Public Assessment Report

Decentralised Procedure

Losartan potassium 12.5mg, 25mg, 50mg and 100mg Film-coated Tablet

Losartan Potassium

UK/H/2670/01-04/DC

UK licence no: PL 20796/0008-0011

Applicant: Pharmakal Limited
LAY SUMMARY

On the 18\textsuperscript{th} January 2010 the MHRA granted Pharmakal Limited Marketing Authorisations (licences) Losartan Potassium 12.5mg, 25mg, 50mg and 100mg Film-coated Tablets. These are prescription-only medicines (POM).

Losartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body which binds to receptors in blood vessels, causing them to tighten. This results in an increased in blood pressure. Losartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax which in turn lowers the blood pressure.

Losartan potassium is used
- to treat patients with high blood pressure (hypertension)
- to treat patients with chronic heart failure when therapy with specific medicines called angiotensin-converting -enzyme inhibitors (ACE inhibitors, medicine used to lower high blood pressure) is not considered suitable by your doctor. If your heart failure has been stabilised with an ACE inhibitor you should not be switched to losartan.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Losartan Potassium 12.5mg, 25mg, 50mg and 100mg Film-coated Tablets outweigh the risks. Hence, Marketing Authorisations have been granted.
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### Module 1

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Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Losartan potassium 12.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 12.5 mg of losartan potassium equivalent to 11.4 mg of losartan.
Excipient:
16.75 mg lactose monohydrate/tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Losartan potassium 12.5 mg: White, round film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
• Treatment of essential hypertension.
• Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
• Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.
• Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

4.2 Posology and method of administration
Losartan tablets should be swallowed with a glass of water. Losartan potassium may be administered with or without food.

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 potassium may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

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

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

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

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.
It is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m², as no data are available (see also section 4.4).

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

Hypertensive type II diabetic patients with proteinuria ≥ 0.5 g/day
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month after initiation of therapy onwards. Losartan Pharmakal may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

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

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG
The usual starting dose is 50 mg of Losartan Pharmakal once daily. A low dose of hydrochlorothiazide should be added and/ or the dose of Losartan Pharmakal should be increased to 100 mg once daily based on blood pressure response.

Use in patients with intravascular volume depletion:
For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see section 4.4).

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

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

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

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

4.4 Special warnings and precautions for use
Hypersensitivity
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 potassium, or a lower starting dose should be used (see section 4.2). This also applies to children.

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 potassium as compared to the placebo group (see section 4.8, 'Hypertension and type 2 diabetes with renal disease - Investigations'
and ‘Post-marketing experience - Investigations’ 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).

Liver Function Impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan must not be administered in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

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

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

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

Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

Renal transplantation
There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan tablets 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 drugs 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.

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

**Pregnancy**

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

**Other warnings and precautions**

As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

### 4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents may increase the hypotensive action of Losartan. Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, 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 concomitantly treatment with fluvastatin (weak inhibitor of CYP2C9).

Concomitant use of other drugs 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 Losartan is 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 Losartan 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**

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued ARB 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.
Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3 'Preclinical safety data'). Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

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

**Lactation**

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

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

The frequency of adverse events 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).

In controlled clinical trials for essential hypertension, hypertensive patients with left ventricular hypertrophy, chronic heart failure as well as for hypertension and type 2 diabetes mellitus with renal disease, the most common adverse event was dizziness.

**Hypertension**

In controlled clinical trials for essential hypertension with losartan the following adverse events were reported:

- **Nervous system disorders:**
  - Common: dizziness, vertigo
  - Uncommon: somnolence, headache, sleep disorders

- **Cardiac disorder:**
  - Uncommon: palpitations, angina pectoris

- **Vascular disorders:**
  - Uncommon: symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash.

- **Gastrointestinal disorders:**
  - Uncommon: abdominal pain, obstipation

- **General disorders and administration site conditions:**
  - Uncommon: asthenia, fatigue, oedema

**Hypertensive patients with left ventricular hypertrophy**

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy the following adverse events were reported:

- **Nervous system disorders:**
  - common: dizziness

- **Ear and labyrinth disorders:**
  - common: vertigo
General disorders and administration site conditions:
common: asthenia/fatigue

Chronic heart failure
In a controlled clinical trial in patients with cardiac insufficiency the following adverse events were reported:

Nervous system disorders:
uncommon: dizziness, headache
rare: paraesthesia

Cardiac disorders:
rare: syncope, atrial fibrillation, cerebrovascular accident

Vascular disorders:
uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
uncommon: dyspnoea

Gastrointestinal disorders:
uncommon: diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders:
uncommon: urticaria, pruritus, rash

General disorders and administration site conditions:
uncommon: asthenia/fatigue

Hypertension and type 2 diabetes with renal disease
In a controlled clinical trial in type 2 diabetic patients with proteinuria (RENAAL study, see section 5.1) the most common drug-related adverse events which were reported for losartan are as follows:

Nervous system disorders:
common: dizziness

Vascular disorders:
common: hypotension

General disorders and administration site conditions:
common: asthenia/fatigue

Investigations:
common: hypoglycaemia, hyperkalaemia

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

Blood and lymphatic system disorders:
not known: anaemia

Cardiac disorders:
not known: syncope, palpitations

Vascular disorders:
not known: orthostatic hypotension

Gastrointestinal disorders:
not known: diarrhoea

Musculoskeletal and connective tissue disorders:
not known: back pain
Renal and urinary disorders:
not known: urinary tract infections

General disorders and administration site conditions:
not known: flu-like symptoms

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

Blood and lymphatic system disorders:
not known: Anaemia, thrombocytopenia

Immune system disorders:
rare: hypersensitivity: anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angioedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors; vasculitis, including Henoch-Schonlein purpura.

Nervous system disorders:
not known: migraine

Respiratory, thoracic and mediastinal disorders:
not known: cough

Gastrointestinal disorders:
not known: diarrhoea

Hepatobiliary disorders:
rare: hepatitis
not known: liver function abnormalities

Skin and subcutaneous tissue disorders:
not known: urticaria, pruritus, rash

Muscoskeletal and connective tissue disorders:
not known: myalgia, arthralgia

Renal 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)

Investigations:
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Losartan tablets. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan tablets developed hyperkalaemia >5.5 mEq/l and 3.4% of patients treated with placebo (see section 4.4, ‘Electrolyte imbalances’).

In a controlled clinical trial on patients with cardiac insufficiency, increase in blood urea, serum creatinine and serum potassium has been reported.

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

4.9 Overdose
Symptoms of intoxication
No experience with overdose in man is available so far. The most likely symptoms, depending on the extent of overdose, are hypotension, tachycardia, possibly bradycardia.
Treatment of intoxication
Measures are depending on the time of drug intake and kind and severity of symptoms. Stabilisation of the circulatory 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, 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 bradykininmediated 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 postdose. 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 a blood lowering 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 angiotension 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 endstage 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 events that was comparable to the placebo group.

**ELITE I and ELITE II Study**
In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between the patients treated with Losartan and those treated with captopril was observed with regard to the primary endpoint of a long-term change in renal function. The observation of the ELITE 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 m, 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 3152 patients with heart failure (NYHA Class II-IV) were followed for almost two years (median: 1.5 years) in order to determine whether Losartan is superior to captopril in reducing all cause mortality. The primary endpoint 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 events and a significantly lower frequency of cough.

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

Pediatric Hypertension
The antihypertensive effect of Losartan potassium was established in a clinical study involving 177 hypertensive pediatric patients 6 to 16 years of age with a body weight > 20 kg and a glomerular filtration rate > 30 ml/min/1.73 m². Patients who weighted >20kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighted > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious in the low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg), but was attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/ kg, did not appear to offer consistent antihypertensive efficacy.

These results were confirmed during period II of the study where patients were randomized to continue losartan or placebo, after three weeks of treatment. The difference in blood pressure increase as compared to placebo was largest in the middle dose group (6.70 mmHg middle dose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

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

5.2 Pharmacokinetic properties
Absorption
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. 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 and intravenous administration of 14C-labeled 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 14C-labeled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58% / 50% in the faeces.

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

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

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

Plasma concentrations of Losartan are not altered in patients with 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 dialysis 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.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses).

The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughly similar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/toddlers was comparatively high.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse effects on the late foetal development, resulting in foetal death and malformations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
microcrystalline cellulose (E460)
lactose monohydrate
pregelatinised maize starch
magnesium stearate (E572)
hypromellose (E464)
titanium dioxide (E171)
macrogol/PEG 400

6.2 Incompatibilities
Not applicable.
6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Pack sizes containing 7, 10, 14, 21, 28, 30, 50, 56, 98 film-coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORIZATION HOLDER
Pharmakal Ltd.
4 Eastbourne Road, Willingdon
Eastbourne, East Sussex
BN20 9LB
United Kingdom

8 MARKETING AUTHORIZATION NUMBER(S)
PL 20796/0008

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
15/01/2010

10 DATE OF REVISION OF THE TEXT
15/01/2010
1 NAME OF THE MEDICINAL PRODUCT
Losartan potassium 25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 25 mg of losartan potassium equivalent to 22.9 mg of losartan.

