UKPAR Losartan Potassium 25, 50 and 100mg Film-Coated Tablets
(PL 20176/0053)

LOSARTAN POTASSIUM 25MG FILM-COATED TABLETS
(PL 20176/0053)

LOSARTAN POTASSIUM 50MG FILM-COATED TABLETS
(PL 20176/0054)

LOSARTAN POTASSIUM 100MG FILM-COATED TABLETS
(PL 20176/0055)

UKPAR

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(PL 20176/0054)

LOSARTAN POTASSIUM 100MG FILM-COATED TABLETS  
(PL 20176/0055)

LAY SUMMARY

On 28th February 2008, the MHRA granted Technopharm Limited Marketing Authorisations (licences) for the medicinal products Losartan Potassium 25mg, 50mg and 100mg Film-Coated Tablets. These are prescription-only medicines that are used to reduce high blood pressure.

Losartan belongs to a group of medicines called angiotensin receptor antagonists. Angiotensin is a naturally occurring chemical in the body that narrows blood vessels and makes it harder for blood to pass through, causing blood pressure to increase. Losartan blocks the effects of angiotensin, causing blood vessels to relax.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Losartan Potassium 25mg, 50mg and 100mg Film-Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
LOSARTAN POTASSIUM 25MG FILM-COATED TABLETS
(PL 20176/0053)

LOSARTAN POTASSIUM 50MG FILM-COATED TABLETS
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LOSARTAN POTASSIUM 100MG FILM-COATED TABLETS
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Losartan Potassium 25mg, 50mg and 100mg Film-Coated Tablets (PL 20176/0053-55) to Technopharm Limited on 28th February 2008. The products are prescription-only medicines.

The applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC, claiming to be generic medicinal products to the original products Cozaar 25mg, 50mg and 100mg Film-Coated Tablets (Merck, Sharp and Dohme), which have been authorised in the EEA for over 10 years.

The products contain the active ingredient losartan potassium and are indicated for the treatment of patients with hypertension, hypertensive patients with left ventricle atrophy, and for renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria).

Losartan potassium is an angiotensin II receptor antagonist.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

INN: Losartan Potassium

Chemical Names: 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl-phenyl)benzyl]imidazole-5-methanol monopotassium salt
2-n-butyl-4-chloro-5-hydroxymethyl-1-[[2'-1H-tetrazol-5-yl]biphenyl-4-yl)methyl] imidazole potassium salt

Molecular Formula: C_{22}H_{22}ClK_{6}N_{6}O

Structure:

![Structure Image]

CAS Number: 124750-99-8

Molecular Weight: 461.01

Appearance: A white to yellowish crystalline powder, freely soluble in water and methanol, and insoluble in chloroform.

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

Appropriate specifications are provided for the active substance losartan potassium. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and all comply with the proposed specifications.

Specifications have been provided for all packaging used. All primary packaging complies with current European Directives concerning contact with food.

Based on stability data provided, a suitable retest period has been set. Suitable post approval commitments have been given to provide additional stability data as and when it becomes available.
**DRUG PRODUCT**

**Other Ingredients**
Other ingredients consist of pharmaceutical excipients microcrystalline cellulose, calcium hydrogen phosphate dihydrate, colloidal anhydrous silica, croscarmellose sodium, talc, magnesium stearate and a coating (Opadry II) made up of hypromellose, lactose monohydrate, titanium dioxide (E171) and glycerol triacetate.

Other excipients in the coating specific to each product included: indigocarmine lake in the 25mg tablets (to make up Opadry II blue); iron oxide red in the 50mg tablets (to make up Opadry II pink); the 100mg tablets contained no additional excipients as the coating was Opadry II white.

With the exception of the Opadry II coatings, all excipients have a respective European Pharmacopoeia monograph. For each Opadry II coating, suitable in-house specifications have been provided.

Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph.

With the exception of lactose monohydrate, none of the excipients is of animal or human origin. The supplier of lactose monohydrate has stated that this is sourced from healthy animals under the same conditions as milk for human consumption.

**Pharmaceutical development**
The objective of the pharmaceutical development programme was to produce products that were tolerable and could be considered as generic medicinal products to the originator products Cozaar 25mg, 50mg and 100mg Film-Coated Tablets (Merck, Sharp and Dohme).

