once daily.
The dose may be increased to 100 mg once daily based on blood pressure response.
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 hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

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

Method of administration
Losartan should be swallowed with a glass of water.
Losartan 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)
- Pregnancy (see section 4.6)
- Severe hepatic impairment
- Concomitant use of angiotensin receptor antagonists (ARBs) - including losartan - or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren in patients with Type 2 diabetes (see section 4.5, *Dual blockade of the Renin-Angiotensin-System (RAS) with ACEIs, ARBs or aliskiren*)
- The concomitant use of losartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m^2) (see section 4.5).

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, diarrhea 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 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).

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.

The use of ARBs - including losartan - or of ACEIs with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 ml/min) (see section 4.5, *Dual blockade of the Renin-Angiotensin-System (RAS) with ACEIs, ARBs or aliskiren*).

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.

Dual Blockade of the Renin-Angiotensin System (RAS)
Caution is required while co-administering ARBs, including losartan, with other agents blocking the RAS such as ACEIs or aliskiren (see section 4.5, *Dual blockade of the Renin-Angiotensin-System (RAS) with ACEIs, ARBs or aliskiren*).

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

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

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

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

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.

This medicament contains lactose. Patients with hereditary intolerance to glucose, Lapp lactase insufficiency or glucose or galactose absorption problems should not take this medicament.

4.5 Interaction with other medicinal products and other forms of interaction
Dual blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren
The concomitant use of ARBs, including losartan, with other agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalaemia, and changes in renal function compared to monotherapy. It is recommended to monitor blood pressure, renal function and electrolytes in patients on losartan and other agents that affect the RAS (see section 4.4).

The concomitant use of ARBs – including losartan - or of ACEIs with aliskiren, should be avoided in patients with severe renal impairment (GFR < 30 ml/min) (see section 4.4).

The concomitant use of ARBs - including losartan - or of ACEIs with aliskiren is contraindicated in patients with Type 2 diabetes (see section 4.3).

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 and 4.4).

Other antihypertensive agents may increase the hypotensive action of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofene, and amifostine) may increase the risk of hypotension.

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

As with other medicinal products that block angiotensin II or its effects, concomitant use of other medicinal products which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin), 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.

4.6 Pregnancy and lactation

Pregnancy

Due to the mechanism of action of angiotensin II antagonists, a risk for the foetus cannot be excluded. *In utero* exposure to ACE inhibitors (a specific class of medicinal products acting on the RAAS) during the second and third trimesters has been reported to cause injury and death to the developing foetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken the angiotensin II antagonist valsartan. As for any medicinal products that also acts directly on the RAAS, losartan should not be used during pregnancy (see section 4.3) or in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, losartan should be discontinued as soon as possible.

Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Losartan has been evaluated in clinical studies as follows:

- In a controlled clinical trials in > 3000 adult patients 18 years of age and older for essential hypertension
- In a controlled clinical trial in > 9000 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy
- In a controlled clinical trial in > 1500 type 2 diabetic patients 31 years of age and older with proteinuria.

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

The frequency of adverse reactions listed below is defined using the following convention:
Very common (≥1/10); common (≥1/100, to <1/10), uncommon (≥1/1,000, to <1/100); rare (≥ 1/10,000, to <1/1,000); very rare (<1/10.000), not known (cannot be estimated from the available data).

Losartan Hexal
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Hypertension
Nervous system disorders
Common: Dizziness
Uncommon: Somnolence, headache, sleep disorders

Ear and labyrinth disorders
Common: Vertigo

Cardiac disorders
Uncommon: Palpitations, angina pectoris

Vascular disorders
Uncommon: (Orthostatic) hypotension (including dose-related orthostatic effects)[II]

Gastrointestinal disorders
Uncommon: Abdominal pain, obstipation

Skin and subcutaneous disorders
Uncommon: Rash

General disorders and administration site conditions
Uncommon: Asthenia, fatigue, oedema

Investigations
Common: Hyperkalaemia
Rare: Increased alanine aminotransferase (ALT)[§]

Hypertensive patients with left ventricular hypertrophy
Nervous system disorders
Common: Dizziness