Excipient:
33.5 mg lactose monohydrate/tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Losartan potassium 25 mg tablet: Blue, round film-coated tablets scored on one side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
• Treatment of essential hypertension.
• Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
• Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.
• Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

4.2 Posology and method of administration
Losartan tablets should be swallowed with a glass of water.
Losartan potassium may be administered with or without food.

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 potassium may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

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

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

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

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.
It is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m², as no data are available (see also section 4.4).

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

**Hypertensive type II diabetic patients with proteinuria ≥ 0.5 g/day**
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month after initiation of therapy onwards. Losartan Pharmacal may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

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

**Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG**
The usual starting dose is 50 mg of Losartan Pharmacal once daily. A low dose of hydrochlorothiazide should be added and/or the dose of Losartan Pharmacal should be increased to 100 mg once daily based on blood pressure response.

**Use in patients with intravascular volume depletion:**
*For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see section 4.4).*

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

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

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

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

### 4.4 Special warnings and precautions for use
**Hypersensitivity**
*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 potassium, or a lower starting dose should be used (see section 4.2). This also applies to children.*

**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 potassium as compared to the placebo group (see section 4.8, 'Hypertension and type 2 diabetes with renal disease - Investigations’
and ‘Post-marketing experience - Investigations’ 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).

Liver Function Impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan must not be administered in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).
Losartan is also not recommended in children with hepatic impairment (see section 4.2).

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

Use in pediatric patients with renal function impairment
Losartan is not recommended in children with glomerular filtration rate < 30ml/min/1.73 m² as no data are available (see section 4.2).
Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

Renal transplantation
There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan tablets 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 drugs 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.

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

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

**Other warnings and precautions**
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

**4.5 Interaction with other medicinal products and other forms of interaction**

Other antihypertensive agents may increase the hypotensive action of Losartan. Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, 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 concomitantly treatment with fluvastatin (weak inhibitor of CYP2C9).

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued ARB 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.
Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3 'Preclinical safety data'). Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

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

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

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

4.8 Undesirable effects
The frequency of adverse events 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).

In controlled clinical trials for essential hypertension, hypertensive patients with left ventricular hypertrophy, chronic heart failure as well as for hypertension and type 2 diabetes mellitus with renal disease, the most common adverse event was dizziness.

Hypertension
In controlled clinical trials for essential hypertension with losartan the following adverse events were reported:

Nervous system disorders:
Common: dizziness, vertigo
Uncommon: somnolence, headache, sleep disorders

Cardiac disorder:
Uncommon: palpitations, angina pectoris

Vascular disorders:
Uncommon: symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash.

Gastrointestinal disorders:
Uncommon: abdominal pain, obstipation

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

Hypertensive patients with left ventricular hypertrophy
In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy the following adverse events were reported:

Nervous system disorders:
common: dizziness

Ear and labyrinth disorders:
common: vertigo
General disorders and administration site conditions:
common: asthenia/fatigue

Chronic heart failure
In a controlled clinical trial in patients with cardiac insufficiency the following adverse events were reported:

Nervous system disorders:
uncommon: dizziness, headache
rare: paraesthesia

Cardiac disorders:
rare: syncope, atrial fibrillation, cerebrovascular accident

Vascular disorders:
uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
uncommon: dyspnoea

Gastrointestinal disorders:
uncommon: diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders:
uncommon: urticaria, pruritus, rash

General disorders and administration site conditions:
uncommon: asthenia/fatigue

Hypertension and type 2 diabetes with renal disease
In a controlled clinical trial in type 2 diabetic patients with proteinuria (RENAAL study, see section 5.1) the most common drug-related adverse events which were reported for losartan are as follows:

Nervous system disorders:
common: dizziness

Vascular disorders:
common: hypotension

General disorders and administration site conditions:
common: asthenia/fatigue

Investigations:
common: hypoglycaemia, hyperkalaemia

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

Blood and lymphatic system disorders:
not known: anaemia

Cardiac disorders:
not known: syncope, palpitations

Vascular disorders:
not known: orthostatic hypotension

Gastrointestinal disorders:
not known: diarrhoea

Musculoskeletal and connective tissue disorders:
not known: back pain
Renal and urinary disorders:
not known: urinary tract infections

General disorders and administration site conditions:
not known: flu-like symptoms

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

Blood and lymphatic system disorders:
not known: Anaemia, thrombocytopenia

Immune system disorders:
rare: hypersensitivity: anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angioedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors; vasculitis, including Henoch-Schonlein purpura.

Nervous system disorders:
not known: migraine

Respiratory, thoracic and mediastinal disorders:
not known: cough

Gastrointestinal disorders:
not known: diarrhoea

Hepatobiliary disorders:
rare: hepatitis
not known: liver function abnormalities

Skin and subcutaneous tissue disorders:
not known: urticaria, pruritus, rash

Musculoskeletal and connective tissue disorders:
not known: myalgia, arthralgia

Renal 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)

Investigations:
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Losartan tablets. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan tablets developed hyperkalaemia >5.5 mEq/l and 3.4% of patients treated with placebo (see section 4.4, ‘Electrolyte imbalances’).

In a controlled clinical trial on patients with cardiac insufficiency, increase in blood urea, serum creatinine and serum potassium has been reported.

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

4.9 Overdose
Symptoms of intoxication
No experience with overdose in man is available so far. The most likely symptoms, depending on the extent of overdose, are hypotension, tachycardia, possibly bradycardia.
Treatment of intoxication

Measures are depending on the time of drug intake and kind and severity of symptoms. Stabilisation of the circulatory 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, ATC code: C09CA01

5.1 Pharmacodynamic properties
Losartan is a synthetic oral angiotensin-II receptor (type AT_1) 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 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 AT_1 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 bradykininmediated 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 AT_1-receptor than for the AT_2-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 postdose.

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 a blood lowering 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 endstage 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 events that was comparable to the placebo group.

ELITE I and ELITE II Study
In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between the patients treated with Losartan and those treated with captopril was observed with regard to the primary endpoint of a long-term change in renal function. The observation of the ELITE 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 3152 patients with heart failure (NYHA Class II-IV) were followed for almost two years (median: 1.5 years) in order to determine whether Losartan is superior to captopril in reducing all cause mortality. The primary endpoint 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 events and a significantly lower frequency of cough.

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

Pediatric Hypertension
The antihypertensive effect of Losartan potassium was established in a clinical study involving 177 hypertensive pediatric patients 6 to 16 years of age with a body weight > 20 kg and a glomerular filtration rate > 30 ml/min/1.73 m². Patients who weighted >20kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighted > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious in the low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg), but was attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/kg, did not appear to offer consistent antihypertensive efficacy. These results were confirmed during period II of the study where patients were randomized to continue losartan or placebo, after three weeks of treatment. The difference in blood pressure increase as compared to placebo was largest in the middle dose group (6.70 mmHg middle dose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

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

5.2 Pharmacokinetic properties

Absorption
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. 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 and intravenous administration of 14C-labeled 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 14C-labeled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58% / 50% in the faeces.

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

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

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

Plasma concentrations of Losartan are not altered in patients with 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 dialysis 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.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughly similar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/toddlers was comparatively high.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse effects on the late foetal development, resulting in foetal death and malformations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
microcrystalline cellulose (E460)
lactose monohydrate
pregelatinised maize starch
magnesium stearate (E572)
hypromellose (E464)
titanium dioxide (E171)
microgol/PEG 4000
Indigo carmine aluminum lake (E132)

6.2 Incompatibilities
Not applicable.
6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Pack sizes containing 7, 10, 14, 28, 30, 50, 56, 98 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Pharmakal Ltd.
4 Eastbourne Road, Willingdon
Eastbourne, East Sussex
BN20 9LB
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20796/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/01/2010

10 DATE OF REVISION OF THE TEXT
15/01/2010
NAME OF THE MEDICINAL PRODUCT
Losartan potassium 50 mg film-coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 50 mg of losartan potassium equivalent to 45.8 mg of losartan.

Excipient:
23.5 mg lactose monohydrate/tablet.

For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Film-coated tablet

Losartan potassium 50 mg tablet: White, round film-coated tablets scored on one side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

CLINICAL PARTICULARS

Therapeutic indications
- Treatment of essential hypertension.
- Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria \( \geq 0.5 \) g/day as part of an antihypertensive treatment.
- Treatment of chronic heart failure (in patients \( \geq 60 \) years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction \( \leq 40\% \) and should be stabilised under the treatment of the chronic heart failure.
- Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

Posology and method of administration
Losartan tablets should be swallowed with a glass of water.
Losartan potassium may be administered with or without food.

