# Public Assessment Report

Losartan Potassium 25mg Tablets  
Losartan Potassium 50mg Tablets  
Losartan Potassium 100mg Tablets  

Losartan potassium  
PL 16002/0077-79  
PL 16002/0081-83  
Pharmafile Ltd  

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Lay Summary

The MHRA granted Pharmafile Ltd marketing authorisations (licences) for the medicinal products Losartan Potassium 25, 50 and 100mg Film-coated Tablets on 10/01/2008. These are prescription only medicines for the treatment of high blood pressure, enlarged heart due to high blood pressure and protection of the kidney from diabetes induced damage.

The active ingredient is losartan potassium. The products were found to be generic medical products of the reference products Cozaar 25mg, 50mg and 100mg Tablets (Merck Sharp and Dohme).
Scientific Discussion

INTRODUCTION

Based on the review of the quality, safety and efficacy, the UK granted marketing authorisations for the following medicinal products on 10/01/2008. The application consisted of two duplicate sets of 3 strengths. The products are prescription only medicines.

Losartan Potassium 25mg Film-coated tablets (PL 16002/0077 and PL 16002/0081)
Losartan Potassium 50mg Film-coated tablets (PL 16002/0078 and PL 16002/0082)
Losartan Potassium 100mg Film-coated tablets (PL 16002/0079 and PL 16002/0083)

The applications were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC

The products were found to be generic medical products of the reference products. The reference products in the UK are Cozaar 25 mg film coated tablets (Merck, Sharp and Dohme, PL 00025/0336, granted 15.12.1994) for the 25 mg strength, Cozaar 50 mg film coated tablets (Merck, Sharp and Dohme, PL 00025/0324, granted 15.12.1994) for the 50 mg strength and Cozaar 100 mg film coated tablets (Merck, Sharp and Dohme, PL 00025/0416, granted 28.11.2001) for the 100 mg strength tablets. The reference product used in the bioequivalence study is Cozaar 50mg Film Coated tablets, manufactured in the Netherlands by Merck, Sharp and Dohme and marketed in Denmark and Iceland.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

Generic name: Losartan potassium
Chemical name (applicant):
2-butyl-4-chloro-1-[[2’-(1H-tetrazol-5-yl)-[1,1’-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol potassium
CAS: 114798-26-4 (Losartan)
124750-99-8 (Losartan potassium)

Structure

![Structure of Losartan potassium]

Molecular formula: $\text{C}_{22}\text{H}_{22}\text{ClKN}_6\text{O}$
Mr: 461.001 g/mol

General properties

Losartan is a white to off-white crystalline powder, which is freely soluble in water and soluble in methanol and ethanol (96 %). It is polymorphic, with the route of synthesis producing Form 1. Losartan also exhibits structural isomerism, forming losartan potassium and iso-losartan potassium.

An appropriate specification based on the USP monograph has been provided.

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

Active 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 active substance manufacturer and finished product manufacturer during validation studies.

The active substance has been assigned a re-test period of 24 months.
DRUG PRODUCT

Other Ingredients
The other ingredients of the drug product are listed below,

- Mannitol (E 421)
- Cellulose microcrystalline
- Croscarmellose sodium
- Povidone K-30
- Magnesium stearate
- Hypromellose 6
- Titanium dioxide (E 171)
- Talc
- Propylene glycol

All excipients are controlled by relevant Ph Eur monographs and satisfactory specification and certificates of analysis were provided. Magnesium stearate is of vegetable origin.

Dissolution and impurity profiles
Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been 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 tablets are packaged in transparent PVC/PVDC/Al heat-sealed blisters, formed by thermoforming the PVC/PVDC foil and then soldering it with the aluminium foil (0.02 mm thickness). Specifications are satisfactory.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set for Losartan Potassium 25mg Film-coated tablets (PL 16002/0077 and PL 16002/0081), 4 years for Losartan Potassium 50mg Film-coated tablets (PL 16002/0078 and PL 16002/0082) and 2 years for Losartan Potassium 100mg Film-coated tablets (PL 16002/0079 and
PL 16002/0077-79/0081-83

PL 16002/0083). Storage conditions for all three strengths are “Store in the original packet”, and for Losartan Potassium 100mg Film coated tablets (PL 16002/0079 and PL 16002/0083) only “Do not store above 30°C”.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.
PRE-CLINICAL ASSESSMENT

No pre-clinical data were provided for these applications and none were required.
MEDICAL ASSESSMENT

General

Losartan is an oral, specific angiotensin-II receptor (type AT\textsubscript{1}) antagonist. 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 proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT\textsubscript{1} receptor.

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. Both losartan and its active metabolite are $\geq 99\%$ bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Bioequivalence Study

This was a randomised, open label, single centre, single-dose, two-period, two –way, cross-over study in 18 healthy volunteers comparing the test (Losartan potassium, Omega Farma, Iceland) to the reference products (Cozaar, MS&D, Netherlands). The strength utilised was 50mg with a washout period of 7 days. The following parameters were estimated; AUC\textsubscript{t}, AUC\textsubscript{\infty}, C\textsubscript{\text{max}}, Residual area, T\text{\text{max}}, Kel and T\textsubscript{1/2} el. Blood samples were obtained at following times; pre-dose, 0.250, 0.50, 0.750, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, and 36.00 hours post dose. Appropriate statistical methods (parametric ANOVA) were applied to analyse the results.

Results:

Losartan

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test (Omega Farma)</th>
<th>Reference (Cozaar)</th>
<th>Point Est. and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t ng*h/mL</td>
<td>393.86 ± 173.81</td>
<td>363.14 ±145.61</td>
<td>107.5 (101.99 to 113.28)</td>
</tr>
<tr>
<td>AUC0-\text{\infty}. ng*h/mL</td>
<td>403.69 ± 174.48</td>
<td>372.95 ±145.49</td>
<td>107.22 (101.83 to 112.89)</td>
</tr>
<tr>
<td>Residual area (%)</td>
<td>2.74 ±1.35</td>
<td>2.99 ±1.37</td>
<td></td>
</tr>
<tr>
<td>C\text{\max} ng/mL</td>
<td>203.64 ± 137.03</td>
<td>168.25 ±73.89</td>
<td>110.43 (91.26 to 133.64)</td>
</tr>
<tr>
<td>Kel</td>
<td>0.355 ±0.07</td>
<td>0.365 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>T\text{\text{max}} h</td>
<td>0.750 ±0.88</td>
<td>1.38 ±1.63</td>
<td></td>
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</tbody>
</table>

Active metabolite (losartan carboxy acid)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test (Omega Farma)</th>
<th>Reference (Cozaar)</th>
<th>Point Est. and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t ng*h/mL</td>
<td>1901.25 ±411.64</td>
<td>1869.85 ± 397.59</td>
<td>101.5 (96.38 to 107.09)</td>
</tr>
<tr>
<td>AUC0-\text{\infty}. ng*h/mL</td>
<td>1930.47 ±409.69</td>
<td>1898.01 ±397.31</td>
<td>101.67 (96.56 to 107.04)</td>
</tr>
<tr>
<td>C\text{\max} ng/mL</td>
<td>256.04 ± 77.34</td>
<td>248.24 ± 87.03</td>
<td>104.30 (94.80 to 114.74)</td>
</tr>
<tr>
<td>Kel</td>
<td>0.128 ± 0.026</td>
<td>0.126 ± 0.021</td>
<td></td>
</tr>
<tr>
<td>T\text{\text{max}} h</td>
<td>4.00 ± 1.38</td>
<td>4.50 ±0.88</td>
<td></td>
</tr>
</tbody>
</table>

Comments;

Based on prior knowledge of Losartan kinetics and half-life, the sampling frequency appears appropriate. The point of extrapolation is acceptable as residual area was $<20\%$.

UKPAR Pharmafile Ltd, Losartan Potassium 25, 50, 100mg Film-coated Tablets
The AUCt and AUC for both parent and active metabolite were within the preset acceptability limits (80-125%). The 90% CI for Cmax of the parent compound however, was wider. In view of the 90% CI being outside the preset acceptability limits the applications were referred to the Commission on Human Medicines (CHM) for advice regarding the bioequivalence study. At that time, it was the decision of the CHM that a wider Cmax limit could be accepted for the parent molecule and that this would not result in any additional safety concerns and that market authorisations could be granted.

**Efficacy and Safety**

Data on the efficacy and safety of losartan potassium was not presented in this application and none were required. The clinical expert report contained a satisfactory review of efficacy and safety and was written by a suitably qualified person.

**Summary of Product Characteristics**

This was satisfactory

**Patient Information Leaflet**

This was satisfactory

**Conclusion**

Market Authorisations may be granted.
Overall Conclusion and Risk/Benefit Analysis

Quality
The important quality characteristics of Losartan potassium 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.

Pre-Clinical
No new preclinical data were submitted and none were required.

Clinical
After consideration by the Commission on Human Medicines the clinical characteristics of losartan potassium Film-coated tablets were found to be acceptable. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference product.

Risk/Benefit Analysis
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.
## Steps Taken During Assessment

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<table>
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<tr>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the application on 01/12/2004.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 13/12/2004.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 23/05/2005 and 17/05/2006 and on the medical assessment on 23/05/2005.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant provided further information in regard to the quality assessment on 17/11/2005, 30/06/2006 and 12/01/2006 and on the medical assessment on 12/01/2006.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 10/01/2008.</td>
</tr>
</tbody>
</table>
Steps Taken after Assessment

None.
SUMMARY OF PRODUCT CHARACTERISTICS

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.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Losartan Potassium 25 mg Film-Coated Tablet is a white, film coated, round biconvex tablet. Diameter 8mm. Marked 2 L on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- **Hypertension**
  Losartan is indicated for the treatment of hypertension.

- **Hypertensive patients with left ventricular hypertrophy**
  In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated. The data do not support the use of losartan for this indication in black patients (see section 4.4 Special warnings and Precautions for Use-Race and section 5.1 Pharmacodynamic Properties, LIFE study, Race).

- **Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)**
  Losartan is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

4.2 Posology and method of administration
Losartan may be administered with or without food.
Losartan may be administered with other antihypertensive agents. However, the concomitant use of losartan and ACE inhibitors has not been adequately studied.

Hypertension
The 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.

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

Renal protection in type 2 diabetic patients with nephropathy.
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily according to blood pressure response from one month after initiation of therapy onwards. Losartan may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers and centrally-acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

Losartan was not studied in type 2 diabetic patients with severe renal impairment.

Use in patients with intravascular volume depletion: For the very small proportion of patients who have intravascular volume depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see 4.4 'Special warnings and precautions for use').

Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.

Use in hepatic impairment: A lower dose should be considered for patients with a history of hepatic impairment (see 4.4 'Special warnings and precautions for use').

Use in children: Use in children under 18 years is not recommended.

Use in the elderly:

Patients up to 75 years: No initial dosage adjustment is necessary for this group of patients.

Patients over 75 years: Currently there is limited clinical experience in this group of patients; a lower starting dose of 25 mg once daily is recommended.

4.3 Contraindications
Losartan is contraindicated in
- pregnancy (see 4.6 'Pregnancy and lactation')
- hypersensitivity to losartan
- hypersensitivity to other angiotensin receptor blockers
- hypersensitivity to any of the excipients in the tablet.