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Comparative *in vitro* dissolution profiles have been generated for the proposed and originator products with satisfactory results.

**Manufacturing Process**
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength. The results are satisfactory.

**Finished Product Specification**
The finished product specifications proposed for all strengths are acceptable. 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**
Product is packaged in polyethylene/polyvinylidene chloride/polyvinylchloride blisters with aluminium lidding, in pack sizes of 28 tablets. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines, using product manufactured by the proposed finished product manufacturer and in the packaging proposed for marketing. The results support a shelf-life of 18 months, with storage conditions ‘Do not store above 25°C’ and ‘Store in the original package’.

**Bioequivalence/bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

**SPC, PIL, Labels**
The SPC, PIL and Labels are pharmaceutically acceptable.

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

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

The proposed products are considered to be generic medicinal products to the reference products with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.
PRECLINICAL ASSESSMENT

In these applications, the products are claiming to be generic medicinal products of Cozaar 25mg, 50mg and 100mg Film-Coated Tablets (Merck, Sharp and Dohme), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

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 L. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Metabolism
About 14% of an orally-administered dose of losartan is converted to its active metabolite (carboxylosartan) by CYP2C9 and CYP3A4. The active metabolite is 10-40-fold more potent than the parent drug. 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.

Excretion
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 accumulate significantly in plasma.

Special populations
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.
Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups (> 1 month to < 16 years) and consistent with pharmacokinetic historic data in adults.

**BIOEQUIVALENCE**

**Study design**
A randomised, open label, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioequivalence study to compare Losartan Potassium 100mg Tablets (test) versus Cozaar 100mg Tablets (reference) in healthy fasted volunteers.

Blood samples were taken pre- and up to 36 hours postdose and each treatment arm was separated by a 7-day washout period.

**Results**
The results for losartan and its active metabolite are presented below:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pliva’s 100 mg tablets (test)</th>
<th>Cozaar 100 mg tablets (reference)</th>
<th>Point Estimate (test/reference) (%)</th>
<th>90 % C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Losartan</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>428 ± 282</td>
<td>461 ± 386</td>
<td>92.85</td>
<td>80.06 – 107.70</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{t}}$ (ng/h/ml)</td>
<td>758 ± 253</td>
<td>772 ± 365</td>
<td>98.21</td>
<td>91.90 – 104.96</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{inf}}$ (ng/h/ml)</td>
<td>792 ± 257</td>
<td>811 ± 379</td>
<td>97.64</td>
<td>91.46 – 104.23</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>0.9 ± 1.2</td>
<td>1.3 ± 0.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$T_{\text{el}}$ (h)</td>
<td>2.0 ± 0.8</td>
<td>2.2 ± 1.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Carboxylosartan (active metabolite)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>769 ± 402</td>
<td>750 ± 343</td>
<td>102.47</td>
<td>93.68 – 112.09</td>
</tr>
<tr>
<td>$\text{AUC}_{\text{0-\text{t}}}$ (ng/h/ml)</td>
<td>4632 ± 1389</td>
<td>4597 ± 1298</td>
<td>100.7</td>
<td>95.69 – 106.08</td>
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<tr>
<td>$\text{AUC}_{\text{0-\text{inf}}}$ (ng/h/ml)</td>
<td>4745 ± 1381</td>
<td>4722 ± 1299</td>
<td>100.5</td>
<td>95.62 – 105.6</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>2.5 ± 1.5</td>
<td>2.8 ± 1.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$T_{\text{el}}$ (h)</td>
<td>5.6 ± 1.6</td>
<td>6.4 ± 2.3</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Geometric mean ± SD represented

**Conclusions**
The 90% confidence intervals for the test/reference lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 Note for Guidance. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria and can be approved.

As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 100mg strength can be extrapolated to the other strength tablets.

**PHARMACODYNAMICS**
No new data are submitted and none are required for these types of applications.

**EFFICACY**
No new data are submitted and none are required for these types of applications.

**SAFETY**
No new data are submitted and none are required for these types of applications.
EXPERT REPORTS
A clinical expert report is provided, written by an appropriately qualified physician. It is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPCs are consistent with those approved for the reference products and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
The PIL has been provided and is consistent with the SPC and that for the reference product.

LABELLING
Labelling has been provided and these are satisfactory.