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 potassium may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

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

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

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

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.
It is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m², as no data are available (see also section 4.4).

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

**Hypertensive type II diabetic patients with proteinuria ≥ 0.5 g/day**
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month after initiation of therapy onwards. Losartan Pharmacal may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

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

**Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG**
The usual starting dose is 50 mg of Losartan Pharmacal once daily. A low dose of hydrochlorothiazide should be added and/ or the dose of Losartan Pharmacal should be increased to 100 mg once daily based on blood pressure response.

Use in patients with intravascular volume depletion; 
For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see section 4.4).

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

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

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

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

### 4.4 Special warnings and precautions for use

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

**Hypotension and Electrolyte/Fluid Imbalance**
*Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of Losartan potassium, or a lower starting dose should be used (see section 4.2). This also applies to children.*

**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 potassium as compared to the placebo group (see section 4.8, 'Hypertension and type 2 diabetes with renal disease - Investigations’ and ‘Post-marketing experience - Investigations’ 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).

Liver Function Impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan must not be administered in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2). Losartan is also not recommended in children with hepatic impairment (see section 4.2).

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

Use in pediatric patients with renal function impairment
Losartan is not recommended in children with glomerular filtration rate < 30ml/min/1.73 m² as no data are available (see section 4.2). Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

Renal transplantation
There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan tablets 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 drugs 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.

Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption
This medicinal product contains Lactose monohydrate
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Pregnancy
Losartan should not be initiated during pregnancy. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Other warnings and precautions
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

4.5 Interaction with other medicinal products and other forms of interaction
Other antihypertensive agents may increase the hypotensive action of Losartan. Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofen, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, 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 concomitantly treatment with fluvastatin (weak inhibitor of CYP2C9).

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued ARB 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.
Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3 'Preclinical safety data'). Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

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

**Lactation**

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

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

The frequency of adverse events 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).

In controlled clinical trials for essential hypertension, hypertensive patients with left ventricular hypertrophy, chronic heart failure as well as for hypertension and type 2 diabetes mellitus with renal disease, the most common adverse event was dizziness.

#### Hypertension

In controlled clinical trials for essential hypertension with losartan the following adverse events were reported:

- **Nervous system disorders**: Common: dizziness, vertigo
  Uncommon: somnolence, headache, sleep disorders

- **Cardiac disorder**: Uncommon: palpitations, angina pectoris

- **Vascular disorders**: Uncommon: symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash.

- **Gastrointestinal disorders**: Uncommon: abdominal pain, obstipation

- **General disorders and administration site conditions**: Uncommon: asthenia, fatigue, oedema

- **Hypertensive patients with left ventricular hypertrophy**

  In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy the following adverse events were reported:

  - **Nervous system disorders**: common: dizziness

  - **Ear and labyrinth disorders**: common: vertigo
General disorders and administration site conditions:
common: asthenia/fatigue

Chronic heart failure
In a controlled clinical trial in patients with cardiac insufficiency the following adverse events were reported:

Nervous system disorders:
uncommon: dizziness, headache
rare: paraesthesia

Cardiac disorders:
rare: syncope, atrial fibrillation, cerebrovascular accident

Vascular disorders:
uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
uncommon: dyspnoea

Gastrointestinal disorders:
uncommon: diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders:
uncommon: urticaria, pruritus, rash

General disorders and administration site conditions:
uncommon: asthenia/fatigue

Hypertension and type 2 diabetes with renal disease
In a controlled clinical trial in type 2 diabetic patients with proteinuria (RENAAL study, see section 5.1) the most common drug-related adverse events which were reported for losartan are as follows:

Nervous system disorders:
common: dizziness

Vascular disorders:
common: hypotension

General disorders and administration site conditions:
common: asthenia/fatigue

Investigations:
common: hypoglycaemia, hyperkalaemia

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

Blood and lymphatic system disorders:
not known: anaemia

Cardiac disorders:
not known: syncope, palpitations

Vascular disorders:
not known: orthostatic hypotension

Gastrointestinal disorders:
not known: diarrhoea

Mucoskeletal and connective tissue disorders:
not known: back pain
Renal and urinary disorders:
not known: urinary tract infections

General disorders and administration site conditions:
not known: flu-like symptoms

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

Blood and lymphatic system disorders:
not known: Anaemia, thrombocytopenia

Immune system disorders:
rare: hypersensitivity: anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angioedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors; vasculitis, including Henoch-Schonlein purpura.

Nervous system disorders:
not known: migraine

Respiratory, thoracic and mediastinal disorders:
not known: cough

Gastrointestinal disorders:
not known: diarrhoea

Hepatobiliary disorders:
rare: hepatitis
not known: liver function abnormalities

Skin and subcutaneous tissue disorders:
not known: urticaria, pruritus, rash

Musculoskeletal and connective tissue disorders:
not known: myalgia, arthralgia

Renal 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)

Investigations:
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Losartan tablets. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan tablets developed hyperkalaemia >5.5 mEq/l and 3.4% of patients treated with placebo (see section 4.4, ‘Electrolyte imbalances’).

In a controlled clinical trial on patients with cardiac insufficiency, increase in blood urea, serum creatinine and serum potassium has been reported.

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

4.9 Overdose
Symptoms of intoxication
No experience with overdose in man is available so far. The most likely symptoms, depending on the extent of overdose, are hypotension, tachycardia, possibly bradycardia.

Treatment of intoxication
Measures are depending on the time of drug intake and kind and severity of symptoms. Stabilisation of the circulatory 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, 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 bradykininmediated 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 postdose. 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 a blood lowering 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 angiotension 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 endstage 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 events that was comparable to the placebo group.

**ELITE I and ELITE II Study**
In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between the patients treated with Losartan and those treated with captopril was observed with regard to the primary endpoint of a long-term change in renal function. The observation of the ELITE 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 3152 patients with heart failure (NYHA Class II-IV) were followed for almost two years (median: 1.5 years) in order to determine whether Losartan is superior to captopril in reducing all-cause mortality. The primary endpoint 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 events and a significantly lower frequency of
cough.

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

**Pediatric Hypertension**
The antihypertensive effect of Losartan potassium was established in a clinical study involving 177
hypertensive pediatric patients 6 to 16 years of age with a body weight > 20 kg and a glomerular
filtration rate > 30 ml/min/1.73 m². Patients who weighted >20kg to < 50 kg received either 2.5, 25 or
50 mg of losartan daily and patients who weighted > 50 kg received either 5, 50 or 100 mg of losartan
daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a
dose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious in the low
dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg), but was
attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg
vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose
of 0.07 mg/ kg, did not appear to offer consistent antihypertensive efficacy.

These results were confirmed during period II of the study where patients were randomized to continue
losartan or placebo, after three weeks of treatment. The difference in blood pressure increase as
compared to placebo was largest in the middle dose group (6.70 mmHg middle dose vs. 5.38 mmHg
high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and
in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in
each group did not have significant antihypertensive effect.

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

### 5.2 Pharmacokinetic properties

**Absorption**
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming
an active carboxylic acid metabolite and other inactive metabolites. 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 and intravenous administration of 14C-labeled 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 14C-labeled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58% / 50% in the faeces.

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

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

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

Plasma concentrations of Losartan are not altered in patients with 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 dialysis 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.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses).

The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughly similar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/toddlers was comparatively high.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse effects on the late foetal development, resulting in foetal death and malformations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- microcrystalline cellulose (E460)
- lactose monohydrate
- pregelatinised maize starch
- magnesium stearate (E572)
- hypromellose (E464)
- titanium dioxide (E171)
- macrogol/PEG 400

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Pack sizes containing 7, 10, 14, 28, 30, 50, 56, 98 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Pharmakal Ltd.
4 Eastbourne Road, Willingdon
Eastbourne, East Sussex
BN20 9LB
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20796/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/01/2010

10 DATE OF REVISION OF THE TEXT
15/01/2010
1 NAME OF THE MEDICINAL PRODUCT
Losartan potassium 100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg of losartan potassium equivalent to 91.6 mg of losartan.

Excipient:
47.0 mg lactose monohydrate/tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Losartan potassium 100 mg tablet: White, oblong film-coated tablets scored on one side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
• Treatment of essential hypertension.
• Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with
  proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
• Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not
  considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart
  failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients
  should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of
  the chronic heart failure.
• Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy
  documented by ECG (see section 5.1 LIFE study, Race).

4.2 Posology and method of administration
Losartan tablets should be swallowed with a glass of water.
Losartan potassium may be administered with or without food.

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 potassium may be administered with other antihypertensive agents, especially with diuretics
(e.g. hydrochlorothiazide).