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema involving the extremities, face, mucous membranes, tongue, lips, glottis or larynx has been seen in patients treated with losartan. Treatment should be discontinued if these symptoms occur. See 4.8 'Undesirable effects'. The use of losartan in patients with haemodynamically significant obstructive valvular disease or cardiomyopathy has not been adequately studied.

**Hypotension and electrolyte/fluid imbalance**

In patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used (see 4.2 'Posology and method of administration').

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group (see 4.8 'Undesirable effects' and *Laboratory test findings*).

**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 (see 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').

**Renal function impairment**

As a consequence of inhibiting the renin-angiotensin-aldosterone 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.

Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with losartan.

**Race (Black patients):**

There is no evidence that losartan reduces the risk of stroke in black patients with hypertension and left ventricular hypertrophy (see Section 5.1 Pharmacodynamic properties, LIFE Study, *Race*).

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

In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, ketoconazole, erythromycin and phenobarbital (phenobarbitone). Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium or may increase potassium levels (e.g. potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium) may lead to increases in serum potassium. Co-medication is not advisable.
As with other antihypertensive agents, the antihypertensive effect of losartan may be attenuated by non-steroidal anti-inflammatory drugs such as indometacin.

4.6 **Pregnancy and lactation**

*Use during pregnancy*

Although there is no experience with the use of losartan in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.

In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the foetus increases if losartan is administered during the second or third trimesters of pregnancy.

**When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing foetus. Losartan should not be used in pregnancy, and if pregnancy is detected losartan should be discontinued as soon as possible.**

*Use during lactation*

It is not known whether losartan is excreted in human milk. However, significant levels of losartan and the active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

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

Dizziness caused by losartan may affect the ability to drive and use machines.

4.8 **Undesirable effects**

Frequency estimate: common \( \geq 1\% \); uncommon \( \geq 0.1\% \) to \(<1\% \); rare \(<0.1\% \);

Side effects have usually been mild and transient in nature and have not required discontinuation of therapy.

**Frequency of adverse effects according to body organ class.**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Body Organ Class</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Central and peripheral nervous system</td>
<td>Dizziness, asthenia, fatigue</td>
</tr>
<tr>
<td></td>
<td>Ear / labyrinth</td>
<td>Vertigo</td>
</tr>
<tr>
<td></td>
<td>Electrolyte</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Diarrhoea, nausea and vomiting</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Cardiovascular</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Rare</td>
<td>Cardiovascular</td>
<td>Vasculitis including Henoch-Schonlein purpura</td>
</tr>
</tbody>
</table>
Rare cont.

<table>
<thead>
<tr>
<th>Central and peripheral nervous system</th>
<th>Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Hepatitis, liver function abnormalities</td>
</tr>
<tr>
<td>Immune system</td>
<td>Hypersensitivity reactions – Anaphylactoid reactions, angioedema including swelling of the larynx and glottis causing airway obstruction (and/or swelling of the face, lips, pharynx and tongue)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Myalgia, arthralgia</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Cough</td>
</tr>
<tr>
<td>Skin</td>
<td>Urticaria, pruritus, rash</td>
</tr>
</tbody>
</table>

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy, the most common drug-related side effects were dizziness, asthenia/fatigue and vertigo.

In a controlled clinical trial in type 2 diabetic patients with nephropathy, the most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalaemia. In this study, few patients discontinued due to hyperkalaemia (see 4.4 'Special warnings and precautions for use', Hypotension and electrolyte/fluid imbalance).

4.9 Overdose
Significant lethality was observed in mice and rats after oral administration of 1,000 mg/kg (3,000 mg/m²) and 2,000 mg/kg (11,800 mg/m²) (500 and 1,000 times the maximum recommended daily human dose), respectively.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

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

* Based on a patient weight of 50 kg.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: CO9C A01
Losartan is an oral, specific angiotensin-II receptor (type AT₁) antagonist. 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 proliferation.
Based on binding and pharmacological bioassays, it binds selectively to the AT$_1$ receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis. During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT$_1$ receptor and does not bind to or 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, effects not directly related to blocking the AT$_1$ receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

A study was carried out which was specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors. In this study and in the controlled clinical trials for hypertension, the incidence of cough reported by patients receiving losartan or an agent not associated with ACE-inhibitor-induced cough (hydrochlorothiazide or placebo) was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4,131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually <24 micromol) which was persistent in chronic therapy.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma noradrenaline.

Losartan potassium administered in doses of up to 150 mg once daily did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

**Hypertension Studies:**

In clinical studies, once-daily administration of 50 mg losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood
pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.

The antihypertensive effect of 50 mg of losartan is similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of 50-100 mg of losartan is comparable to once-daily administration of atenolol 50–100 mg. The effect of administration of 50-100 mg of losartan once daily also is equivalent to felodipine extended-release 5-10 mg in older hypertensives (>65 years) after 12 weeks of therapy. Although losartan is antihypertensive in all races, as with other drugs that affect the renin-angiotensin-aldosterone system, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.

If losartan is given together with thiazide-type diuretics, the blood-pressure-lowering effects are approximately additive.

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The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.

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

**Race:** There were 533 black patients in the study. In this group, treatment with losartan resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint (p=0.033, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke (p=0.030, 95% confidence interval 1.08-4.40).

**Heart failure**

In the 48-week ELITE study in patients (n=722) with heart failure (NYHA Class II - IV), no difference was observed in the primary endpoint of persistent
renal dysfunction between those patients treated with 'Cozaar' and those treated with captopril. The unexpected observation of superior benefit of 'Cozaar' in reducing the risk of death relative to captopril observed in the ELITE study was not confirmed in the definitive ELITE II survival study [1] as described below.

In a study in patients with heart failure that was prospectively designed to evaluate the mortality (ELITE II), a regimen of 'Cozaar' 50 mg once daily (starting dose of 12.5 mg titrated to 25 mg and 50 mg once daily) was compared to captopril 50 mg three times daily (starting dose of 12.5 mg titrated to 25 mg and 50 mg three times daily). In this study (n=3,152), patients with heart failure (NYHA Class II - IV) were followed for approximately two years (median follow-up 1.5 years) to evaluate whether 'Cozaar' was superior to captopril in reducing total mortality. The primary endpoint showed no statistically significant difference between 'Cozaar' and captopril in total mortality (17.7% for 'Cozaar' and 15.9% for captopril, p=0.16). The secondary endpoint showed no statistically significant difference in sudden cardiac death and/or resuscitated cardiac arrest (9.0% for 'Cozaar' and 7.3% for captopril, p=0.08). The tertiary endpoint of all-cause mortality and/or all cause hospitalisation showed no statistically significant difference between 'Cozaar' and captopril (47.7% for 'Cozaar' and 44.9% for captopril, p=0.18). In general, other morbidity and mortality endpoints including improvement in NYHA Class were not different between the treatment groups.

In both of these controlled clinical trials in patients with heart failure, 'Cozaar' was generally well tolerated, and the tolerability profile of 'Cozaar' was superior to captopril as measured by significantly lower incidence of discontinuations due to side effects and significantly lower incidence of cough.

RENAAL Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a multicentre, randomised, placebo-controlled, double-blind study 1,513 type 2 diabetic patients with nephropathy (751 treated with losartan), with or without hypertension. Patients were recruited with proteinuria as defined by urinary albumin to creatinine ratio >25 mg/mmol or 24-hour urinary protein excretion >500 mg and a serum creatinine of 115-265 micromol/l (a lower limit of 133 micromol/l was used for patients weighing more than 60 kg). The patients were randomised to receive losartan 50 mg once daily, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg daily as appropriate after one month; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Patients were followed for 3.4 years on average.

The results showed that treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary
composite end point, the results also showed significant risk reduction in the
group treated with losartan: 25.3% risk reduction in doubling of serum
creatinine \((p=0.006)\); 28.6% risk reduction in end-stage renal disease
\((p=0.002)\); 19.9% risk reduction in end-stage renal disease or death \((p=0.009)\);
21.0% risk reduction in doubling of serum creatinine or end-stage renal
disease \((p=0.010)\). All-cause mortality alone was not significantly different
between the two treatment groups.

For the secondary endpoints, the results showed an average reduction of
34.3% in the level of proteinuria in the group treated with losartan \((p<0.001)\)
over the mean of 3.4 years. Treatment with losartan reduced the rate of decline
in renal function during the chronic phase of the study by 13.9%, \(p=0.003\)
(median rate of decline of 25.5%, \(p<0.0001\)) as measured by the reciprocal of
the serum creatinine concentration-time curve. There was no significant
difference between the group treated with losartan (247 events) and the
placebo group (268 events) in the composite endpoint of cardiovascular
morbidity and mortality, although the study was not powered to detect such an
effect.

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. There was no
clinically significant effect on the plasma concentration profile of losartan
when the drug was administered with a standardised meal.

Distribution
Both losartan and its active metabolite are \(99\%\) bound to plasma proteins,
primarily albumin. The volume of distribution of losartan is 34 litres. Studies
in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Biotransformation
About 14% of an intravenously or orally-administered dose of losartan is
converted to its active metabolite. Following oral and intravenous
administration of \(^{14}\)C-labelled losartan potassium, circulating plasma
radioactivity primarily is attributed to losartan and its active metabolite.
In addition to the active metabolite, inactive metabolites are formed, including
two major metabolites formed by hydroxylation of the butyl side chain and a
minor metabolite, an N-2 tetrazole glucuronide.

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 of $^{14}$C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

**Characteristics in patients**

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers. Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

5.3 **Preclinical safety data**

The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice.

There was no evidence of direct genotoxicity in studies conducted with losartan potassium or its primary pharmacologically active metabolite (E-3174).

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the recommended daily dose. Losartan potassium has been shown to produce adverse effects in rat foetuses and neonates. The effects include decreased bodyweight, mortality and/or renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Losartan Potassium Tablets contain the following excipients: Mannitol (E 421)
Cellulose microcrystalline
Croscarmellose sodium
Povidone K-30
Magnesium stearate
Hypermellose 6
Titanium dioxide (E 171)
Talc
Propylene glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store in the original package

6.5 Nature and contents of container
Transparent PVC/PVDC/Al blisters
Packs of 5, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 98, 100, 210 and 280 Tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Pharmafile Limited,
Medici House,
Ashbourne Industrial Estate,
Ashbourne,
Co. Meath,
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 16002/0077

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/01/2008

10 DATE OF REVISION OF THE TEXT
10/01/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Losartan Potassium 50mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 50 mg of losartan potassium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Losartan Potassium 50 mg Film-Coated Tablet is a white, film coated, round biconvex tablet. Diameter 10mm. Marked 3 L on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
• Hypertension
  Losartan is indicated for the treatment of hypertension.
• Hypertensive patients with left ventricular hypertrophy
  In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated. The data do not support the use of losartan for this indication in black patients (see section 4.4 Special warnings and Precautions for Use-Race and section 5.1 Pharmacodynamic Properties, LIFE study, Race).
• Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)
  Losartan is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

4.2 Posology and method of administration
Losartan may be administered with or without food.
Losartan may be administered with other antihypertensive agents. However, the concomitant use of losartan and ACE inhibitors has not been adequately studied.
• Hypertension
  The 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.
Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy
The usual starting dose is 50 mg of losartan once daily. A low dose of hydrochlorothiazide may be added and/or the dose of losartan may be increased to 100 mg once daily based on blood pressure.