APPLICATION FORM (MAA)
The MAA forms are satisfactory.

DISCUSSION
Bioequivalence has been satisfactorily demonstrated for the 100mg product in accordance with CPMP criteria. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 100mg strength can be extrapolated to the other strengths.

The SPC, PIL and Labelling are consistent with those approved in the UK for the originator product and are satisfactory.

MEDICAL CONCLUSION
Marketing authorisations may be granted for these products.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

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

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Losartan Potassium 100mg Tablets and the originator product Cozaar 100mg Tablets. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 100mg strength can be extrapolated to the other strengths.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with losartan potassium is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
 LOSARTAN POTASSIUM 25MG FILM-COATED TABLETS  
(PL 20176/0053)

 LOSARTAN POTASSIUM 50MG FILM-COATED TABLETS  
(PL 20176/0054)

 LOSARTAN POTASSIUM 100MG FILM-COATED TABLETS  
(PL 20176/0055)

### STEPS TAKEN FOR ASSESSMENT

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<tr>
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<th>Step Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 11\textsuperscript{th} July 2006</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 17\textsuperscript{th} August 2006</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the dossier on 15\textsuperscript{th} November 2006 and 1\textsuperscript{st} June 2007.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 24\textsuperscript{th} May 2007 and 10\textsuperscript{th} July 2007</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 28\textsuperscript{th} February 2008</td>
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</table>
LOSARTAN POTASSIUM 25MG FILM-COATED TABLETS  
(PL 20176/0053)

LOSARTAN POTASSIUM 50MG FILM-COATED TABLETS  
(PL 20176/0054)

LOSARTAN POTASSIUM 100MG FILM-COATED TABLETS  
(PL 20176/0055)

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Losartan potassium 25mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Losartan potassium 25mg film-coated Tablet contains 22.9mg of losartan as 25mg of losartan potassium.

Excipients: Lactose monohydrate. For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablet

Light blue, round, biconvex, film-coated tablet marked ‘LS 25’ on one side and a score line on the other.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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. 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.

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

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

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

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients > 20 to < 50 kg. The dose can be increased to a maximum of 50 mg once daily. In patients > 50 kg, the starting dose is 50 mg once daily. The dose can be adjusted to a maximum of 100 mg once daily.

Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 m2, as no data are available.

Losartan is also not recommended in children with hepatic impairment.

4.3 Contraindications
Losartan is contraindicated in
- the 2nd and 3rd trimester of pregnancy (see sections 4.4 ‘Special warnings’ and 4.6 ‘Pregnancy and lactation’),
- hypersensitivity to losartan
- hypersensitivity to any excipients in the tablet.

4.4 Special warnings and precautions for use
Hypersensitivity: Angioedema. 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’).

In paediatric patients who are intravascularly volume-depleted, these conditions should be corrected prior to administration of Losartan.

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).

Pregnancy: Losartan should not be initiated during pregnancy. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.

When pregnancy is diagnosed, treatment with losartan should be stopped immediately, and, if appropriate, alternative therapy should be started. (see sections 4.3 and 4.6).

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’).

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

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.

Similarly there is an increased risk of hyperkalaemia (increased potassium levels) when ciclosporin is given with Losartan.

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and
neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data')

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

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

*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**

Losartan may have a minor or moderate influence on the ability to drive and use machines. Losartan can cause dizziness, asthenia and vertigo. If the patient experiences these adverse reactions, they should not drive or use machines.

4.8 **Undesirable effects**

Side effects have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with Losartan was comparable to placebo.

In controlled clinical trials for essential hypertension, dizziness was the only side effect reported as drug related that occurred with an incidence greater than placebo in 1% or more of patients treated with Losartan. In addition, dose-related orthostatic effects were seen in less than 1% of patients.

The adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

Losartan was generally well tolerated 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.

Losartan was generally well tolerated 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).

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

*Hypersensitivity:* Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue have been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schonlein purpura, has been reported rarely.

*Gastro-intestinal:* Hepatitis (reported rarely), diarrhoea, liver function abnormalities.

*Haematologic:* Anaemia (see 4.4 ‘Special warnings and precautions for use’), thrombocytopenia (reported rarely).

*Musculoskeletal:* Myalgia, arthralgia.