Ear and labyrinth disorders
Common: Vertigo

General disorders and administration site conditions
Common: Asthenia, fatigue

Chronic heart failure
Blood and lymphatic system disorders
Common: Anaemia

Nervous system disorders
Common: Dizziness
Uncommon: Headache
Rare: Paraesthesia

Cardiac disorders
Rare: Syncope, atrial fibrillation, cerebrovascular accident

Vascular disorders
Common: (Orthostatic) hypotension (including dose-related orthostatic effects)[II]

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, cough

Gastrointestinal disorders
Uncommon: Diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders
Uncommon: Urticaria, pruritus, rash

Renal and urinary disorders
Common: Renal impairment, renal failure

General disorders and administration site conditions
Uncommon: Asthenia, fatigue

Investigations
Common: Increase in blood urea, serum creatinine and serum potassium
Uncommon: Hyperkalaemia†

Hypertension and type 2 diabetes with renal disease
Nervous system disorders
Common: Dizziness

Vascular disorders
Common: (Orthostatic) hypotension (including dose-related orthostatic effects)‖

General disorders and administration site conditions
Common: Asthenia, fatigue

Investigations
Common: Hypoglycaemia, hyperkalaemia‡

Post-marketing experience
Blood and lymphatic system disorders
Not known: Anaemia, thrombocytopenia

Immune system disorders
Rare: Hypersensitivity reactions, anaphylactic reactions, angioedema*, and vasculitis**

Psychiatric disorders
Not known: Depression

Nervous system disorders
Not known: Migraine, dysgeusia

Ear and labyrinth disorders
Not known: Tinnitus

Respiratory, thoracic and mediastinal disorders
Not known: Cough

Gastrointestinal disorders
Not known: Diarrhoea

Hepatobiliary disorders
Rare: Hepatitis
Not known: Pancreatitis, liver function abnormalities

Skin and subcutaneous tissue disorders
Not known: Urticaria, pruritus, rash, photosensitivity

Musculoskeletal and connective tissue disorders
Not known: Myalgia, arthralgia, rhabdomyolysis

Reproductive system and breast disorders
Not known: Erectile dysfunction/impotence

General disorders and administration site conditions
Not known: Malaise

Investigations
Not known: Hyponatraemia

* Including swelling of the larynx, glottis, face, lips, pharynx, and/or tongue (causing airway obstruction); in some of these patients angio-oedema 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).

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II-antagonists, plain
ATC code: C09CA01

Losartan is a synthetically produced, 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 AT_1 receptor found in many tissues (e.g. vascular smooth muscles, adrenal gland, kidneys and the heart) and elicits several important biological mechanisms, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

Both losartan and the pharmacologically active metabolite bind selectively to the AT_1 receptor. Losartan and its active metabolite have no agonistic effects. Losartan does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Losartan differs from ACE inhibitors in that it does not inhibit ACE (kininase II), the enzyme that breaks down bradykinin.

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 thus no increase in bradykinin-mediated undesirable effects.

During the administration of losartan the 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 the plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After the discontinuation of losartan, PRA and angiotensin II values fell within 3 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 randomized 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.

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, 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 or 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 1% of individuals studied.

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

Elimination

Plasma clearance of losartan and its active metabolite is approximately 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is approximately 74 ml/min and 26 ml/min, respectively.

When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

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

Both biliary and urinary excretions contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of ^{14}C-labelled losartan in man, about 35%/43% of the 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 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
Each Losartan Hexal 50mg/100mg film-coated tablet contains:
Core:
Sodium glycolate starch (type A)
Microcrystalline cellulose
Magnesium stearate
Povidone
Silica, colloidal anhydrous

Film-Coating:
White Opadry (OY-L-28900)
- Titanium dioxide
- Hypromellose
- Lactose monohydrate
- Macrogol 4000

6.2 Incompatibilities
None.

6.3 Shelf life
Losartan 50mg/100mg in PVC/PVDC/Aluminium blister: Please refer to outer carton.

6.4 Special precautions for storage
Store at or below 30°C. Store in carton to protect from light.

6.5 Nature and contents of container
PVC/PVDC/Aluminium blister with 10 or 15 film-coated tablets.
Pack sizes:
- 5x10 film-coated tablets
- 10x10 film-coated tablets
- 2x15 film-coated tablets
- 3x10 film-coated tablets

Not all pack sizes will be available.

6.6 Special precautions for disposal and other handling
None.

7. Product Registrant
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Singapore 049315

8. DATE OF REVISION OF THE TEXT
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