Renal protection in type 2 diabetic patients with nephropathy.
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily according to blood pressure response from one month after initiation of therapy onwards. Losartan may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers and centrally-acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

Losartan was not studied in type 2 diabetic patients with severe renal impairment.

Use in patients with intravascular volume depletion: For the very small proportion of patients who have intravascular volume depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see 4.4 'Special warnings and precautions for use').

Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.

Use in hepatic impairment: A lower dose should be considered for patients with a history of hepatic impairment (see 4.4 'Special warnings and precautions for use').

Use in children: Use in children under 18 years is not recommended.

Use in the elderly:
Patients up to 75 years: No initial dosage adjustment is necessary for this group of patients.

Patients over 75 years: Currently there is limited clinical experience in this group of patients; a lower starting dose of 25 mg once daily is recommended.

4.3 Contraindications
Losartan is contraindicated in
- pregnancy (see 4.6 'Pregnancy and lactation')
- hypersensitivity to losartan
- hypersensitivity to other angiotensin receptor blockers
- hypersensitivity to any of the excipients in the tablet.

4.4 Special warnings and precautions for use
Hypersensitivity:
Angioedema involving the extremities, face, mucous membranes, tongue, lips, glottis or larynx has been seen in patients treated with losartan. Treatment should be discontinued if these symptoms occur. See 4.8 'Undesirable effects'.
The use of losartan in patients with haemodynamically significant obstructive valvular disease or cardiomyopathy has not been adequately studied. 

**Hypotension and electrolyte/fluid imbalance**

In patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used (see 4.2 'Posology and method of administration'). Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group (see 4.8 'Undesirable effects' and Laboratory test findings).

**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 (see 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').

**Renal function impairment**

As a consequence of inhibiting the renin-angiotensin-aldosterone 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.

Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with losartan.

**Race (Black patients):**

There is no evidence that losartan reduces the risk of stroke in black patients with hypertension and left ventricular hypertrophy (see Section 5.1 Pharmacodynamic properties, LIFE Study, Race).

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

In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, ketoconazole, erythromycin and phenobarbital (phenobarbitone). Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium or may increase potassium levels (e.g. potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium) may lead to increases in serum potassium. Co-medication is not advisable.

As with other antihypertensive agents, the antihypertensive effect of losartan may be attenuated by non-steroidal anti-inflammatory drugs such as indometacin.
4.6 Pregnancy and lactation

Use during pregnancy

Although there is no experience with the use of losartan in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.

In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the foetus increases if losartan is administered during the second or third trimesters of pregnancy.

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing foetus. Losartan should not be used in pregnancy, and if pregnancy is detected losartan should be discontinued as soon as possible.

Use during lactation

It is not known whether losartan is excreted in human milk. However, significant levels of losartan and the active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Dizziness caused by losartan may affect the ability to drive and use machines.

4.8 Undesirable effects

Frequency estimate: common ≥1%; uncommon ≥0.1% to <1%; rare <0.1%;

Side effects have usually been mild and transient in nature and have not required discontinuation of therapy.

Frequency of adverse effects according to body organ class.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Body Organ Class</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td><em>Central and peripheral nervous system</em></td>
<td>Dizziness, asthenia, fatigue</td>
</tr>
<tr>
<td></td>
<td><em>Ear / labyrinth</em></td>
<td>Vertigo</td>
</tr>
<tr>
<td></td>
<td><em>Electrolyte</em></td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td><em>Cardiovascular</em></td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td><em>Gastrointestinal</em></td>
<td>Diarrhoea, nausea and vomiting</td>
</tr>
<tr>
<td>Uncommon</td>
<td><em>Cardiovascular</em></td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Rare</td>
<td><em>Cardiovascular</em></td>
<td>Vasculitis including Henoch-Schonlein purpura</td>
</tr>
<tr>
<td></td>
<td><em>Central and peripheral nervous system</em></td>
<td>Migraine</td>
</tr>
<tr>
<td></td>
<td><em>Haematological</em></td>
<td>Anaemia</td>
</tr>
</tbody>
</table>
### Hepatic
Hepatitis, liver function abnormalities

### Immune system
Hypersensitivity reactions – Anaphylactoid reactions, angioedema including swelling of the larynx and glottis causing airway obstruction (and/or swelling of the face, lips, pharynx and tongue)

### Musculoskeletal
Myalgia, arthralgia

### Respiratory
Cough

### Skin
Urticaria, pruritus, rash

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy, the most common drug-related side effects were dizziness, asthenia/fatigue and vertigo.

In a controlled clinical trial in type 2 diabetic patients with nephropathy, the most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalaemia. In this study, few patients discontinued due to hyperkalaemia (see 4.4 'Special warnings and precautions for use', Hypotension and electrolyte/fluid imbalance).

### 4.9 Overdose
Significant lethality was observed in mice and rats after oral administration of 1,000 mg/kg (3,000 mg/m²) and 2,000 mg/kg (11,800 mg/m²) (500 and 1,000 times the maximum recommended daily human dose), respectively. Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

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

* Based on a patient weight of 50 kg.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: CO9C A01

Losartan is an oral, specific angiotensin-II receptor (type AT₁) antagonist. 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 proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT₁ receptor. In vitro and in vivo, both losartan and its pharmacologically
active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis. During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT$_1$ receptor and does not bind to or 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, effects not directly related to blocking the AT$_1$ receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

A study was carried out which was specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors. In this study and in the controlled clinical trials for hypertension, the incidence of cough reported by patients receiving losartan or an agent not associated with ACE-inhibitor-induced cough (hydrochlorothiazide or placebo) was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4,131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually <24 micromol) which was persistent in chronic therapy. Losartan has no effect on autonomic reflexes and no sustained effect on plasma noradrenaline.

Losartan potassium administered in doses of up to 150 mg once daily did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

**Hypertension Studies:**

In clinical studies, once-daily administration of 50 mg losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The
antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.

The antihypertensive effect of 50 mg of losartan is similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of 50-100 mg of losartan is comparable to once-daily administration of atenolol 50–100 mg. The effect of administration of 50-100 mg of losartan once daily also is equivalent to felodipine extended-release 5-10 mg in older hypertensives (≥65 years) after 12 weeks of therapy. Although losartan is antihypertensive in all races, as with other drugs that affect the renin-angiotensin-aldosterone system, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.

If losartan is given together with thiazide-type diuretics, the blood-pressure-lowering effects are approximately additive.

LIFE Study
The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.

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

Race: There were 533 black patients in the study. In this group, treatment with losartan resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint (p=0.033, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke (p=0.030, 95% confidence interval 1.08-4.40).

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'Cozaar' in reducing the risk of death relative to captopril observed in the ELITE study was not confirmed in the definitive ELITE II survival study [1] as described below.

In a study in patients with heart failure that was prospectively designed to evaluate the mortality (ELITE II), a regimen of 'Cozaar' 50 mg once daily (starting dose of 12.5 mg titrated to 25 mg and 50 mg once daily) was compared to captopril 50 mg three times daily (starting dose of 12.5 mg titrated to 25 mg and 50 mg three times daily). In this study (n=3,152), patients with heart failure (NYHA Class II - IV) were followed for approximately two years (median follow-up 1.5 years) to evaluate whether 'Cozaar' was superior to captopril in reducing total mortality. The primary endpoint showed no statistically significant difference between 'Cozaar' and captopril in total mortality (17.7% for 'Cozaar' and 15.9% for captopril, p=0.16). The secondary endpoint showed no statistically significant difference in sudden cardiac death and/or resuscitated cardiac arrest (9.0% for 'Cozaar' and 7.3% for captopril, p=0.08). The tertiary endpoint of all-cause mortality and/or all cause hospitalisation showed no statistically significant difference between 'Cozaar' and captopril (47.7% for 'Cozaar' and 44.9% for captopril, p=0.18). In general, other morbidity and mortality endpoints including improvement in NYHA Class were not different between the treatment groups.

In both of these controlled clinical trials in patients with heart failure, 'Cozaar' was generally well tolerated, and the tolerability profile of 'Cozaar' was superior to captopril as measured by significantly lower incidence of discontinuations due to side effects and significantly lower incidence of cough.

RENAAL Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a multicentre, randomised, placebo-controlled, double-blind study of 1,513 type 2 diabetic patients with nephropathy (751 treated with losartan), with or without hypertension. Patients were recruited with proteinuria as defined by urinary albumin to creatinine ratio >25 mg/mmol or 24-hour urinary protein excretion >500 mg and a serum creatinine of 115-265 micromol/l (a lower limit of 133 micromol/l was used for patients weighing more than 60 kg). The patients were randomised to receive losartan 50 mg once daily, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg daily as appropriate after one month; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Patients were followed for 3.4 years on average.

The results showed that treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary composite end point, the results also showed significant risk reduction in the group treated with losartan: 25.3% risk reduction in doubling of serum
creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease (p=0.002); 19.9% risk reduction in end-stage renal disease or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal disease (p=0.010). All-cause mortality alone was not significantly different between the two treatment groups.

For the secondary endpoints, the results showed an average reduction of 34.3% in the level of proteinuria in the group treated with losartan (p<0.001) over the mean of 3.4 years. Treatment with losartan reduced the rate of decline in renal function during the chronic phase of the study by 13.9%, p=0.003 (median rate of decline of 25.5%, p<0.0001) as measured by the reciprocal of the serum creatinine concentration-time curve. There was no significant difference between the group treated with losartan (247 events) and the placebo group (268 events) in the composite endpoint of cardiovascular morbidity and mortality, although the study was not powered to detect such an effect.

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. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardised meal.

Distribution
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Biotransformation
About 14% of an intravenously or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of \(^{14}\)C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

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 of $^{14}$C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

**Characteristics in patients**

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers. Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

5.3 **Preclinical safety data**

The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice. There was no evidence of direct genotoxicity in studies conducted with losartan potassium or its primary pharmacologically active metabolite (E-3174).

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the recommended daily dose.

Losartan potassium has been shown to produce adverse effects in rat foetuses and neonates. The effects include decreased bodyweight, mortality and/or renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Losartan Potassium Tablets contain the following excipients:

- Mannitol (E 421)
- Cellulose microcrystalline
Croscarmellose sodium
Povidone K-30
Magnesium stearate
Hypromellose 6
Titanium dioxide (E 171)
Talc
Propylene glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
4 years

6.4 Special precautions for storage
Store in the original package

6.5 Nature and contents of container
Transparent PVC/PVDC/Al blisters
Packs of 5, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 98, 100, 210 and 280 Tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Pharmafile Limited,
Medici House,
Ashbourne Industrial Estate,
Ashbourne,
Co. Meath,
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 16002/0078

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/01/2008

10 DATE OF REVISION OF THE TEXT
10/01/2008
1 NAME OF THE MEDICINAL PRODUCT
Losartan Potassium 100mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg of losartan potassium. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Losartan Potassium 100 mg Film-Coated Tablet is a white, film coated, oval biconvex tablet. Diameter 18.3mm x 9.2mm. Marked 4 L on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- Hypertension
  Losartan is indicated for the treatment of hypertension.
- Hypertensive patients with left ventricular hypertrophy
  In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated. The data do not support the use of losartan for this indication in black patients (see section 4.4 Special warnings and Precautions for Use-Race and section 5.1 Pharmacodynamic Properties, LIFE study, Race).
- Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)
  Losartan is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

4.2 Posology and method of administration
Losartan may be administered with or without food.
Losartan may be administered with other antihypertensive agents. However, the concomitant use of losartan and ACE inhibitors has not been adequately studied.
- Hypertension
  The 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.
- Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy
The usual starting dose is 50 mg of losartan once daily. A low dose of hydrochlorothiazide may be added and/or the dose of losartan may be increased to 100 mg once daily based on blood pressure. 