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

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

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

Losartan is not recommended for use in children under 6 years old, as limited data are available in
these patient groups.
PAR Losartan Potassium 12.5, 25, 50, and 100mg Film-coated Tablets

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

Hypertensive type II diabetic patients with proteinuria ≥ 0.5 g/day
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month after initiation of therapy onwards. Losartan Pharmakal may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

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

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG
The usual starting dose is 50 mg of Losartan Pharmakal once daily. A low dose of hydrochlorothiazide should be added and/or the dose of Losartan Pharmakal should be increased to 100 mg once daily based on blood pressure response.

Use in patients with intravascular volume depletion:
For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see section 4.4).

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

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

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

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

4.4 Special warnings and precautions for use
Hypersensitivity
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 potassium, or a lower starting dose should be used (see section 4.2). This also applies to children.

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 potassium as compared to the placebo group (see section 4.8, 'Hypertension and type 2 diabetes with renal disease - Investigations')
and ‘Post-marketing experience - Investigations’ 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).

Liver Function Impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan must not be administered in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2). Losartan is also not recommended in children with hepatic impairment (see section 4.2).

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

Use in pediatric patients with renal function impairment
Losartan is not recommended in children with glomerular filtration rate < 30ml/min/1.73 m² as no data are available (see section 4.2). Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

Renal transplantation
There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan tablets 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 drugs 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.

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

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

**Other warnings and precautions**
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

**4.5 Interaction with other medicinal products and other forms of interaction**
Other antihypertensive agents may increase the hypotensive action of Losartan. Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, 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 concomitantly treatment with fluvastatin (weak inhibitor of CYP2C9).

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued ARB 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.
Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3 ‘Preclinical safety data’).

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

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

**Lactation**

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

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

The frequency of adverse events 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).

In controlled clinical trials for essential hypertension, hypertensive patients with left ventricular hypertrophy, chronic heart failure as well as for hypertension and type 2 diabetes mellitus with renal disease, the most common adverse event was dizziness.

**Hypertension**

In controlled clinical trials for essential hypertension with losartan the following adverse events were reported:

**Nervous system disorders:**

Common: dizziness, vertigo

Uncommon: somnolence, headache, sleep disorders

**Cardiac disorder:**

Uncommon: palpitations, angina pectoris

**Vascular disorders:**

Uncommon: symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash.

**Gastrointestinal disorders:**

Uncommon: abdominal pain, obstipation

**General disorders and administration site conditions:**

Uncommon: asthenia, fatigue, oedema

**Hypertensive patients with left ventricular hypertrophy**

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy the following adverse events were reported:

**Nervous system disorders:**

common: dizziness

**Ear and labyrinth disorders:**

common: vertigo
General disorders and administration site conditions:
common: asthenia/fatigue

Chronic heart failure
In a controlled clinical trial in patients with cardiac insufficiency the following adverse events were reported:

Nervous system disorders:
uncommon: dizziness, headache
rare: paraesthesia

Cardiac disorders:
rare: syncope, atrial fibrillation, cerebrovascular accident

Vascular disorders:
uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
uncommon: dyspnoea

Gastrointestinal disorders:
uncommon: diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders:
uncommon: urticaria, pruritus, rash

General disorders and administration site conditions:
uncommon: asthenia/fatigue

Hypertension and type 2 diabetes with renal disease
In a controlled clinical trial in type 2 diabetic patients with proteinuria (RENAAL study, see section 5.1) the most common drug-related adverse events which were reported for losartan are as follows:

Nervous system disorders:
common: dizziness

Vascular disorders:
common: hypotension

General disorders and administration site conditions:
common: asthenia/fatigue

Investigations:
common: hypoglycaemia, hyperkalaemia

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

Blood and lymphatic system disorders:
not known: anaemia

Cardiac disorders:
not known: syncope, palpitations

Vascular disorders:
not known: orthostatic hypotension

Gastrointestinal disorders:
not known: diarrhoea

Musculoskeletal and connective tissue disorders:
not known: back pain
Renal and urinary disorders:
not known: urinary tract infections

General disorders and administration site conditions:
not known: flu-like symptoms

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

Blood and lymphatic system disorders:
not known: Anaemia, thrombocytopenia

Immune system disorders:
rare: hypersensitivity: anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angioedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors; vasculitis, including Henoch-Schönlein purpura.

Nervous system disorders:
not known: migraine

Respiratory, thoracic and mediastinal disorders:
not known: cough

Gastrointestinal disorders:
not known: diarrhoea

Hepatobiliary disorders:
rare: hepatitis
not known: liver function abnormalities

Skin and subcutaneous tissue disorders:
not known: urticaria, pruritus, rash

Muscoskeletal and connective tissue disorders:
not known: myalgia, arthralgia

Renal 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)

Investigations:
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Losartan tablets. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan tablets developed hyperkalaemia >5.5 mEq/l and 3.4% of patients treated with placebo (see section 4.4, ‘Electrolyte imbalances’).

In a controlled clinical trial on patients with cardiac insufficiency, increase in blood urea, serum creatinine and serum potassium has been reported.

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

4.9 Overdose

Symptoms of intoxication
No experience with overdose in man is available so far. The most likely symptoms, depending on the extent of overdose, are hypotension, tachycardia, possibly bradycardia.
Treatment of intoxication
Measures are depending on the time of drug intake and kind and severity of symptoms. Stabilisation of the circulatory 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, 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. \textit{In vitro} and \textit{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 bradykininmediated 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 postdose.

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 a blood lowering 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 endstage 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 events that was comparable to the placebo group.

**ELITE I and ELITE II Study**
In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between the patients treated with Losartan and those treated with captopril was observed with regard to the primary endpoint of a long-term change in renal function. The observation of the ELITE 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 m, 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 3152 patients with heart failure (NYHA Class II-IV) were followed for almost two years (median: 1.5 years) in order to determine whether Losartan is superior to captopril in reducing all cause mortality. The primary endpoint 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 events and a significantly lower frequency of cough.

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

**Pediatric Hypertension**

The antihypertensive effect of Losartan potassium was established in a clinical study involving 177 hypertensive pediatric patients 6 to 16 years of age with a body weight > 20 kg and a glomerular filtration rate > 30 ml/min/1.73 m². Patients who weighted >20kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighted > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious in the low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg), but was attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/ kg, did not appear to offer consistent antihypertensive efficacy. These results were confirmed during period II of the study where patients were randomized to continue losartan or placebo, after three weeks of treatment. The difference in blood pressure increase as compared to placebo was largest in the middle dose group (6.70 mmHg middle dose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

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

### 5.2 Pharmacokinetic properties

#### Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. 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 and intravenous administration of 14C-labeled 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 14C-labeled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58% / 50% in the faeces.

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

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

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

Plasma concentrations of Losartan are not altered in patients with 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 dialysis 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.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses).

The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughly similar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/toddlers was comparatively high.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse effects on the late foetal development, resulting in foetal death and malformations.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
microcrystalline cellulose (E460)
lactose monohydrate
pregelatinised maize starch
magnesium stearate (E572)
hypromellose (E464)
titanium dioxide (E171)
macrogol/PEG 400

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Pack sizes containing 7, 10, 14, 28, 30, 50, 56, 98 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Pharmakal Ltd.
4 Eastbourne Road, Willingdon
Eastbourne, East Sussex
BN20 9LB
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20796/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/01/2010

10 DATE OF REVISION OF THE TEXT
15/01/2010
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Losartan potassium film-coated tablets

Read all of this leaflet carefully before taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Losartan potassium is and what it is used for
2. Before you take Losartan potassium
3. How to take Losartan potassium
4. Possible side effects
5. How to store Losartan potassium
6. Further information

1. WHAT Losartan potassium IS AND WHAT IT IS USED FOR

Losartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body which binds to receptors in blood vessels, causing them to tighten. This results in an increase in blood pressure. Losartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax which in turn lowers the blood pressure. Losartan slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes.

Losartan potassium is used
- to treat patients with high blood pressure (hypertension)
- to protect the kidney in hypertensive type 2 diabetic patients with laboratory evidence of impaired renal function and proteinuria ≥ 0.5 g per day (a condition in which urine contains an abnormal amount of protein).
- to treat patients with chronic heart failure when therapy with specific medicines called angiotensin-converting-enzyme inhibitors (ACE inhibitors, medicine used to lower high blood pressure) is not considered suitable by your doctor. If your heart failure has been stabilised with an ACE inhibitor you should not be switched to losartan.
- in patients with high blood pressure and a thickening of the left ventricle. Losartan potassium has been shown to decrease the risk of stroke (“LIFE indication”).