*Nervous system/Psychiatric:* Migraine.
Respiratory: Cough.

Skin: Urticaria, pruritus, rash.

Laboratory test findings
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Losartan. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan and 3.4% of patients treated with placebo developed hyperkalaemia (see 4.4 ‘Special warnings and precautions for use’, Hypotension and electrolyte/fluid imbalance). Serum potassium should be monitored, particularly in the elderly and patients with renal impairment. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

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 overdose in humans. The most likely manifestation of overdose 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 50kg.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Therapeutic classification: C09C A01
Pharmacotherapeutic group: Angiotensin II Antagonists, Plain

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, 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 150mg 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 50mg 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 50mg of Losartan is similar to once-daily administration of enalapril 20mg. The antihypertensive effect of once-daily administration of 50-100mg 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).

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.

Paediatric Hypertension
The antihypertensive effect of Losartan was established in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age, with a body weight ≥20kg and a glomerular filtration rate ≥30ml/min/1.73m2. Patients who weighed ≥20kg to <50kg received either 2.5, 25 or 50mg of losartan daily and patients who weighed ≥50kg received either 5, 50 or 100mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner. Overall, the two higher doses reduced diastolic blood pressure by 5 to 6mmHg more than the lowest dose used by each group. The dose response to losartan was observed across all subgroups (e.g. age, Tanner stage, gender, race). However, the lowest doses studied, 2.5mg and 5mg, corresponding to an average daily dose of 0.07mg/kg, did not appear to offer consistent antihypertensive efficacy. When patients were randomised to continue losartan or placebo, after three weeks of therapy, trough diastolic blood pressure rose in patients on placebo between 5 and 7mmHg more than patients on losartan at the two higher doses. However, the rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the
lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

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

5.2 Pharmacokinetic properties

Absorption
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. 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.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients >1 month to <16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The results showed that the active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

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

Tablet core:
- Microcrystalline cellulose
- Calcium hydrogen phosphate dihydrate
- Colloidal anhydrous silica
- Croscarmellose sodium
- Talc
- Magnesium stearate

Coating:
- Opadry II 32K50835 blue
- Hypromellose
- Lactose monohydrate
- Titanium dioxide (E171)
- Glycerol triacetate
- Indigo carmine lake (E132)

6.2 Incompatibilities

None.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Blisters with PVC 250µm/PE 25µm/PVDC 60g/m2 as forming foil and Al 20µm as lidding foil. Pack of 28 tablets, as four blisters each containing 7 tablets.

6.6 Special precautions for disposal
No special requirements. Any unused product or waste material should be disposed in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
TechnoPharm Ltd
Fanin House, South County Business Park
Leopardstown, Dublin 18, Ireland

8 MARKETING AUTHORIZATION NUMBER(S)
PL 20176/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
28/02/2008

10 DATE OF REVISION OF THE TEXT
28/02/2008
1 NAME OF THE MEDICINAL PRODUCT
Losartan potassium 50mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Losartan potassium 50mg film-coated Tablet contains 45.8mg of losartan as 50mg of losartan potassium.

Excipients: Lactose monohydrate. For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablet

Light pink, round, biconvex, film-coated tablet with a score line on one side and marked ‘LS50’ on the other side.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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. 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.

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

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

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients > 20 to < 50 kg. The dose can be increased to a maximum of 50 mg once daily. In patients > 50 kg, the starting dose is 50 mg once daily. The dose can be adjusted to a maximum of 100 mg once daily.

Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 m2, as no data are available.

Losartan is also not recommended in children with hepatic impairment.

4.3 Contraindications
Losartan is contraindicated in
- the 2nd and 3rd trimester of pregnancy (see sections 4.4 ‘Special warnings’ and 4.6 ‘Pregnancy and lactation’),
- hypersensitivity to losartan
- hypersensitivity to other angiotensin receptor blockers
- hypersensitivity to any excipients in the tablet.

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema. 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’).

In paediatric patients who are intravascularly volume-depleted, these conditions should be corrected prior to administration of Losartan.

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).

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

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’).

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

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.

Similarly there is an increased risk of hyperkalaemia (increased potassium levels) when ciclosporin is given with Losartan.

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 ‘Preclinical safety data’)

Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken losartan should be closely observed for hypotension (see also section 4.3 and 4.4).