Renal protection in type 2 diabetic patients with nephropathy.

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

Losartan was not studied in type 2 diabetic patients with severe renal impairment.

Use in patients with intravascular volume depletion: For the very small proportion of patients who have intravascular volume depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see 4.4 'Special warnings and precautions for use').

Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.

Use in hepatic impairment: A lower dose should be considered for patients with a history of hepatic impairment (see 4.4 'Special warnings and precautions for use').

Use in children: Use in children under 18 years is not recommended.

Use in the elderly:
Patients up to 75 years: No initial dosage adjustment is necessary for this group of patients.

Patients over 75 years: Currently there is limited clinical experience in this group of patients; a lower starting dose of 25 mg once daily is recommended.

4.3 Contraindications
Losartan is contraindicated in
- pregnancy (see 4.6 'Pregnancy and lactation')
- hypersensitivity to losartan
- hypersensitivity to other angiotensin receptor blockers
- hypersensitivity to any of the excipients in the tablet.

4.4 Special warnings and precautions for use

Hypersensitivity:

Angioedema involving the extremities, face, mucous membranes, tongue, lips, glottis or larynx has been seen in patients treated with losartan. Treatment should be discontinued if these symptoms occur. See 4.8 'Undesirable effects'.

The use of losartan in patients with haemodynamically significant obstructive valvular disease or cardiomyopathy has not been adequately studied.

Hypotension and electrolyte/fluid imbalance
In patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used (see 4.2 'Posology and method of administration').

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group (see 4.8 'Undesirable effects' and Laboratory test findings).

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 (see 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').

Renal function impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone 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.
Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with losartan.

Race (Black patients):
There is no evidence that losartan reduces the risk of stroke in black patients with hypertension and left ventricular hypertrophy (see Section 5.1 Pharmacodynamic properties, LIFE Study, Race).

4.5 Interaction with other medicinal products and other forms of interaction
In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, ketoconazole, erythromycin and phenobarbital (phenobarbitone). Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.
As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium or may increase potassium levels (e.g. potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium) may lead to increases in serum potassium. Co-medication is not advisable.
As with other antihypertensive agents, the antihypertensive effect of losartan may be attenuated by non-steroidal anti-inflammatory drugs such as indomethacin.
4.6 Pregnancy and lactation

Use during pregnancy
Although there is no experience with the use of losartan in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system. In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the foetus increases if losartan is administered during the second or third trimesters of pregnancy.

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing foetus. Losartan should not be used in pregnancy, and if pregnancy is detected losartan should be discontinued as soon as possible.

Use during lactation
It is not known whether losartan is excreted in human milk. However, significant levels of losartan and the active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines
Dizziness caused by losartan may affect the ability to drive and use machines.

4.8 Undesirable effects
Frequency estimate: common ≥1%; uncommon ≥0.1% to <1%; rare <0.1%; Side effects have usually been mild and transient in nature and have not required discontinuation of therapy.

Frequency of adverse effects according to body organ class.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Body Organ Class</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Central and peripheral nervous system</td>
<td>Dizziness, asthenia, fatigue</td>
</tr>
<tr>
<td></td>
<td>Ear / labyrinth</td>
<td>Vertigo</td>
</tr>
<tr>
<td></td>
<td>Electrolyte</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Diarrhoea, nausea and vomiting</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Cardiovascular</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Rare</td>
<td>Cardiovascular</td>
<td>Vasculitis including Henoch-Schonlein purpura</td>
</tr>
<tr>
<td></td>
<td>Central and peripheral nervous system</td>
<td>Migraine</td>
</tr>
<tr>
<td></td>
<td>Haematological</td>
<td>Anaemia</td>
</tr>
<tr>
<td></td>
<td>Hepatic</td>
<td>Hepatitis, liver function abnormalities</td>
</tr>
</tbody>
</table>

UKPAR Pharmafile Ltd, Losartan Potassium 25, 50, 100mg Film-coated Tablets 38
Immune system
Hypersensitivity reactions – Anaphylactoid reactions, angioedema including swelling of the larynx and glottis causing airway obstruction (and/or swelling of the face, lips, pharynx and tongue)

Musculoskeletal
Myalgia, arthralgia

Respiratory
Cough

Skin
Urticaria, pruritus, rash

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy, the most common drug-related side effects were dizziness, asthenia/fatigue and vertigo.

In a controlled clinical trial in type 2 diabetic patients with nephropathy, the most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalaemia. In this study, few patients discontinued due to hyperkalaemia (see 4.4 'Special warnings and precautions for use', Hypotension and electrolyte/fluid imbalance).

4.9 Overdose
Significant lethality was observed in mice and rats after oral administration of 1,000 mg/kg (3,000 mg/m²) and 2,000 mg/kg (11,800 mg/m²) (500 and 1,000 times the maximum recommended daily human dose), respectively.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

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

* Based on a patient weight of 50 kg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: CO9C A01
Losartan is an oral, specific angiotensin-II receptor (type AT₁) antagonist. 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 proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT₁ receptor. In vitro and in vivo, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.
During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT\(_1\) receptor and does not bind to or 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, effects not directly related to blocking the AT\(_1\) receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

A study was carried out which was specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors. In this study and in the controlled clinical trials for hypertension, the incidence of cough reported by patients receiving losartan or an agent not associated with ACE-inhibitor-induced cough (hydrochlorothiazide or placebo) was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4,131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually <24 micromol) which was persistent in chronic therapy.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma noradrenaline.

Losartan potassium administered in doses of up to 150 mg once daily did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

**Hypertension Studies:**

In clinical studies, once-daily administration of 50 mg losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the...
effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.

The antihypertensive effect of 50 mg of losartan is similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of 50-100 mg of losartan is comparable to once-daily administration of atenolol 50–100 mg. The effect of administration of 50-100 mg of losartan once daily also is equivalent to felodipine extended-release 5-10 mg in older hypertensives (>65 years) after 12 weeks of therapy.

Although losartan is antihypertensive in all races, as with other drugs that affect the renin-angiotensin-aldosterone system, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.

If losartan is given together with thiazide-type diuretics, the blood-pressure-lowering effects are approximately additive.

**LIFE Study**

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.

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

**Race:** There were 533 black patients in the study. In this group, treatment with losartan resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint (p=0.033, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke (p=0.030, 95% confidence interval 1.08-4.40).

**Heart failure**

In the 48-week ELITE study in patients (n=722) with heart failure (NYHA Class II - IV), no difference was observed in the primary endpoint of persistent renal dysfunction between those patients treated with 'Cozaar' and those treated with captopril. The unexpected observation of superior benefit of 'Cozaar' in reducing the risk of death relative to captopril observed in the
ELITE study was not confirmed in the definitive ELITE II survival study [1] as described below.

In a study in patients with heart failure that was prospectively designed to evaluate the mortality (ELITE II), a regimen of 'Cozaar' 50 mg once daily (starting dose of 12.5 mg titrated to 25 mg and 50 mg once daily) was compared to captopril 50 mg three times daily (starting dose of 12.5 mg titrated to 25 mg and 50 mg three times daily). In this study (n=3,152), patients with heart failure (NYHA Class II - IV) were followed for approximately two years (median follow-up 1.5 years) to evaluate whether 'Cozaar' was superior to captopril in reducing total mortality. The primary endpoint showed no statistically significant difference between 'Cozaar' and captopril in total mortality (17.7% for 'Cozaar' and 15.9% for captopril, p=0.16). The secondary endpoint showed no statistically significant difference in sudden cardiac death and/or resuscitated cardiac arrest (9.0% for 'Cozaar' and 7.3% for captopril, p=0.08). The tertiary endpoint of all-cause mortality and/or all cause hospitalisation showed no statistically significant difference between 'Cozaar' and captopril (47.7% for 'Cozaar' and 44.9% for captopril, p=0.18). In general, other morbidity and mortality endpoints including improvement in NYHA Class were not different between the treatment groups.

In both of these controlled clinical trials in patients with heart failure, 'Cozaar' was generally well tolerated, and the tolerability profile of 'Cozaar' was superior to captopril as measured by significantly lower incidence of discontinuations due to side effects and significantly lower incidence of cough.

RENAAL Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a multicentre, randomised, placebo-controlled, double-blind study 1,513 type 2 diabetic patients with nephropathy (751 treated with losartan), with or without hypertension. Patients were recruited with proteinuria as defined by urinary albumin to creatinine ratio>25 mg/mmol or 24-hour urinary protein excretion>500 mg and a serum creatinine of 115-265 micromol/l (a lower limit of 133 micromol/l was used for patients weighing more than 60 kg). The patients were randomised to receive losartan 50 mg once daily, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg daily as appropriate after one month; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Patients were followed for 3.4 years on average.

The results showed that treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary composite end point, the results also showed significant risk reduction in the group treated with losartan: 25.3% risk reduction in doubling of serum creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease.
(p=0.002); 19.9% risk reduction in end-stage renal disease or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal disease (p=0.010). All-cause mortality alone was not significantly different between the two treatment groups.

For the secondary endpoints, the results showed an average reduction of 34.3% in the level of proteinuria in the group treated with losartan (p<0.001) over the mean of 3.4 years. Treatment with losartan reduced the rate of decline in renal function during the chronic phase of the study by 13.9%, p=0.003 (median rate of decline of 25.5%, p<0.0001) as measured by the reciprocal of the serum creatinine concentration-time curve. There was no significant difference between the group treated with losartan (247 events) and the placebo group (268 events) in the composite endpoint of cardiovascular morbidity and mortality, although the study was not powered to detect such an effect.

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. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardised meal.

Distribution
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

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-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

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 of $^{14}$C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

**Characteristics in patients**

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers. Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

### 5.3 Preclinical safety data

The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice.

There was no evidence of direct genotoxicity in studies conducted with losartan potassium or its primary pharmacologically active metabolite (E-3174).

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the recommended daily dose.

Losartan potassium has been shown to produce adverse effects in rat foetuses and neonates. The effects include decreased bodyweight, mortality and/or renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

Losartan Potassium Tablets contain the following excipients:

- Mannitol (E 421)
- Cellulose microcrystalline
- Croscarmellose sodium
Povidone K-30
Magnesium stearate
Hyromellose 6
Titanium dioxide (E 171)
Talc
Propylene glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container
Transparent PVC/PVDC/Al blisters
Pack of 5, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 98, 100, 210 and 280 Tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Pharmafile Limited,
Medici House,
Ashbourne Industrial Estate,
Ashbourne,
Co. Meath,
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 16002/0079

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/01/2008

10 DATE OF REVISION OF THE TEXT
10/01/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Losartan Potassium 25mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 25 mg of losartan potassium. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Losartan Potassium 25 mg Film-Coated Tablet is a white, film coated, round biconvex tablet. Diameter 8mm. Marked 2 L on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- **Hypertension**
  Losartan is indicated for the treatment of hypertension.
- **Hypertensive patients with left ventricular hypertrophy**
  In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated. The data do not support the use of losartan for this indication in black patients (see section 4.4 Special warnings and Precautions for Use-Race and section 5.1 Pharmacodynamic Properties, LIFE study, Race).
- **Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)**
  Losartan is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

4.2 Posology and method of administration
Losartan may be administered with or without food.
Losartan may be administered with other antihypertensive agents. However, the concomitant use of losartan and ACE inhibitors has not been adequately studied.