2. BEFORE YOU TAKE Losartan potassium

Do not take Losartan potassium
- if you are allergic (hypersensitive) to losartan or to any of its other ingredients,
- if your liver function is severely impaired,
- if you are more than 3 months pregnant. (It is also better to avoid Losartan potassium in early pregnancy – see section “Pregnancy and breast-feeding”.)
- if you are breast-feeding.
Take special care with Losartan potassium

It is important to tell your doctor before taking Losartan potassium:

- if you have a history of angioedema (swelling of the face, lips, throat, and/or tongue) (see also section 4 ‘Possible side effects’),
- if you suffer from excessive vomiting or diarrhoea leading to an extreme loss of fluid and/or salt in your body,
- if you receive diuretics (medicines that increase the amount of water that you pass out through your kidneys) or are under dietary salt restriction leading to an extreme loss of fluid and salt in your body (see section 3 ‘Dosage in special patient groups’),
- if you are known to have narrowing or blockage of the blood vessels leading to your kidneys or if you have received a kidney transplant recently,
- if your liver function is impaired (see sections 2 “Do not take Losartan” and 3 ‘Dosage in special patient groups’),
- if you suffer from heart failure with or without renal impairment or concomitant severe life threatening cardiac arrhythmias. Special caution is necessary when you are treated with a β-blocker concomitantly,
- if you have problems with your heart valves or heart muscle,
- if you suffer from coronary heart disease (caused by a reduced blood flow in the blood vessels of the heart) or from cerebrovascular disease (caused by a reduced blood circulation in the brain),
- if you suffer from primary hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldosterone by the adrenal gland, caused by an abnormality within the gland),
- if you think that you are (or might become) pregnant. Losartan potassium is not recommended in early pregnancy and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see section “Pregnancy and breast-feeding”).

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or herbal medicines and natural products. Take particular care if you are taking the following medicines while under treatment with Losartan potassium:

- other blood pressure lowering medicines as they may additionally reduce your blood pressure. Blood pressure may also be lowered by one of the following drugs/ class of drugs: tricyclic antidepressants, antipsychotics, baclofen, anifostine,
- medicines which retain potassium or may increase potassium levels (e.g. potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines such as certain diuretics [amiloride, triamterene, spironolactone] or heparine),
- non-steroidal anti-inflammatory drugs such as indomethacin, including cox-2-inhibitors (medicines that reduce inflammation, and can be used to help relieve pain) as they may reduce the blood lowering effect of losartan.

If your kidney function is impaired, the concomitant use of these medicines may lead to a worsening of the kidney function.

Lithium containing medicines should not be taken in combination with losartan without close supervision by your doctor. Special precautionary measures (e.g. blood tests) may be appropriate.

Taking Losartan potassium with food and drink

Losartan potassium may be taken with or without food.

Pregnancy and breast-feeding

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Losartan potassium before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Losartan potassium. Losartan potassium is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.
Breastfeeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Losartan potassium is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely. Ask your doctor or pharmacist for advice before taking any medicine.

Use in children and adolescents
Losartan potassium has been studied in children. For more information, talk to your doctor.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed. Losartan potassium is unlikely to affect your ability to drive or use machines. However, as with many other medicines used to treat high blood pressure, losartan may cause dizziness or drowsiness in some people. If you experience dizziness or drowsiness, you should consult your doctor before attempting such activities.

Important information about some of the ingredients of Losartan potassium
Losartan potassium contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE Losartan potassium
Always take Losartan potassium exactly as your doctor has instructed you. Your doctor will decide on the appropriate dose of Losartan potassium, depending on your condition and whether you are taking other medicines. It is important to continue taking Losartan potassium for as long as your doctor prescribes it in order to maintain smooth control of your blood pressure.

This medicinal product is available in several strengths (12.5 mg, 25 mg, 50 mg and 100 mg) to simplify the administration per indication.

Patients with High Blood Pressure
Treatment usually starts with 50 mg losartan (one tablet Losartan potassium 50 mg) once a day. The maximal blood pressure lowering effect should be reached 3-6 weeks after beginning treatment. In some patients the dose may later be increased to 100 mg losartan (two tablets Losartan potassium 50 mg) once daily.

If you have the impression that the effect of losartan is too strong or too weak, please talk to your doctor or pharmacist.

Patients with high blood pressure and type 2 diabetes
Treatment usually starts with 50 mg Losartan (one tablet Losartan potassium 50 mg) once a day. The dose may later be increased to 100 mg losartan (two tablets Losartan potassium 50 mg) once daily depending on your blood pressure response.

Losartan tablets may be administered with other blood pressure lowering medicines (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used medicines that decrease the level of glucose in the blood (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Patients with Heart Failure
Treatment usually starts with 12.5 mg losartan (one tablet Losartan potassium 12.5 mg) once a day. Generally, the dose should be increased weekly step-by-step (i.e., 12.5 mg daily during the first week, 25 mg daily during the second week, 50 mg daily during the third week) up to the usual maintenance dose of 50 mg losartan (one tablet Losartan potassium 50 mg) once daily, according to your condition.
In the treatment of heart failure, losartan is usually combined with a diuretic (medicine that increases the amount of water that you pass out through your kidneys) and/or digitalis (medicine that helps to make the heart stronger and more efficient) and/or a beta-blocker.

**Dosage in special patient groups**
The doctor may advise a lower dose, especially when starting treatment in certain patients such as those treated with diuretics in high doses, in patients with liver impairment, or in patients over the age of 75 years. The use of losartan is not recommended in patients with severe hepatic impairment (see section "Do not take losartan").

**Administration**
The tablets should be swallowed with a glass of water. You should try to take your daily dose at about the same time each day. It is important that you continue to take Losartan potassium until your doctor tells you otherwise.

**If you take more Losartan potassium than you should**
If you accidentally take too many tablets, or a child swallows some, contact your doctor immediately. Symptoms of overdose are low blood pressure, increased heartbeat, possibly decreased heartbeat.

**If you forget to take Losartan potassium**
If you accidentally miss a daily dose, just take the next dose as normal. Do not take a double dose to make up for a forgotten tablet. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Losartan potassium can cause side effects, although not everybody gets them.

If you experience the following, stop taking losartan tablets and tell your doctor immediately or go to the casualty department of your nearest hospital:

A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing).

This is a serious but rare side effect, which affects more than 1 out of 10,000 patients but fewer than out of 1,000 patients. You may need urgent medical attention or hospitalisation.

The side effects of medicines are classified as follows:

- **very common:** affects more than 1 user in 10
- **common:** affects 1 to 10 users in 100
- **uncommon:** affects 1 to 10 users in 1000
- **rare:** affects 1 to 10 users I 10000
- **very rare:** affects less than 1 user in 10000
- **not known:** frequency can not be estimated from the available data

The following side effects have been reported with Losartan:

- **Common:**
  - dizziness,
  - low blood pressure,
  - debility,
  - fatigue,
  - too less sugar in the blood (hypoglycaemia),
• too much potassium in the blood (hyperkalaemia).

Uncommon:
• somnolence,
• headache,
• sleep disorders,
• feeling of increased heart rate (palpitations),
• severe chest pain (angina pectoris),
• low blood pressure (especially after excessive loss of water from the body within blood vessels e.g. in patients with severe heart failure or under treatment with high dose diuretics),
• dose-related orthostatic effects such as lowering of blood pressure appearing when rising from a lying or sitting position,
• shortness of breath (dyspnoea),
• abdominal pain,
• obstipation,
• diarrhoea,
• nausea,
• vomiting,
• livers (urticaria),
• itching (pruritus),
• rash,
• localised swelling (oedema).

Rare:
• inflammation of blood vessels (vasculitis including Henoch-Schonlein purpura),
• numbness or tingling sensation (paraesthesia),
• fainting (syncope),
• very rapid and irregular heartbeat (atrial fibrillation) brain attack (stroke),
• inflammation of the liver (hepatitis),
• elevated blood alanine aminotransferase (ALT) levels, usually resolved upon discontinuation of treatment.

not known:
• reduced number of red blood cells (anaemia),
• reduced number of thrombocytes,
• migraine,
• cough,
• liver function abnormalities,
• muscle and joint pain,
• changes in kidney function (may be reversible upon discontinuation of treatment) including kidney failure,
• flu-like symptoms,
• increase in blood urea,
• serum creatinine and serum potassium in patients with heart failure,
• back pain and urinary track infection.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE Losartan potassium

Keep out of the reach and sight of children.
Do not use Losartan potassium after the expiry date which is stated on the carton after {EXP}. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Losartan potassium contains
The active substance is losartan potassium. Each Losartan potassium 12.5 mg tablet contains 12.5 mg of losartan potassium. Each Losartan potassium 25 mg tablet contains 25 mg of losartan potassium. Each Losartan potassium 50 mg tablet contains 50 mg of losartan potassium. Each Losartan potassium 100 mg tablet contains 100 mg of losartan potassium.