**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
Losartan may have a minor or moderate influence on the ability to drive and use machines. Losartan can cause dizziness, asthenia and vertigo. If the patient experiences these adverse reactions, they should not drive or use machines.

4.8 Undesirable effects
Side effects have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with Losartan was comparable to placebo.

In controlled clinical trials for essential hypertension, dizziness was the only side effect reported as drug related that occurred with an incidence greater than placebo in 1% or more of patients treated with Losartan. In addition, dose-related orthostatic effects were seen in less than 1% of patients.

The adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

Losartan was generally well tolerated 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.

Losartan was generally well tolerated 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).

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

**Hypersensitivity:** Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue have been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schonlein purpura, has been reported rarely.

**Gastro-intestinal:** Hepatitis (reported rarely), diarrhoea, liver function abnormalities.

**Haematologic:** Anaemia (see 4.4 ‘Special warnings and precautions for use’), thrombocytopenia (reported rarely).

**Musculoskeletal:** Myalgia, arthralgia.

**Nervous system/Psychiatric:** Migraine.

**Respiratory:** Cough.

**Skin:** Urticaria, pruritus, rash.

**Laboratory test findings**
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Losartan. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan and 3.4% of patients treated with placebo developed hyperkalaemia (see 4.4 ‘Special warnings and precautions for use’, Hypotension and electrolyte/fluid imbalance). Serum potassium should be monitored, particularly in the elderly and patients with renal impairment. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

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

Limited data are available in regard to overdose in humans. The most likely manifestation of overdose 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 50kg.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Therapeutic classification: C09C A01
Pharmacotherapeutic group: Angiotensin II Antagonists, Plain

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 150mg 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 50mg 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 50mg of Losartan is similar to once-daily administration of enalapril 20mg. The antihypertensive effect of once-daily administration of 50-100mg 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).

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.

Paediatric Hypertension
The antihypertensive effect of Losartan was established in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age, with a body weight ≥20kg and a glomerular filtration rate ≥30ml/min/1.73m2. Patients who weighed >20kg to <50kg received either 2.5, 25 or 50mg of losartan daily and patients who weighed 50kg received either 5, 50 or 100mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner. Overall, the two higher doses reduced diastolic blood pressure by 5 to 6mmHg more than the lowest dose used by each group. The dose response to losartan was observed across all subgroups (e.g. age, Tanner stage, gender, race). However, the lowest doses studied, 2.5mg and 5mg, corresponding to an average daily dose of 0.07mg/kg, did not appear to offer consistent antihypertensive efficacy. When patients were randomised to continue losartan or placebo, after three weeks of therapy, trough diastolic blood pressure rose in patients on placebo between 5 and 7mmHg more than patients on losartan at the two higher doses. However, the rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

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

Absorption
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. 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.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients >1 month to <16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The results showed that the active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.
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
Tablet core:
- Microcrystalline cellulose
- Calcium hydrogen phosphate dihydrate
- Colloidal anhydrous silica
- Croscarmellose sodium
- Talc
- Magnesium stearate

Coating:
- Opadry II 32K54870 pink
- Hypromellose
- Lactose monohydrate
- Titanium dioxide (E171)
- Glycerol triacetate
- Iron oxide red (E172)

6.2 Incompatibilities
None.

6.3 Shelf life
18 months

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Blisters with PVC 250µm/PE 25µm/PVDC 60g/m² as forming foil and Al 20µm as lidding foil. Pack of 28 tablets, as two blisters each containing 14 tablets.

6.6 Special precautions for disposal
No special requirements. Any unused product or waste material should be disposed in accordance with local requirements.
7 MARKETING AUTHORISATION HOLDER
TechnoPharm Ltd
Fanin House, South County Business Park
Leopardstown, Dublin 18, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 20176/0054

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/02/2008

10 DATE OF REVISION OF THE TEXT
28/02/2008
1 NAME OF THE MEDICINAL PRODUCT
Losartan potassium 100mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Losartan potassium 100mg film-coated Tablet contains 91.6mg of losartan as 100mg of losartan potassium.

Excipients: Lactose monohydrate. For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablet

White, round, biconvex, film-coated tablet with a score line on one side and marked ‘LS 100’ on the other side.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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. 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.