**Hypertension**
The 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.
Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy

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

Renal protection in type 2 diabetic patients with nephropathy.

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

Losartan was not studied in type 2 diabetic patients with severe renal impairment.

Use in patients with intravascular volume depletion: For the very small proportion of patients who have intravascular volume depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see 4.4 'Special warnings and precautions for use').

Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.

Use in hepatic impairment: A lower dose should be considered for patients with a history of hepatic impairment (see 4.4 'Special warnings and precautions for use').

Use in children: Use in children under 18 years is not recommended.

Use in the elderly:

Patients up to 75 years: No initial dosage adjustment is necessary for this group of patients.

Patients over 75 years: Currently there is limited clinical experience in this group of patients; a lower starting dose of 25 mg once daily is recommended.

4.3 Contraindications

Losartan is contraindicated in

- pregnancy (see 4.6 'Pregnancy and lactation')
- hypersensitivity to losartan
- hypersensitivity to other angiotensin receptor blockers
- hypersensitivity to any of the excipients in the tablet.

4.4 Special warnings and precautions for use

Hypersensitivity:

Angioedema involving the extremities, face, mucous membranes, tongue, lips, glottis or larynx has been seen in patients treated with losartan. Treatment should be discontinued if these symptoms occur. See 4.8 'Undesirable effects'.
The use of losartan in patients with haemodynamically significant obstructive valvular disease or cardiomyopathy has not been adequately studied.

**Hypotension and electrolyte/fluid imbalance**

In patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used (see 4.2 'Posology and method of administration').

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group (see 4.8 'Undesirable effects' and **Laboratory test findings**).

**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 (see 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').

**Renal function impairment**

As a consequence of inhibiting the renin-angiotensin-aldosterone 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.

Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with losartan.

**Race (Black patients):**

There is no evidence that losartan reduces the risk of stroke in black patients with hypertension and left ventricular hypertrophy (see Section 5.1 Pharmacodynamic properties, LIFE Study, **Race**).

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

In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, ketoconazole, erythromycin and phenobarbital (phenobarbitone). Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium or may increase potassium levels (e.g. potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium) may lead to increases in serum potassium. Co-medication is not advisable.
As with other antihypertensive agents, the antihypertensive effect of losartan may be attenuated by non-steroidal anti-inflammatory drugs such as indometacin.

4.6 Pregnancy and lactation

Use during pregnancy

Although there is no experience with the use of losartan in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.

In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the foetus increases if losartan is administered during the second or third trimesters of pregnancy.

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing foetus. Losartan should not be used in pregnancy, and if pregnancy is detected losartan should be discontinued as soon as possible.

Use during lactation

It is not known whether losartan is excreted in human milk. However, significant levels of losartan and the active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Dizziness caused by losartan may affect the ability to drive and use machines.

4.8 Undesirable effects

Frequency estimate: common ≥1%; uncommon ≥0.1% to <1%; rare <0.1%; Side effects have usually been mild and transient in nature and have not required discontinuation of therapy.

Frequency of adverse effects according to body organ class.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Body Organ Class</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Central and peripheral nervous system</td>
<td>Dizziness, asthenia, fatigue</td>
</tr>
<tr>
<td></td>
<td>Ear / labyrinth</td>
<td>Vertigo</td>
</tr>
<tr>
<td></td>
<td>Electrolyte</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Diarrhoea, nausea and vomiting</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Cardiovascular</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Rare</td>
<td>Cardiovascular</td>
<td>Vasculitis including Henoch-Schlonlein purpura</td>
</tr>
</tbody>
</table>
Central and peripheral nervous system | Migraine
---|---
Haematological | Anaemia

**Rare cont.**

Hepatic | Hepatitis, liver function abnormalities

Immune system | Hypersensitivity reactions – Anaphylactoid reactions, angioedema including swelling of the larynx and glottis causing airway obstruction (and/or swelling of the face, lips, pharynx and tongue)

Musculoskeletal | Myalgia, arthralgia

Respiratory | Cough

Skin | Urticaria, pruritus, rash

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy, the most common drug-related side effects were dizziness, asthenia/fatigue and vertigo.

In a controlled clinical trial in type 2 diabetic patients with nephropathy, the most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalaemia. In this study, few patients discontinued due to hyperkalaemia (see 4.4 'Special warnings and precautions for use', Hypotension and electrolyte/fluid imbalance).

### 4.9 Overdose

Significant lethality was observed in mice and rats after oral administration of 1,000 mg/kg (3,000 mg/m²) and 2,000 mg/kg (11,800 mg/m²) (500 and 1,000 times the maximum recommended daily human dose), respectively.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

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

* Based on a patient weight of 50 kg.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: CO9C A01

Losartan is an oral, specific angiotensin-II receptor (type AT₁) antagonist. 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 proliferation.
Based on binding and pharmacological bioassays, it binds selectively to the AT1 receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis. During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT1 receptor and does not bind to or 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, effects not directly related to blocking the AT1 receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

A study was carried out which was specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors. In this study and in the controlled clinical trials for hypertension, the incidence of cough reported by patients receiving losartan or an agent not associated with ACE-inhibitor-induced cough (hydrochlorothiazide or placebo) was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4,131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually <24 micromol) which was persistent in chronic therapy. Losartan has no effect on autonomic reflexes and no sustained effect on plasma noradrenaline.

Losartan potassium administered in doses of up to 150 mg once daily did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

**Hypertension Studies:**

In clinical studies, once-daily administration of 50 mg losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood
pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.

The antihypertensive effect of 50 mg of losartan is similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of 50-100 mg of losartan is comparable to once-daily administration of atenolol 50–100 mg. The effect of administration of 50-100 mg of losartan once daily also is equivalent to felodipine extended-release 5-10 mg in older hypertensives (≥65 years) after 12 weeks of therapy. Although losartan is antihypertensive in all races, as with other drugs that affect the renin-angiotensin-aldosterone system, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.

If losartan is given together with thiazide-type diuretics, the blood-pressure-lowering effects are approximately additive.

**LIFE Study**

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.

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

**Race:** There were 533 black patients in the study. In this group, treatment with losartan resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint (p=0.033, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke (p=0.030, 95% confidence interval 1.08-4.40).

**Heart failure**

In the 48-week ELITE study in patients (n=722) with heart failure (NYHA Class II - IV), no difference was observed in the primary endpoint of persistent
renal dysfunction between those patients treated with 'Cozaar' and those treated with captopril. The unexpected observation of superior benefit of 'Cozaar' in reducing the risk of death relative to captopril observed in the ELITE study was not confirmed in the definitive ELITE II survival study [1] as described below.

In a study in patients with heart failure that was prospectively designed to evaluate the mortality (ELITE II), a regimen of 'Cozaar' 50 mg once daily (starting dose of 12.5 mg titrated to 25 mg and 50 mg once daily) was compared to captopril 50 mg three times daily (starting dose of 12.5 mg titrated to 25 mg and 50 mg three times daily). In this study (n=3,152), patients with heart failure (NYHA Class II - IV) were followed for approximately two years (median follow-up 1.5 years) to evaluate whether 'Cozaar' was superior to captopril in reducing total mortality. The primary endpoint showed no statistically significant difference between 'Cozaar' and captopril in total mortality (17.7% for 'Cozaar' and 15.9% for captopril, p=0.16). The secondary endpoint showed no statistically significant difference in sudden cardiac death and/or resuscitated cardiac arrest (9.0% for 'Cozaar' and 7.3% for captopril, p=0.08). The tertiary endpoint of all-cause mortality and/or all cause hospitalisation showed no statistically significant difference between 'Cozaar' and captopril (47.7% for 'Cozaar' and 44.9% for captopril, p=0.18). In general, other morbidity and mortality endpoints including improvement in NYHA Class were not different between the treatment groups.

In both of these controlled clinical trials in patients with heart failure, 'Cozaar' was generally well tolerated, and the tolerability profile of 'Cozaar' was superior to captopril as measured by significantly lower incidence of discontinuations due to side effects and significantly lower incidence of cough.

**RENAAL Study**

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a multicentre, randomised, placebo-controlled, double-blind study of 1,513 type 2 diabetic patients with nephropathy (751 treated with losartan), with or without hypertension. Patients were recruited with proteinuria as defined by urinary albumin to creatinine ratio>25 mg/mmol or 24-hour urinary protein excretion>500 mg and a serum creatinine of 115-265 micromol/l (a lower limit of 133 micromol/l was used for patients weighing more than 60 kg). The patients were randomised to receive losartan 50 mg once daily, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg daily as appropriate after one month; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Patients were followed for 3.4 years on average.

The results showed that treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary
composite end point, the results also showed significant risk reduction in the
group treated with losartan: 25.3% risk reduction in doubling of serum
creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease
(p=0.002); 19.9% risk reduction in end-stage renal disease or death (p=0.009);
21.0% risk reduction in doubling of serum creatinine or end-stage renal
disease (p=0.010). All-cause mortality alone was not significantly different
between the two treatment groups.
For the secondary endpoints, the results showed an average reduction of
34.3% in the level of proteinuria in the group treated with losartan (p<0.001)
over the mean of 3.4 years. Treatment with losartan reduced the rate of decline
in renal function during the chronic phase of the study by 13.9%, p=0.003
(median rate of decline of 25.5%, p=0.0001) as measured by the reciprocal of
the serum creatinine concentration-time curve. There was no significant
difference between the group treated with losartan (247 events) and the
placebo group (268 events) in the composite endpoint of cardiovascular
morbidity and mortality, although the study was not powered to detect such an
effect.

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. There was no
clinically significant effect on the plasma concentration profile of losartan
when the drug was administered with a standardised meal.

Distribution
Both losartan and its active metabolite are 99% bound to plasma proteins,
primarily albumin. The volume of distribution of losartan is 34 litres. Studies
in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Biotransformation
About 14% of an intravenously or orally-administered dose of losartan is
converted to its active metabolite. Following oral and intravenous
administration of \(^{14}\)C-labelled losartan potassium, circulating plasma
radioactivity primarily is attributed to losartan and its active metabolite.
In addition to the active metabolite, inactive metabolites are formed, including
two major metabolites formed by hydroxylation of the butyl side chain and a
minor metabolite, an N-2 tetrazole glucuronide.

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 of $^{14}$C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

**Characteristics in patients**

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers. Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

5.3 Preclinical safety data

The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice.

There was no evidence of direct genotoxicity in studies conducted with losartan potassium or its primary pharmacologically active metabolite (E-3174).

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the recommended daily dose.