The other ingredients are microcrystalline cellulose (E460), lactose monohydrate, pregelatinised maize starch, magnesium stearate (E572), hypromellose (E464), titanium dioxide (E171), macrogol/PEG 400 (only in Losartan potassium 12.5 mg/ 50 mg/ 100 mg film-coated tablets), macrogol/PEG 4000 (only in Losartan potassium 25 mg film-coated tablets), Indigo carmine aluminum lake (E132) (only in Losartan potassium 25 mg film-coated tablets).

What Losartan potassium looks like and contents of the pack
Losartan potassium 12.5 mg is supplied in the following pack sizes:
Pack sizes containing 7, 10, 14, 21, 28, 30, 50, 56, 98 white, round film-coated tablets.

Losartan potassium 25 mg is supplied in the following pack sizes:
Pack sizes containing 7, 10, 14, 28, 30, 50, 56, 98 blue, round film-coated tablets scored on one side.

Losartan potassium 50 mg is supplied in the following pack sizes:
Pack sizes containing 7, 10, 14, 28, 30, 50, 56, 98 white, round film-coated tablets scored on one side.

Losartan potassium 100 mg is supplied in the following pack sizes:
Pack sizes containing 7, 10, 14, 28, 30, 50, 56, 98 white, oblong film-coated tablets scored on one side.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Pharmaka Ltd.
4 Eastbourne Road, Willingdon
Eastbourne, East Sussex
BN20 9LB
United Kingdom

Manufacturer: Bluepharma Indústria Farmacêutica, S.A.
S. Martinho do Bispo
3045-016 Coimbra
Portugal
This medicinal product is authorised in the Member States of the EEA under the following names:

Germany: Losartan-Kalium Pharmakal 12.5 mg/25 mg/50 mg/100 mg Filmtabletten
Italy: Losartan potassio Pharmakal 12.5 mg/25 mg/50 mg/100 mg compressa rivestita con film
United Kingdom: Losartan potassium 12.5 mg/25 mg/50 mg/100 mg film-coated tablets

This leaflet was last approved in {MM/YYYY}
Module 4

Labelling

<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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1. **NAME OF THE MEDICINAL PRODUCT**

Losartan potassium 12.5 mg film-coated tablets
Losartan potassium

Losartan potassium 25 mg film-coated tablets
Losartan potassium

Losartan potassium 50 mg film-coated tablets
Losartan potassium

Losartan potassium 100 mg film-coated tablets
Losartan potassium

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Pharmakal Ltd.

3. **EXPIRY DATE**

EXP

4. **BATCH NUMBER**

Batch

5. **OTHER**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Losartan potassium 12.5 mg film-coated tablets
Losartan potassium

Losartan potassium 25 mg film-coated tablets
Losartan potassium

Losartan potassium 50 mg film-coated tablets
Losartan potassium

Losartan potassium 100 mg film-coated tablets
Losartan potassium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 12.5 mg Losartan potassium.
Each tablet contains 25 mg Losartan potassium.
Each tablet contains 50 mg Losartan potassium.
Each tablet contains 100 mg Losartan potassium.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS


5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmakal Ltd.
4 Eastbourne Road, Willingdon
Eastbourne, East Sussex
BN20 9LB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 20796/0008
PL 20796/0009
PL 20796/0010
PL 20796/0011

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Losartan potassium 12.5 mg
Losartan potassium 25 mg
Losartan potassium 50 mg
Losartan potassium 100 mg
Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Losartan Potassium 12.5 mg, 25 mg, 50 mg & 100 mg Film-coated tablets, in the treatment of hypertension, heart failure and diabetic renal disease, could be approvable.

These are applications for Losartan Potassium 12.5 mg, 25 mg, 50 mg & 100 mg Film-coated tablets using the decentralised procedure. These were submitted on the basis of Directive 2001/83/EC (as amended) Article 10(1) generic application. The applicant claims that this is a generic product to Cozaar® Tablets (Merck Sharp & Dohme). Cozaar® Tablets were first authorised in the UK in 1994 (PL: 00025/0324 & 36).

With the UK as the Reference Member State in these Decentralised Procedure, Pharmakal Limited is applying for the Marketing Authorisation for Losartan Potassium 12.5 mg, 25 mg, 50 mg & 100 mg Film-coated tablets in DE and IT.

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.

The submitted dossier is of an acceptable standard.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
## ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Losartan Potassium 12.5 mg, 25 mg, 50 mg &amp; 100 mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Losartan potassium</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Angiotensin II antagonists (C09 CA01)</td>
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<td>Pharmaceutical form and strength(s)</td>
<td>12.5 mg, 25 mg, 50 mg &amp; 100 mg Film-coated Tablets</td>
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<td>Reference numbers for the Mutual Recognition Procedure</td>
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<td>Member States Concerned</td>
<td>DE and IT</td>
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</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Pharmakal Ltd. 4 Eastbourne Road, Willingdon, Eastbourne, East Sussex, BN20 9LB, UK</td>
</tr>
</tbody>
</table>
SCIENTIFIC OVERVIEW AND DISCUSSION

II. QUALITY ASPECTS

DRUG SUBSTANCE

INN: Losartan Potassium

Chemical Name: 2-Butyl-4chloro-1-[(2’-(1H-tetrazol-5-yl)[1,1’-biphenyl]-4-yl)methyl]-1H-imidazole-5-methanol, potassium salt
2-Butyl-4chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-imidazole-5-methanol, monopotassium salt

Structure:

![Structure of Losartan Potassium]

Molecular Formula: C$_{22}$H$_{22}$ClKN$_6$O

Molecular Weight: 461.0

Losartan potassium is a white or almost white crystalline powder, which is freely soluble in water and methanol and very slightly soluble in chloroform. It is also freely soluble in alkaline pH, but becomes practically insoluble at acidic pH (pH 6 and below).

The drug substance is the subject of a European Drug Master File (EDMF). A letter of access has been provided by the drug substance manufacturer.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Losartan potassium is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.
Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the drug substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data has been provided which support the re-test period.
DRUG PRODUCT

Other ingredients
Other ingredients consist of the pharmaceutical excipients lactose monohydrate, cellulose microcrystalline, pregelatinised starch, magnesium stearate, water purified and opadry Y-1-7000 White.

All excipients comply with their respective European Pharmacopoeia monographs except Opadry Y-1-7000 White which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin. The lactose used is from Meggle and appropriate TSE documentation regarding sourcing has been supplied.

None of the other excipients are of human origin.

Pharmaceutical Development
Suitable pharmaceutical development data have been provided for these applications.

The aim of the development work was to produce a product demonstrating essential similarity to the innovator product (Cozaar®).

Manufacture
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory, based on process validation data and controls on the finished product. Process validation has been carried out on pilot scale batches of the product. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is packed in PVC/ PVdC/PE/Aluminium blister packs.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years has been set, with no storage instructions.

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Satisfactory bioequivalence is seen between the test and reference product.

**SPC, PIL, Labels**

The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Conclusion**

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for a generic product of the originator product have been met with respect to qualitative and quantitative content of the active substance. In addition, similar physico-chemical properties have been demonstrated for the proposed and originator product.

**III. PRE-CLINICAL ASPECTS**

No new preclinical data have been supplied with this application. However, a preclinical expert report summarising relevant non-clinical studies has been included in the dossier. This is satisfactory.

**IV. CLINICAL ASPECTS**

1. **Introduction**

1.1. **Type of Application and Regulatory Background**

These decentralised applications concern generic versions of losartan potassium, under Losartan potassium 12.5 mg, 25 mg, 50 mg & 100mg Film-coated Tablets trade names. The originator product is Cozaar 25 mg, 50mg and 100mg film-coated tablets by Merck, Sharp & Dohme, registered since 1994.

With UK as the Reference Member State in these Decentralised Procedures, Pharmakal Ltd is applying for the Marketing Authorisations for Losartan potassium 12.5 mg, 25 mg, 50mg & 100mg Film-coated Tablets in DE and IT.

Losartan potassium is an Angiotensin-II (AT\textsubscript{1}) receptor blocker that is used for control of hypertension as monotherapy or in combination with other agents, primarily thiazide diuretics.

1.2. **Clinical Background**

Losartan is a synthetic oral angiotensin-II receptor (type AT\textsubscript{1}) 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\textsubscript{1} 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.
1.3. Indications
- Treatment of essential hypertension.
- Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
- Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.
- Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

1.4. Posology and method of administration
Losartan tablets should be swallowed with a glass of water. Losartan potassium may be administered with or without food.

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 potassium may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

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

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

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

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

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

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

Hypertensive type II diabetic patients with proteinuria ≥ 0.5 g/day
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month after initiation of therapy onwards. Losartan Pharmacal may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as
with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Heart Failure
The usual initial dose of Losartan potassium 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 and 50 mg daily) to the usual maintenance dose of 50 mg once daily, as tolerated by the patient.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG
The usual starting dose is 50 mg of Losartan Pharmakal once daily. A low dose of hydrochlorothiazide should be added and/or the dose of Losartan Pharmakal should be increased to 100 mg once daily based on blood pressure response.