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

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

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients > 20 to < 50 kg. The dose can be increased to a maximum of 50 mg once daily. In patients > 50 kg, the starting dose is 50 mg once daily. The dose can be adjusted to a maximum of 100 mg once daily.

Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 m2, as no data are available.

Losartan is also not recommended in children with hepatic impairment.

4.3 Contraindications
Losartan is contraindicated in
- the 2nd and 3rd trimester of pregnancy (see sections 4.4 ‘Special warnings’ and 4.6 ‘Pregnancy and lactation’),
- hypersensitivity to losartan
- hypersensitivity to other angiotensin receptor blockers
- hypersensitivity to any excipients in the tablet.

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema. 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’).

In paediatric patients who are intravascularly volume-depleted, these conditions should be corrected prior to administration of Losartan.

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).

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

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’).

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

### 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.

Similarly there is an increased risk of hyperkalaemia (increased potassium levels) when ciclosporin is given with Losartan.

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

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data')

Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken losartan should be closely observed for hypotension (see also section 4.3 and 4.4).

**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**
Losartan may have a minor or moderate influence on the ability to drive and use machines. Losartan can cause dizziness, asthenia and vertigo. If the patient experiences these adverse reactions, they should not drive or use machines.

**4.8 Undesirable effects**
Side effects have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with Losartan was comparable to placebo.

In controlled clinical trials for essential hypertension, dizziness was the only side effect reported as drug related that occurred with an incidence greater than placebo in 1% or more of patients treated with Losartan. In addition, dose-related orthostatic effects were seen in less than 1% of patients.

The adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

Losartan was generally well tolerated 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.

Losartan was generally well tolerated 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).

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

**Hypersensitivity:** Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue have been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schonlein purpura, has been reported rarely.

**Gastro-intestinal:** Hepatitis (reported rarely), diarrhoea, liver function abnormalities.

**Haematologic:** Anaemia (see 4.4 ‘Special warnings and precautions for use’), thrombocytopenia (reported rarely).

**Musculoskeletal:** Myalgia, arthralgia.

**Nervous system/Psychiatric:** Migraine.

**Respiratory:** Cough.

**Skin:** Urticaria, pruritus, rash.

**Laboratory test findings**
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Losartan. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan and 3.4% of patients treated with placebo developed hyperkalaemia (see 4.4 ‘Special warnings and precautions for use’, Hypotension and electrolyte/fluid imbalance). Serum potassium should be monitored, particularly in the elderly and patients with renal impairment. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

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 overdose in humans. The most likely manifestation of overdose 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 50kg.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Therapeutic classification: C09C A01
Pharmacotherapeutic group: Angiotensin II Antagonists, Plain

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 150mg 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 50mg 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 50mg of Losartan is similar to once-daily administration of enalapril 20mg. The antihypertensive effect of once-daily administration of 50-100mg 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).

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.

Paediatric Hypertension
The antihypertensive effect of Losartan was established in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age, with a body weight ≥20kg and a glomerular filtration rate ≥30ml/min/1.73m². Patients who weighed >20kg to <50kg received either 2.5, 25 or 50mg of losartan daily and patients who weighed ≥50kg received either 5, 50 or 100mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner. Overall, the two higher doses reduced diastolic blood pressure by 5 to 6mmHg more than the lowest dose used by each group. The dose response to losartan was observed across all subgroups (e.g. age, Tanner stage, gender, race). However, the lowest doses studied, 2.5mg and 5mg, corresponding to an average daily dose of 0.07mg/kg, did not appear to offer consistent antihypertensive efficacy. When patients were randomised to continue losartan or placebo, after three weeks of therapy, trough diastolic blood pressure rose in patients on placebo between 5 and 7mmHg more than patients on losartan at the two higher doses. However, the rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

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

Absorption
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. 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.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients >1 month to <16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The results showed that the active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.
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

Tablet core:
- Microcrystalline cellulose
- Calcium hydrogen phosphate dihydrate
- Colloidal anhydrous silica
- Croscarmellose sodium
- Talc
- Magnesium stearate

Coating:
- Opadry II 32K28708 white
- Hypromellose
- Lactose monohydrate
- Titanium dioxide (E171)
- Glycerol triacetate

6.2 Incompatibilities

None.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Blisters with PVC 250µm/PE 25µm/PVDC 60g/m² as forming foil and Al 20µm as lidding foil. Pack of 28 tablets, as two blisters each containing 14 tablets.