Losartan potassium has been shown to produce adverse effects in rat foetuses and neonates. The effects include decreased bodyweight, mortality and/or renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Losartan Potassium Tablets contain the following excipients:

Mannitol (E 421)
Cellulose microcrystalline
Croskarmellose sodium
Povidone K-30
Magnesium stearate
Hypermellose 6
Titanium dioxide (E 171)
Talc
Propylene glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Transparent PVC/PVDC/Al blisters
Packs of 5, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 98, 100, 210 and 280 Tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Pharmafile Limited,
Medici House,
Ashbourne Industrial Estate,
Ashbourne,
Co. Meath,
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 16002/0081

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/01/2008

10 DATE OF REVISION OF THE TEXT
10/01/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Losartan Potassium 50mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 50 mg of losartan potassium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Losartan Potassium 50 mg Film-Coated Tablet is a white, film coated, round biconvex tablet. Diameter 10mm. Marked 3 L on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- **Hypertension**
  Losartan is indicated for the treatment of hypertension.
- **Hypertensive patients with left ventricular hypertrophy**
  In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated. The data do not support the use of losartan for this indication in black patients (see section 4.4 Special warnings and Precautions for Use-Race and section 5.1 Pharmacodynamic Properties, LIFE study, Race).
- **Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)**
  Losartan is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

4.2 Posology and method of administration
Losartan may be administered with or without food.
Losartan may be administered with other antihypertensive agents. However, the concomitant use of losartan and ACE inhibitors has not been adequately studied.
- **Hypertension**
  The 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.

UKPAR Pharmafile Ltd, Losartan Potassium 25, 50, 100mg Film-coated Tablets
Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy

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

Renal protection in type 2 diabetic patients with nephropathy.

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

Losartan was not studied in type 2 diabetic patients with severe renal impairment.

Use in patients with intravascular volume depletion: For the very small proportion of patients who have intravascular volume depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see 4.4 'Special warnings and precautions for use').

Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.

Use in hepatic impairment: A lower dose should be considered for patients with a history of hepatic impairment (see 4.4 'Special warnings and precautions for use').

Use in children: Use in children under 18 years is not recommended.

Use in the elderly:

Patients up to 75 years: No initial dosage adjustment is necessary for this group of patients.

Patients over 75 years: Currently there is limited clinical experience in this group of patients; a lower starting dose of 25 mg once daily is recommended.

4.3 Contraindications

Losartan is contraindicated in

- pregnancy (see 4.6 'Pregnancy and lactation')
- hypersensitivity to losartan
- hypersensitivity to other angiotensin receptor blockers
- hypersensitivity to any of the excipients in the tablet.

4.4 Special warnings and precautions for use

Hypersensitivity:

Angioedema involving the extremities, face, mucous membranes, tongue, lips, glottis or larynx has been seen in patients treated with losartan. Treatment should be discontinued if these symptoms occur. See 4.8 'Undesirable effects'.
The use of losartan in patients with haemodynamically significant obstructive valvular disease or cardiomyopathy has not been adequately studied. 

**Hypotension and electrolyte/fluid imbalance**
In patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used (see 4.2 'Posology and method of administration').

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group (see 4.8 'Undesirable effects' and Laboratory test findings).

**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 (see 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').

**Renal function impairment**
As a consequence of inhibiting the renin-angiotensin-aldosterone 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.

Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with losartan.

**Race (Black patients):**
There is no evidence that losartan reduces the risk of stroke in black patients with hypertension and left ventricular hypertrophy (see Section 5.1 Pharmacodynamic properties, LIFE Study, Race).

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

In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, ketoconazole, erythromycin and phenobarbital (phenobarbitone). Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium or may increase potassium levels (e.g. potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium) may lead to increases in serum potassium. Co-medication is not advisable.
As with other antihypertensive agents, the antihypertensive effect of losartan may be attenuated by non-steroidal anti-inflammatory drugs such as indometacain.

4.6 Pregnancy and lactation

Use during pregnancy
Although there is no experience with the use of losartan in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.

In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the foetus increases if losartan is administered during the second or third trimesters of pregnancy.

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing foetus. Losartan should not be used in pregnancy, and if pregnancy is detected losartan should be discontinued as soon as possible.

Use during lactation
It is not known whether losartan is excreted in human milk. However, significant levels of losartan and the active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines
Dizziness caused by losartan may affect the ability to drive and use machines.

4.8 Undesirable effects
Frequency estimate: common ≥1%; uncommon ≥0.1% to <1%; rare <0.1%; Side effects have usually been mild and transient in nature and have not required discontinuation of therapy.

Frequency of adverse effects according to body organ class.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Body Organ Class</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td><em>Central and peripheral nervous system</em></td>
<td>Dizziness, asthenia, fatigue</td>
</tr>
<tr>
<td></td>
<td><em>Ear / labyrinth</em></td>
<td>Vertigo</td>
</tr>
<tr>
<td></td>
<td><em>Electrolyte</em></td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td><em>Cardiovascular</em></td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td><em>Gastrointestinal</em></td>
<td>Diarrhoea, nausea and vomiting</td>
</tr>
<tr>
<td>Uncommon</td>
<td><em>Cardiovascular</em></td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Rare</td>
<td><em>Cardiovascular</em></td>
<td>Vasculitis including Henoch-Schonlein purpura</td>
</tr>
</tbody>
</table>
In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy, the most common drug-related side effects were dizziness, asthenia/fatigue and vertigo.

In a controlled clinical trial in type 2 diabetic patients with nephropathy, the most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalaemia. In this study, few patients discontinued due to hyperkalaemia (see 4.4 'Special warnings and precautions for use', Hypotension and electrolyte/fluid imbalance).

4.9 Overdose
Significant lethality was observed in mice and rats after oral administration of 1,000 mg/kg (3,000 mg/m²) and 2,000 mg/kg (11,800 mg/m²) (500 and 1,000 times the maximum recommended daily human dose), respectively. Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

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

* Based on a patient weight of 50 kg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: CO9C A01
Losartan is an oral, specific angiotensin-II receptor (type AT₁) antagonist. 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 proliferation.
Based on binding and pharmacological bioassays, it binds selectively to the AT$_1$ receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis. During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT$_1$ receptor and does not bind to or 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, effects not directly related to blocking the AT$_1$ receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

A study was carried out which was specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors. In this study and in the controlled clinical trials for hypertension, the incidence of cough reported by patients receiving losartan or an agent not associated with ACE-inhibitor-induced cough (hydrochlorothiazide or placebo) was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4,131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually <24 micromol) which was persistent in chronic therapy.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma noradrenaline.

Losartan potassium administered in doses of up to 150 mg once daily did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

**Hypertension Studies:**

In clinical studies, once-daily administration of 50 mg losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood
pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.

The antihypertensive effect of 50 mg of losartan is similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of 50-100 mg of losartan is comparable to once-daily administration of atenolol 50–100 mg. The effect of administration of 50-100 mg of losartan once daily also is equivalent to felodipine extended-release 5-10 mg in older hypertensives (≥65 years) after 12 weeks of therapy. Although losartan is antihypertensive in all races, as with other drugs that affect the renin-angiotensin-aldosterone system, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients. If losartan is given together with thiazide-type diuretics, the blood-pressure-lowering effects are approximately additive.

**LIFE Study**

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.

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

**Race:** There were 533 black patients in the study. In this group, treatment with losartan resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint (p=0.033, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke (p=0.030, 95% confidence interval 1.08-4.40).

**Heart failure**

In the 48-week ELITE study in patients (n=722) with heart failure (NYHA Class II - IV), no difference was observed in the primary endpoint of persistent
renal dysfunction between those patients treated with 'Cozaar' and those treated with captopril. The unexpected observation of superior benefit of 'Cozaar' in reducing the risk of death relative to captopril observed in the ELITE study was not confirmed in the definitive ELITE II survival study [1] as described below.

In a study in patients with heart failure that was prospectively designed to evaluate the mortality (ELITE II), a regimen of 'Cozaar' 50 mg once daily (starting dose of 12.5 mg titrated to 25 mg and 50 mg once daily) was compared to captopril 50 mg three times daily (starting dose of 12.5 mg titrated to 25 mg and 50 mg three times daily). In this study (n=3,152), patients with heart failure (NYHA Class II - IV) were followed for approximately two years (median follow-up 1.5 years) to evaluate whether 'Cozaar' was superior to captopril in reducing total mortality. The primary endpoint showed no statistically significant difference between 'Cozaar' and captopril in total mortality (17.7% for 'Cozaar' and 15.9% for captopril, p=0.16). The secondary endpoint showed no statistically significant difference in sudden cardiac death and/or resuscitated cardiac arrest (9.0% for 'Cozaar' and 7.3% for captopril, p=0.08). The tertiary endpoint of all-cause mortality and/or all cause hospitalisation showed no statistically significant difference between 'Cozaar' and captopril (47.7% for 'Cozaar' and 44.9% for captopril, p=0.18). In general, other morbidity and mortality endpoints including improvement in NYHA Class were not different between the treatment groups.

In both of these controlled clinical trials in patients with heart failure, 'Cozaar' was generally well tolerated, and the tolerability profile of 'Cozaar' was superior to captopril as measured by significantly lower incidence of discontinuations due to side effects and significantly lower incidence of cough.

**RENAAL Study**

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a multicentre, randomised, placebo-controlled, double-blind study. 1,513 type 2 diabetic patients with nephropathy (751 treated with losartan), with or without hypertension. Patients were recruited with proteinuria as defined by urinary albumin to creatinine ratio>25 mg/mmol or 24-hour urinary protein excretion>500 mg and a serum creatinine of 115-265 micromol/l (a lower limit of 133 micromol/l was used for patients weighing more than 60 kg). The patients were randomised to receive losartan 50 mg once daily, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg daily as appropriate after one month; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Patients were followed for 3.4 years on average.

The results showed that treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary
composite end point, the results also showed significant risk reduction in the
group treated with losartan: 25.3% risk reduction in doubling of serum
creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease
(p=0.002); 19.9% risk reduction in end-stage renal disease or death (p=0.009);
21.0% risk reduction in doubling of serum creatinine or end-stage renal
disease (p=0.010). All-cause mortality alone was not significantly different
between the two treatment groups.

For the secondary endpoints, the results showed an average reduction of
34.3% in the level of proteinuria in the group treated with losartan (p<0.001)
over the mean of 3.4 years. Treatment with losartan reduced the rate of decline
in renal function during the chronic phase of the study by 13.9%, p=0.003
(median rate of decline of 25.5%, p<0.0001) as measured by the reciprocal of
the serum creatinine concentration-time curve. There was no significant
difference between the group treated with losartan (247 events) and the
placebo group (268 events) in the composite endpoint of cardiovascular
morbidity and mortality, although the study was not powered to detect such an
effect.

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. There was no
clinically significant effect on the plasma concentration profile of losartan
when the drug was administered with a standardised meal.

Distribution
Both losartan and its active metabolite are ≥99% bound to plasma proteins,
primarily albumin. The volume of distribution of losartan is 34 litres. Studies
in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

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-labelled losartan potassium, circulating plasma
radioactivity primarily is attributed to losartan and its active metabolite.
In addition to the active metabolite, inactive metabolites are formed, including
two major metabolites formed by hydroxylation of the butyl side chain and a
minor metabolite, an N-2 tetrazole glucuronide.

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 of 14C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

Characteristics in patients
Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers. Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

5.3 Preclinical safety data
The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level. Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice. There was no evidence of direct genotoxicity in studies conducted with losartan potassium or its primary pharmacologically active metabolite (E-3174).