Use in patients with intravascular volume depletion:
For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see section 4.4).

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

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

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

2. Clinical Pharmacology

2.1. Pharmacokinetics
Losartan Potassium is a well known active substance and the pharmacokinetic characteristics have been studied in the past. The applicant has submitted a bioequivalence study in support of claims of essential similarity.

2.2. Bioequivalence
To support the application, the applicant has submitted as report no clinical trials; but two bioequivalence studies. Both BE studies are two-treatment, two period crossover studies. They follow the randomised open label comparison of Test and Reference products. Although Losartan exhibits linear pharmacokinetics, the 4 strengths sought have differences in composition and are not dose proportional, hence the applicant has provided one 25mg Biostudy and another 100mg biostudy with respective biowaivers for 12.5 and 50mg strengths.

Biowaiver
As detailed above, all strengths are not dose proportional. The two lower strengths are dose proportional with similarity in composition (12.5 and 25mg) while the two higher strengths
(50mg and 100mg) are proportional with similar compositions. In this situation, two biostudies would be appropriate.

The biowaiver is applicable to this sequence in order to fulfil the criteria for biowaiver as set out in the Bioequivalence note for Guidance.

**Pharmacokinetic studies**

The applicant has provided two biostudies;
A 25mg biostudy-------relating to 12.5 and 25mg strengths
A 100mg biostudy-------relating to 50 and 100mg strengths
Each study will be described in turn and results discussed at the end.

**25 mg Biostudy:**

**Study title**
Comparative bioequivalence study of 25 mg losartan after single dose administration (fasting conditions) of Blue 007 (Bluepharma) and Cozaar 25 mg (Merck Sharpe & Dohme Ltd., U.K.) in 46 healthy subjects.

**Study design**
This was a single-dose, randomised, open label, two-treatment, two-period, two-sequence cross-over study was conducted. The study was designed to determine the bioavailability of two formulations containing 25 mg losartan after single dose administration under fasting conditions in healthy subjects. The bioanalytical part of the study was carried out at Anapharm Europe.

**Time schedule**
Date of protocol: 31.07.2007
Study initiation date: 22.10.2007 (enrolment of first subject for screening)
Study completion date: 05.11.2007 (final examination of last subject)
Date of final report: 14.03.2008
Washout period 7 days

The applicant claims that the study complied with GCP and the Helsinki declarations.

**Sampling Schedule:**
After an overnight fasting of at least 12 hours at 8 a.m. (time 0) the subjects were administered 25 mg losartan in sitting position.
27 blood samples were drawn for pharmacokinetic analysis at the prescribed times (pre-dose (collected at least 15 min prior to dosing) and 10 min, 20 min, 30 min, 40 min, 50 min, 1 h, 1 h 10 min, 1 h 20 min, 1 h 30 min, 1 h 40 min, 1 h 50 min, 2 h, 2 h 15 min, 2 h 30 min, 2 h 45 min, 3 h, 3 h 30 min, 4 h, 4 h 30 min, 5 h, 6 h, 8 h, 10 h, 12 h, 16 h and 24 hours after drug administration).

Both Losartan and Losartan Carboxy acid (metabolite) were analysed as detailed before.
The design, the dose applied, the washout period and sampling sequence are considered adequate. The sampling period is of adequate duration to cover 3 times the anticipated half-life of Losartan, the parent compound. The study is stated to comply with GCP and is in accordance with Declaration of Helsinki.

Test and reference products

**Test formulation**
The test formulation was Blue 007, a film coated tablet of containing 25mg Losartan

**Reference formulation**
The reference formulation was Cozaar 25mg

Population(s) studied
The population studied were 46 healthy male and female caucasian subjects, aged 18-55 years with BMI of 19-28 were recruited.

Protocol deviations;
There were minor protocol deviations relating to time of sampling according to the report but no major protocol violations were noted.

Analytical methods
The bioanalysis was performed at the analytical facility of SFBC Anapharm, Europe located in Barcelona. A validated HPLC method using MS was employed to determine the plasma concentrations of Losartan and Losartan carboxy acid. Finasteride was used an internal control. Determination was conducted considering GLP-guideline. Process of validation and acceptance criteria are based on rules and guidelines of the FDA and the ICH Consensus Guideline. Losartan and losartan carboxy acid were analysed in EDTA K3 plasma using a method validated at Anapharm Europe. The method was revalidated before starting measurement of the samples. During the study quality control samples were analysed together with the samples in order to control accuracy and repeatability.

Pharmacokinetic Variables
Calculations of the pharmacokinetic parameters and the assessment of bioequivalence were carried out for losartan and losartan carboxy acid. The bioavailability was estimated using following parameters:

**Primary parameters:**
- $AUC_t$
- $AUC_\infty$
- $C_{max}$

**Additional parameters:**
- $t_{max}$
- $t_{1/2}$
- Residual area; $AUC_t$ (last) - $\infty$ calculated as a difference between $AUC_\infty$ and $AUC_t$ expressed as percentage value.
Statistical methods

The statistical analysis was performed by using SAS (SAS Software Version 9.1.3, Copyright © by SAS Institute Inc., Cary, NC, USA). Non-zero Log-transformed data were used for Analysis of Variance (ANOVA) for \( AUC_t \), \( AUC_\infty \) and \( C_{max} \). The primary pharmacokinetic parameters after logarithmic transformation were subjected to an analysis of variance (ANOVA), using a general linear model with the factors sequence, subjects nested within sequence, period and drug formulation. The test for normality of the residual distribution was performed on ln-transformed data from one of the study periods using the Wilk-Shapiro procedure. In case of significant deviations from the assumption of normal distribution the OLS ANOVA procedure was judged as invalid and data was analysed employing the non-parametric Wilcoxon-Mann-Whitney-tests procedure.

For assessment of bioequivalence 90%-confidence intervals for the formulation ratio in the parameters \( AUC_t \), \( AUC_\infty \) and \( C_{max} \) of losartan and losartan carboxy acid were calculated using the ln-transformed data. Bioequivalence was accepted if the calculated 90%-confidence intervals are within 0.80 - 1.25 for \( AUC_t \) and 0.75 – 1.33 for \( C_{max} \).

Results

Table 1. PK parameters for LOSARTAN (parent)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( AUC_{0-t} ) ng/ml·h</th>
<th>( AUC_{0-\infty} ) ng/ml·h</th>
<th>( C_{max} ) ng/ml</th>
<th>( t_{max} ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arithmetic means</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>225.48 ± 74.825</td>
<td>233.49 ± 78.22</td>
<td>112.69 ± 54.297</td>
<td>0.95 ± 0.534</td>
</tr>
<tr>
<td>Reference</td>
<td>231.52 ± 82.441</td>
<td>239.14 ± 84.789</td>
<td>112.50 ± 65.176</td>
<td>1.21 ± 0.854</td>
</tr>
<tr>
<td><strong>Geometric means</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test*</td>
<td>213.39</td>
<td>221.00</td>
<td>100.31</td>
<td>0.83</td>
</tr>
<tr>
<td>Reference*</td>
<td>218.23</td>
<td>225.62</td>
<td>94.43</td>
<td>0.99</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.978 (0.95 -- 1.01)</td>
<td>0.980 (0.95 -- 1.011)</td>
<td>1.062 (0.91 -- 1.227)</td>
<td></td>
</tr>
<tr>
<td>Intrasubject CV (%)</td>
<td>9.15%</td>
<td>8.75%</td>
<td>42%</td>
<td></td>
</tr>
</tbody>
</table>

*ln-transformed values

Table 2: Pk parameters for Metabolite (Losartan carboxy acid)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( AUC_{0-t} ) ng/ml·h</th>
<th>( AUC_{0-\infty} ) ng/ml·h</th>
<th>( C_{max} ) ng/ml</th>
<th>( t_{max} ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arithmetic means</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>865.80 ± 314.09</td>
<td>940.21 ± 316.07</td>
<td>86.62 ± 41.29</td>
<td>5.42 ± 2.12</td>
</tr>
<tr>
<td>Reference</td>
<td>855.78 ± 303.88</td>
<td>936.58 ± 307.33</td>
<td>84.73 ± 40.59</td>
<td>5.98 ± 2.06</td>
</tr>
<tr>
<td><strong>Geometric means</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test*</td>
<td>804.50</td>
<td>885.49</td>
<td>76.19</td>
<td>5.14</td>
</tr>
<tr>
<td>Reference*</td>
<td>796.06</td>
<td>883.45</td>
<td>74.54</td>
<td>5.71</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.01 (0.98 -- 1.03)</td>
<td>1.00 (0.98 -- 1.026)</td>
<td>1.02 (0.98 -- 1.060)</td>
<td></td>
</tr>
<tr>
<td>Intrasubject CV (%)</td>
<td>6.64</td>
<td>6.65</td>
<td>10.21</td>
<td></td>
</tr>
</tbody>
</table>
*In-transformed values*

No significant period effect was noted apparently and no sequence effect was noted either. The pre-dose samples for period two are claimed to be below the LOQ of the assay. Number of the subjects experienced Cmax at the first sampling time. The residual area was <20% for the overall group (mean values) and for all individuals independently.

There were fifteen adverse events observed in ten subjects. These were headache, rush and dizziness. All were classified as mild. Fourteen were classified as possible and one as probable/likely study drug related. In seven subjects eight events were observed with test medication and in seven subjects seven events were observed with reference medication.

All parameters fulfil the conventional acceptance criteria for bioequivalence in that all 90% CI are within 80-125%. Two subjects were withdrawn from the study voluntarily and this was for non medical reasons. Conclusion of study results is based on pharmacokinetic data evaluation and statistical analysis of 44 subjects.

100mg Biostudy; LSA-P7-088

**Study title:**
Single dose cross over comparative bioavailability study of Losartan 100mg film coated tablets in fasted healthy male and female volunteers.

**Study design**

The design was essentially similar to the 25mg study described above. There were minor differences in inclusion criteria and other aspects. This was a single centre, randomised, laboratory blinded, two period, two treatment study. There was a washout period of 7 days between the two periods.

Blood sampling was carried out as follows after drug administration at the following times for each period; pre dose, and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10, 12, 16, 24 and 36 hours post dose. Dosing in each period was at 8 Am on day 0 after a 10 hours fast and the subjects were confined to the testing facility for 24 hours.

The report claims that the study was conducted in accordance to GCP requirements and the declaration of Helsinki. The date of ethical approval of the study is unclear form the report but other aspects seem to be in order.

The design of the study follows the conventional phase-I study to establish bioequivalence and the inclusion/exclusion criteria, the washout period and the protocol are adequate. As Losartan has an active metabolite (carboxy acid) both parent and metabolite were assayed in the plasma.

**Test and reference products**
Losartan BLPHI 100mg film coated tablets has been compared to Cozaar® 100mg film coated tablets.

**Population(s) studied**
Overall 40 subjects were planned for inclusion into the study. There was on dropout and hence 39 were included in the study report. All were Caucasian healthy male and female subjects, who were non-smokers, aged between 18-45 years with a BMI of 19-30 kg/Sq.M. Female subjects were included only if pregnancy test was confirmed negative. All subjects needed to be HBsAg and HIV negative.

**Analytical methods**
The analytes included Losartan and the metabolite, Losartan carboxy acid. The method of analysis was HPLC with MS detection. Bioanalytical part of the study was carried out at Algorithme Pharma in Laval, Quebec. Finasteride was used as an internal control. The range of assay was 5.00ng/ml to 1500ng/ml.

**Pharmacokinetic Variables**
Standard PK parameters were evaluated; AUCt, AUCinf, and Cmax were primary parameters.
The secondary parameters were, Tmax, t1/2, Kel, and residual area.
A noncompartmental approach with trapezoidal rule to estimate area under the curve were used.

**Statistical methods**
Statistical analysis was based on a parametric ANOVA model of the PK parameters; two sided 90% confidence interval of the ratio of geometric means for Cmax, AUCt and AUCinf based on log transformed data were used. Tmax evaluation was based on non-parametric approach. The overall level of significance was at two sided 5% level.

For the ANOVA model, the following were used as fixed factors; Study group, treatment, period (nested within study group), sequence, study by sequence interaction and study by treatment interaction. Subject effect (nested within the study by sequence interaction) was the random factor.

**Bioequivalence**
Bioequivalence was concluded if the 90% confidence intervals of GM ratio (test /Ref) was between the standard intervals of 80-125% for AUC and AUCinf.
For Cmax, proposals for widening to 75-133% based on the in use CPMP note for guidance were pre-defined in the protocol. All results were within the 80-125% limits.

**Results**

<table>
<thead>
<tr>
<th>Table 1. PK parameters for <strong>LOSARTAN (parent)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Arithmetic means</td>
</tr>
<tr>
<td>Reference</td>
</tr>
</tbody>
</table>
PAR Losartan Potassium 12.5, 25, 50, and 100mg Film-coated Tablets

### Geometric means

<table>
<thead>
<tr>
<th></th>
<th>Test*</th>
<th>Reference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>705.69</td>
<td>696.42</td>
</tr>
<tr>
<td>Cmax</td>
<td>728.94</td>
<td>718.00</td>
</tr>
<tr>
<td>tmax</td>
<td>391.19</td>
<td>392.90</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

<table>
<thead>
<tr>
<th></th>
<th>Test*</th>
<th>Reference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>101.33</td>
<td>101.52</td>
</tr>
<tr>
<td>Cmax</td>
<td>101.52</td>
<td>99.57</td>
</tr>
</tbody>
</table>

*ln-transformed values

| Intrasubject CV (%) | 16.3 | 15.7 | 40.1 |

Table-2: Pk parameters for Metabolite (Losartan carboxy acid)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} ng/ml·h</th>
<th>AUC_{0-∞} ng/ml·h</th>
<th>C_{max} ng/ml</th>
<th>t_{max} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>3903.13 ±1504.08</td>
<td>3962.91 ±1508.72</td>
<td>692.79 ± 309.97</td>
<td>3.14 ±1.06</td>
</tr>
<tr>
<td>Reference</td>
<td>3926.06 ± 417.83</td>
<td>3986.69±1418.83</td>
<td>681.98 ± 291.88</td>
<td>2.96 ±1.06</td>
</tr>
</tbody>
</table>

*ln-transformed values

<table>
<thead>
<tr>
<th></th>
<th>Test*</th>
<th>Reference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>3754.12</td>
<td>3803.96</td>
</tr>
<tr>
<td>Cmax</td>
<td>3824.37</td>
<td>3848.41</td>
</tr>
<tr>
<td>tmax</td>
<td>617.06</td>
<td>632.44</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

<table>
<thead>
<tr>
<th></th>
<th>Test*</th>
<th>Reference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>98.69 (94.73 - 102.81)</td>
<td>98.45 (94.65 -102.42)</td>
</tr>
<tr>
<td>Cmax</td>
<td>97.57 (90.86 -- 104.77)</td>
<td></td>
</tr>
</tbody>
</table>

Intrasubject CV (%) | 10.7 | 10.3 | 18.7 |

*ln-transformed values

No significant period effect was noted apparently and no sequence effect was noted either. The pre-dose samples for period two are claimed to be below the LOQ of the assay. No of the subjects experienced Cmax at the first sampling time. The residual area was <20% for the overall group (mean values) and for all individuals independently.

Twenty five of the 40 subjects experienced a total of 54 ADRs during the study. Twenty-eight (18 types) were reported after the Test product and 26 (15 types) were reported with the reference product. Three possibly drug related events (axillary mass, increase lymphocyte count and lymphadenopathy) were unexpected but not considered serious.

In both studies all parameters (Cmax, AUCt and AUCinf) fulfilled the criteria for bioequivalence as defined in the CPMP note for guidance, CPMP/EWP/QWP/1401/98. The two studies were conducted by different CROs and the study reports are a testament to the differences in approach.

**Pharmacokinetic conclusion**

Based on the submitted bioequivalence studies, LOSARTAN BLPHI tablets could be considered bioequivalent with COZAAAR® tablets.

The results of study LSA-P7-088 with 100mg formulation can be extrapolated to other strengths 50 mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4. and similarly the results of the 25mg study could be extrapolated to the 12.5mg
2.3. Pharmacodynamics
The pharmacodynamic characteristics of Losartan Potassium have been well-studied in the past. There would be no particular concerns for a generic medicinal product.

3. Clinical Efficacy
No new data have been submitted and none are required.

4. Clinical Safety
No new data have been submitted and none are required.

5. Expert Reports
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory.

6. Conclusion
The medical assessor recommended that marketing authorisation was granted for these products.

Module 1 – Administrative information
MAA forms
The MAA form is medically satisfactory.

Summary of Product Characteristics (SPC)
The SPC is medically satisfactory and consistent with that for the reference product.

Patient Information Leaflet (PIL)
The PIL is medically satisfactory and consistent with the SPC.

Packaging
The packaging is medically satisfactory.

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Losartan Potassium 12.5 mg, 25 mg, 50 mg & 100 mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of these type.

EFFICACY
No new or unexpected safety concerns arise from these applications.

The SPC and PIL are satisfactory and consistent with that of the reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Losartan Potassium is considered to
have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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