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the recommended daily dose. Losartan potassium has been shown to produce adverse effects in rat foetuses and neonates. The effects include decreased bodyweight, mortality and/or renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Losartan Potassium Tablets contain the following excipients: Mannitol (E 421)
Cellulose microcrystalline
Croscarmellose sodium
Povidone K-30
Magnesium stearate
Hypermellose 6
Titanium dioxide (E 171)
Talc
Propylene glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
4 years

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container

Transparent PVC/PVDC/Al blisters
Packs of 5, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 98, 100, 210 and 280 Tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Pharmafile Limited,
Medici House,
Ashbourne Industrial Estate,
Ashbourne,
Co. Meath,
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 16002/0082

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/01/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Losartan Potassium 100mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg of losartan potassium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Losartan Potassium 100 mg Film-Coated Tablet is a white, film coated, oval biconvex tablet. Diameter 18.3mm x 9.2mm. Marked 4 L on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
• Hypertension
  Losartan is indicated for the treatment of hypertension.
• Hypertensive patients with left ventricular hypertrophy
  In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated. The data do not support the use of losartan for this indication in black patients (see section 4.4 Special warnings and Precautions for Use-Race and section 5.1 Pharmacodynamic Properties, LIFE study, Race).
• Renal protection in type 2 diabetic patients with nephropathy
  (macroalbuminuria)
  Losartan is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

4.2 Posology and method of administration
Losartan may be administered with or without food.
Losartan may be administered with other antihypertensive agents. However, the concomitant use of losartan and ACE inhibitors has not been adequately studied.
Hypertension
The 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.
Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy
The usual starting dose is 50 mg of losartan once daily. A low dose of hydrochlorothiazide may be added and/or the dose of losartan may be increased to 100 mg once daily based on blood pressure.  

Renal protection in type 2 diabetic patients with nephropathy.  

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

Losartan was not studied in type 2 diabetic patients with severe renal impairment.  

Use in patients with intravascular volume depletion: For the very small proportion of patients who have intravascular volume depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see 4.4 'Special warnings and precautions for use').  

Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.  

Use in hepatic impairment: A lower dose should be considered for patients with a history of hepatic impairment (see 4.4 'Special warnings and precautions for use').  

Use in children: Use in children under 18 years is not recommended.  

Use in the elderly:  
Patients up to 75 years: No initial dosage adjustment is necessary for this group of patients.  
Patients over 75 years: Currently there is limited clinical experience in this group of patients; a lower starting dose of 25 mg once daily is recommended.  

4.3 Contraindications  
Losartan is contraindicated in  
- pregnancy (see 4.6 'Pregnancy and lactation')  
- hypersensitivity to losartan  
- hypersensitivity to other angiotensin receptor blockers  
- hypersensitivity to any of the excipients in the tablet.  

4.4 Special warnings and precautions for use  
Hypersensitivity:  
Angioedema involving the extremities, face, mucous membranes, tongue, lips, glottis or larynx has been seen in patients treated with losartan. Treatment should be discontinued if these symptoms occur. See 4.8 'Undesirable effects'. The use of losartan in patients with haemodynamically significant obstructive valvular disease or cardiomyopathy has not been adequately studied.  
Hypotension and electrolyte/fluid imbalance
In patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used (see 4.2 'Posology and method of administration').

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group (see 4.8 'Undesirable effects' and Laboratory test findings).

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 (see 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').

Renal function impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone 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. Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with losartan.

Race (Black patients):
There is no evidence that losartan reduces the risk of stroke in black patients with hypertension and left ventricular hypertrophy (see Section 5.1 Pharmacodynamic properties, LIFE Study, Race).

4.5 Interaction with other medicinal products and other forms of interaction
In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, ketoconazole, erythromycin and phenobarbital (phenobarbitone). Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium or may increase potassium levels (e.g. potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium) may lead to increases in serum potassium. Co-medication is not advisable.

As with other antihypertensive agents, the antihypertensive effect of losartan may be attenuated by non-steroidal anti-inflammatory drugs such as indomethacin.
4.6 Pregnancy and lactation

Use during pregnancy
Although there is no experience with the use of losartan in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system. In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the foetus increases if losartan is administered during the second or third trimesters of pregnancy.

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing foetus. Losartan should not be used in pregnancy, and if pregnancy is detected losartan should be discontinued as soon as possible.

Use during lactation
It is not known whether losartan is excreted in human milk. However, significant levels of losartan and the active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines
Dizziness caused by losartan may affect the ability to drive and use machines.

4.8 Undesirable effects
Frequency estimate: common ≥1%; uncommon ≥0.1% to <1%; rare <0.1%; Side effects have usually been mild and transient in nature and have not required discontinuation of therapy.

Frequency of adverse effects according to body organ class.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Body Organ Class</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Central and peripheral nervous system</td>
<td>Dizziness, asthenia, fatigue</td>
</tr>
<tr>
<td></td>
<td>Ear / labyrinth</td>
<td>Vertigo</td>
</tr>
<tr>
<td></td>
<td>Electrolyte</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Diarrhoea, nausea and vomiting</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Cardiovascular</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Rare</td>
<td>Cardiovascular</td>
<td>Vasculitis including Henoch-Schonlein purpura</td>
</tr>
<tr>
<td></td>
<td>Central and peripheral nervous system</td>
<td>Migraine</td>
</tr>
<tr>
<td></td>
<td>Haematological</td>
<td>Anaemia</td>
</tr>
<tr>
<td></td>
<td>Hepatic</td>
<td>Hepatitis, liver function abnormalities</td>
</tr>
</tbody>
</table>
In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy, the most common drug-related side effects were dizziness, asthenia/fatigue and vertigo.

In a controlled clinical trial in type 2 diabetic patients with nephropathy, the most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalaemia. In this study, few patients discontinued due to hyperkalaemia (see 4.4 ‘Special warnings and precautions for use’, Hypotension and electrolyte/fluid imbalance).

4.9 Overdose
Significant lethality was observed in mice and rats after oral administration of 1,000 mg/kg (3,000 mg/m²) and 2,000 mg/kg (11,800 mg/m²) (500 and 1,000 times the maximum recommended daily human dose), respectively. Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor the active metabolite can be removed by haemodialysis. * Based on a patient weight of 50 kg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: CO9C A01
Losartan is an oral, specific angiotensin-II receptor (type AT₁) antagonist. 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 proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT₁ receptor. In vitro and in vivo, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.
During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT$_1$ receptor and does not bind to or 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, effects not directly related to blocking the AT$_1$ receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan. Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

A study was carried out which was specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors. In this study and in the controlled clinical trials for hypertension, the incidence of cough reported by patients receiving losartan or an agent not associated with ACE-inhibitor-induced cough (hydrochlorothiazide or placebo) was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4,131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually <24 micromol) which was persistent in chronic therapy. Losartan has no effect on autonomic reflexes and no sustained effect on plasma noradrenaline.

Losartan potassium administered in doses of up to 150 mg once daily did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

**Hypertension Studies:**

In clinical studies, once-daily administration of 50 mg losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the
effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.

The antihypertensive effect of 50 mg of losartan is similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of 50-100 mg of losartan is comparable to once-daily administration of atenolol 50 – 100 mg. The effect of administration of 50-100 mg of losartan once daily also is equivalent to felodipine extended-release 5-10 mg in older hypertensives (≥65 years) after 12 weeks of therapy. Although losartan is antihypertensive in all races, as with other drugs that affect the renin-angiotensin-aldosterone system, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.

If losartan is given together with thiazide-type diuretics, the blood-pressure-lowering effects are approximately additive.

**LIFE Study**

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.

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

**Race:** There were 533 black patients in the study. In this group, treatment with losartan resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint (p=0.033, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke (p=0.030, 95% confidence interval 1.08-4.40).

**Heart failure**

In the 48-week ELITE study in patients (n=722) with heart failure (NYHA Class II - IV), no difference was observed in the primary endpoint of persistent renal dysfunction between those patients treated with 'Cozaar' and those treated with captopril. The unexpected observation of superior benefit of 'Cozaar' in reducing the risk of death relative to captopril observed in the
ELITE study was not confirmed in the definitive ELITE II survival study [1] as described below.

In a study in patients with heart failure that was prospectively designed to evaluate the mortality (ELITE II), a regimen of 'Cozaar' 50 mg once daily (starting dose of 12.5 mg titrated to 25 mg and 50 mg once daily) was compared to captopril 50 mg three times daily (starting dose of 12.5 mg titrated to 25 mg and 50 mg three times daily). In this study (n=3,152), patients with heart failure (NYHA Class II - IV) were followed for approximately two years (median follow-up 1.5 years) to evaluate whether 'Cozaar' was superior to captopril in reducing total mortality. The primary endpoint showed no statistically significant difference between 'Cozaar' and captopril in total mortality (17.7% for 'Cozaar' and 15.9% for captopril, p=0.16). The secondary endpoint showed no statistically significant difference in sudden cardiac death and/or resuscitated cardiac arrest (9.0% for 'Cozaar' and 7.3% for captopril, p=0.08). The tertiary endpoint of all-cause mortality and/or all cause hospitalisation showed no statistically significant difference between 'Cozaar' and captopril (47.7% for 'Cozaar' and 44.9% for captopril, p=0.18). In general, other morbidity and mortality endpoints including improvement in NYHA Class were not different between the treatment groups.

In both of these controlled clinical trials in patients with heart failure, 'Cozaar' was generally well tolerated, and the tolerability profile of 'Cozaar' was superior to captopril as measured by significantly lower incidence of discontinuations due to side effects and significantly lower incidence of cough.

**RENAAL Study**

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a multicentre, randomised, placebo-controlled, double-blind study 1,513 type 2 diabetic patients with nephropathy (751 treated with losartan), with or without hypertension. Patients were recruited with proteinuria as defined by urinary albumin to creatinine ratio>25 mg/mmol or 24-hour urinary protein excretion>500 mg and a serum creatinine of 115-265 micromol/l (a lower limit of 133 micromol/l was used for patients weighing more than 60 kg). The patients were randomised to receive losartan 50 mg once daily, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg daily as appropriate after one month; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Patients were followed for 3.4 years on average.

The results showed that treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary composite end point, the results also showed significant risk reduction in the group treated with losartan: 25.3% risk reduction in doubling of serum creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease...
(p=0.002); 19.9% risk reduction in end-stage renal disease or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal disease (p=0.010). All-cause mortality alone was not significantly different between the two treatment groups.

For the secondary endpoints, the results showed an average reduction of 34.3% in the level of proteinuria in the group treated with losartan (p<0.001) over the mean of 3.4 years. Treatment with losartan reduced the rate of decline in renal function during the chronic phase of the study by 13.9%, p=0.003 (median rate of decline of 25.5%, p<0.0001) as measured by the reciprocal of the serum creatinine concentration-time curve. There was no significant difference between the group treated with losartan (247 events) and the placebo group (268 events) in the composite endpoint of cardiovascular morbidity and mortality, although the study was not powered to detect such an effect.

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. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardised meal.

Distribution
Both losartan and its active metabolite are 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Biotransformation
About 14% of an intravenously or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of $^{14}$C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

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 of $^{14}$C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.  

**Characteristics in patients**

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers. Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

### 5.3 Preclinical safety data

The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level. Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice. There was no evidence of direct genotoxicity in studies conducted with losartan potassium or its primary pharmacologically active metabolite (E-3174). Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the recommended daily dose. Losartan potassium has been shown to produce adverse effects in rat foetuses and neonates. The effects include decreased bodyweight, mortality and/or renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

Losartan Potassium Tablets contain the following excipients:

- Mannitol (E 421)
- Cellulose microcrystalline
- Croscarmellose sodium
Povidone K-30
Magnesium stearate
Hypermellose 6
Titanium dioxide (E 171)
Talc
Propylene glycol

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
Do not store above 30°C.
Store in the original package.

6.5 **Nature and contents of container**
Transparent PVC/PVDC/Al blisters
Pack of 5, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 98, 100, 210 and 280 Tablets.
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Pharmafile Limited,
Medici House,
Ashbourne Industrial Estate,
Ashbourne,
Co. Meath,
Ireland

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 16002/0083

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
10/01/2008

10 **DATE OF REVISION OF THE TEXT**
10 DATE OF REVISION OF THE TEXT

10/01/2008
PHARMAFILE LTD.
Losartan Potassium 25mg, 50mg and 100mg Film-Coated TABLETS

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine:
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What Losartan Potassium Tablets are and what they are used for
2. Before you take Losartan Potassium Tablets
3. How to take Losartan Potassium Tablets
4. Possible side effects
5. Storing Losartan Potassium Tablets

The name of this medicine is Losartan Potassium 25mg, 50mg and 100mg Tablets.
- The active substance is losartan potassium. There are three strengths available containing 25mg, 50mg or 100mg losartan potassium per tablet.
- The film-coated tablets also contain mannitol (E 421), cellulose microcrystalline, croscarmellose sodium, Povidone K-30, magnesium stearate, hypromellose 6, titanium dioxide (E 171), talc, propylene glycol

Losartan Potassium 25 mg Tablets are white in colour, round, biconvex, film-coated tablets marked "L" and supplied in blister packs of 5, 7, 10, 14, 15, 20, 21, 28, 30, 50, 60, 84, 98, 100, 210 and 280 Tablets.
Losartan Potassium 50 mg Tablets are white in colour, scored, round, biconvex, film-coated tablets marked "L" and supplied in blister packs of 5, 7, 10, 14, 15, 20, 21, 28, 30, 50, 60, 84, 98, 100, 210 and 280 Tablets.
Losartan Potassium 100 mg Tablets are white in colour, oval, biconvex, film-coated tablets marked "L" and supplied in blister packs of 5, 7, 10, 14, 15, 20, 21, 28, 30, 50, 60, 84, 98, 100, 210 and 280 Tablets.

Manufactured By: Actavis Limited, Reykjavikurveig 76, IS-220 Hafnarfjordur, Iceland.

1. WHAT LOSARTAN POTASSIUM TABLETS ARE AND WHAT THEY ARE USED FOR

Losartan can help to reduce blood pressure, risk of stroke and kidney damage in type-2 diabetics by blocking the action of the hormone Angiotensin II.

Your doctor has prescribed Losartan Potassium Tablets because:
1) you have hypertension (high blood pressure) or you have hypertension with thickening of the heart muscle (left ventricular hypertrophy) and/or
2) you have type 2 diabetes with damage to your kidneys (shown by the presence of protein in your urine). In these patients, losartan has been shown to delay the worsening of kidney disease

See end of leaflet for further information on your condition.

2. BEFORE YOU TAKE LOSARTAN POTASSIUM TABLETS

Do not take Losartan Potassium Tablets if:
- you are hypersensitive to losartan potassium or any of the other ingredients of Losartan Potassium Tablets.
- you are or think you may be pregnant.
- you are planning to become pregnant.
- you are breast-feeding.

Losartan should not be given to children under 18 years.

If you think any of these apply to you, do not take the tablets. Talk to your doctor first and follow the advice given.

It is important to tell your doctor before taking Losartan Potassium Tablets if:
- you suffer from liver or kidney problems.
- you have received a kidney transplant.
- you have recently suffered from excessive vomiting and/or diarrhoea.
- you have a condition called 'aortic stenosis' which is the narrowing or blockage of a valve in the heart.
- you are known to have narrowing or blockage of the blood vessels leading to your kidneys.
- you know that you have high levels of potassium in your blood (hyperkalaemia) or you are on a low potassium diet.

Taking Losartan Potassium Tablets with other medicines

Losartan does not usually interact with food or the following medicines: hydrochlorothiazide (water tablets), digoxin (for your heart), warfarin (to thin your blood), cimetidine (to treat your ulcers), ketoconazole, erythromycin (to treat infections) and phenobarbital (phenobarbitone, to treat epilepsy).

You should, however, tell your doctor if you are taking potassium supplements, potassium sparing agents (to remove excess water from the body), or potassium-containing salt substitutes. Your doctor will decide whether you should take these agents with losartan. In addition you should tell your doctor if you are taking any of the following medicines:
- rifampicin used in the treatment of tuberculosis (TB)
- fluconazole for the treatment of fungal infections such as thrush
- indometacin, used in the treatment of musculo-skeletal disorders such as arthritis
- high doses of "water-tablets" (diuretics).
- Lithium, a drug used to treat certain mental disorders
- Cisplatin, used to prevent transplanted organs being rejected

You should also tell your doctor about all medicines that you are taking or might take. This includes any medicines obtained without a prescription.

Pregnancy and Breastfeeding

Losartan Potassium Tablets are not recommended in pregnancy. If you are pregnant or plan to become pregnant or breastfeeding, talk to your doctor or pharmacist before taking this medicine. You should not take this medicine if you are pregnant or are breast feeding.

Driving and using machines

These tablets may make you feel dizzy. Therefore, you should be careful when driving or using machines.
3. HOW TO TAKE LOSARTAN POTASSIUM TABLETS

Losartan Potassium Tablets should be taken by mouth. You must keep taking losartan every day and exactly as your doctor has told you. It is important that you take losartan for as long as your doctor prescribes it, in order to keep your blood pressure controlled and/or protect your kidneys from worsening damage. You can take losartan with or without food. It is recommended that you take your tablet at the same time each day.

Your doctor may choose to prescribe a starting dose of 25mg losartan once a day. IMPORTANT: For patients starting treatment with Losartan Potassium 25mg Film-Coated Tablet: You must ensure that you make an appointment to see your doctor before you finish the 7-day pack, in order to get your blood pressure measured and check that you are receiving the correct dose.

The usual dose of losartan for most patients is one 50mg tablet once a day (for hypertension, hypertension with thickening of the heart muscle and type 2 diabetes with kidney disease [protein in the urine]).

If a 50mg daily dose is ineffective, your doctor may prescribe a higher dose (i.e. 100mg). Follow your doctor's instructions exactly.

If you take more Losartan Potassium Tablets than you should:

If you take too many tablets by mistake, contact your doctor immediately or go to the nearest hospital casualty department. If possible, please take the remaining tablets or this leaflet with you to hospital.

If you forget to take Losartan Potassium Tablets:

Try to take losartan as prescribed. However, if you miss a dose, just continue with the next dose as usual. Do not take an extra tablet to make up.

4. POSSIBLE SIDE EFFECTS

Like all medicines, losartan can have side effects.

The most commonly reported side effects in patients with high blood pressure and thickening of the heart muscle were weakness/tiredness, dizziness and vertigo.

The most commonly reported side effects in type 2 diabetic patients with kidney disease [protein in the urine] were weakness/tiredness, dizziness, low blood pressure and high levels of potassium in the blood. Your doctor will take regular blood samples to monitor the levels of potassium in your blood as appropriate.

Rarely, patients have reported developing an allergic reaction involving swelling of the face, lips, throat and/or tongue, which may cause difficulty in breathing or swallowing; and/or inflammation of blood vessels including inflammation of small veins, causing hard, purple blisters on the skin. If you develop any of these symptoms you should stop taking losartan and contact your doctor immediately.

If you develop any of the effects detailed above, or if you have any other unusual symptoms or feelings, contact your doctor or pharmacist promptly.

It will help if you can make a note of what you experienced, when it started and how long it lasted.

5. STORING LOSARTAN POTASSIUM TABLETS

Keep out of the reach and sight of children. 100mg Tablets: Do not store above 30°C. 25mg and 50mg Tablets: No special precautions for storage.

Store in the original package.

Do not remove the tablets from the blister pack until you are ready to take the medicine.

Do not use after the expiry date stated on the blister and carton. Unused tablets should be taken back to the pharmacist for safe disposal.

This leaflet was last revised in December 2006

Information for patients with high blood pressure

Blood pressure is the term given to the pressure produced by your heart pumping blood to all parts of your body. Your blood pressure is measured by two numbers, e.g. 120/80 mmHg. The top number measures the pressure while your heart beats and the bottom number measures the pressure in between heartbeats.

Normal blood pressure is part of good health. High blood pressure is caused when the blood vessels tighten and the measurement goes above the normal range for your age. There are usually no symptoms of high blood pressure and you will only know you have it if you have had your blood pressure measured.

Although you might feel quite well, if your high blood pressure is not treated, it can damage your heart and kidneys, and in some cases lead to strokes, heart attacks, heart and kidney failure, or blindness.

High blood pressure can be treated and controlled with medicines such as losartan.

In addition to prescribing drug(s) to reduce your blood pressure, your doctor may also recommend that you make some changes to your lifestyle to help your high blood pressure, such as losing weight, avoiding alcohol and smoking, and reducing the amount of salt in your diet.

Your doctor may also encourage you to take more mild exercise.

Information for patients with type 2 diabetes and protein in their urine

Insulin is a hormone produced by the body, necessary for sugar (glucose) to be used as energy. In patients with type 2 diabetes the body's cells do not respond to the effects of insulin or too little insulin is produced. In either case, glucose (sugar) cannot enter the body's cells. This causes a build up of sugar in the blood, which is known as hyperglycaemia or high blood sugar.

Diabetes can damage many parts of the body, including the kidneys. When this happens, the kidneys start to leak protein into the urine. If the kidney damage progresses further, the kidneys lose their ability to remove waste products, such as creatinine and urea, from the blood. If this kidney failure is not stopped, dialysis or kidney transplantation may be required. In type 2 diabetic patients with kidney disease [protein in the urine], losartan has been shown to slow the worsening of kidney disease and to reduce the need for dialysis or kidney transplantation.
Losartan Potassium 25mg Tablets

PHARMAFILE®
Losartan Potassium
25mg Tablets

For oral use only
Use as directed by your Doctor.
Please read the enclosed patient information leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
STORE IN THE ORIGINAL PACKAGE.

Each film-coated tablet contains
25mg losartan potassium.
Losartan Potassium 50mg Tablets

For oral use only
Use as directed by your Doctor.
Please read the enclosed patient information leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
STORE IN THE ORIGINAL PACKAGING.

Each film-coated tablet contains
50mg losartan potassium.

PL 16002/0077-0081-83
Losartan Potassium 100mg Tablets

PHARMAFILE
Losartan Potassium 100mg Tablets

For oral use only
Use as directed by your doctor.
Please read the additional patient information leaflet before use.
Do not store above 30°C.
Keep out of the reach and sight of children.
Store in the original package.

Each film-coated tablet contains 100mg losartan potassium.