6.6 Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
UKPAR Losartan Potassium 25, 50 and 100mg Film-Coated Tablets

TechnoPharm Ltd
Fanin House, South County Business Park
Leopardstown, Dublin 18, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
   PL 20176/0055

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   28/02/2008

10 DATE OF REVISION OF THE TEXT
    28/02/2008
Losartan potassium 25mg, 50mg and 100mg film-coated Tablets

Losartan potassium (Losartan Tablets)

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

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

1 What Losartan Tablets are and what they are used for
Losartan belongs to a class of drugs known as antihypertensives which are medicines to lower blood pressure.

2 Before you take Losartan Tablets
Please read the following information carefully as this may stop you from being able to have this medicine.

You should not take Losartan Tablets:
- if you are allergic (hypersensitive) to losartan potassium or any of the other ingredients of Losartan Tablets
- if you are more than 13 weeks pregnant or breast-feeding
If any of these apply to you and you have not already discussed this with your doctor or pharmacist, you should do so as soon as possible and before taking your tablets.

Take special care with Losartan Tablets
Before treatment with Losartan Tablets you should tell your doctor if:
- you have received a kidney transplant
- you have recently suffered with excessive vomiting and/or diarrhoea
- you know that you have high levels of potassium in your blood (hyperkalaemia) or you are on a low potassium diet
- you have a condition called ‘aortic stenosis’ which is the narrowing of a valve in the heart
- you have a condition called hypertrophic cardiomyopathy
- you are known to have narrowing or blockage of the blood vessels leading to the kidneys
- you have liver or kidney problems.

Taking other medicines
The following medicinal products may interact with losartan, either by increasing or decreasing its effect:
- non-steroidal anti-inflammatory drugs (NSAIDs, e.g. indometacin)
- fluconazole (an anti-fungal)
- rifampicin (an antibiotic)
- potassium-sparing diuretics (e.g. triamterene, amiloride)
- potassium supplements or potassium-containing salt substitutes
- the immunosuppressant ciclosporin.
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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

Pregnancy and breast-feeding
You should not take Losartan tablets in the first 12 weeks of pregnancy. You must not take losartan tablets at all after the 13th week as its use during pregnancy may be harmful to the baby. During treatment with Losartan you should avoid becoming pregnant. If you become pregnant while taking this medicine, please tell your doctor immediately. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy. You must not take Losartan if you are breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

Driving and using machines
Losartan may have a minor or moderate influence on the ability to drive and use machines. Losartan can cause dizziness, asthena and vertigo. If you experience these adverse reactions, you should not drive or use machines.

3 How to take Losartan Tablets
Losartan may be taken with or without food.

Adults
The usual starting dose is 50mg once daily. You will probably have to wait for 3 – 6 weeks to see the effect on your blood pressure. Your doctor may tell you to increase this dose to 100mg once daily.
If you are dehydrated, have been using water tablets, have liver or kidney problems or are over 75 years old you may begin with a lower dose.
Always take Losartan exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Children and adolescents
For children and adolescents who can swallow tablets, the recommended dose is:
- weight <20kg: 5mg/kg once daily, which your doctor may increase to 50mg/kg
- weight 20kg –50kg: 25mg/kg once daily, which your doctor may increase to 100mg/kg
Losartan is not recommended in neonates or in children with liver or kidney problems.
If you take more Losartan Tablets than you should
If you take too much losartan you may experience a drop in your blood pressure (this can make you feel short of breath, cause a headache, diarrhoea or vomiting, dizzy or light-headed) and an increased or decreased heart rate. If you think you may have taken too much losartan, please tell your doctor immediately or go to the nearest hospital casualty (emergency) department. If possible, please take the remaining tablets or this leaflet with you to the hospital.

If you miss a dose
If you have forgotten to take your tablet, take it as soon as you remember, unless it is almost time for your next tablet, when you should miss the forgotten dose and continue as usual. Do not take a double dose to make up for a forgotten dose.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

Possible side effects
Like all medicines, Losartan can cause side effects, although not everybody gets them. The following side effects have been observed in patients treated with losartan:

Allergic reactions:
- Anaphylactic reaction – this is a very severe allergic reaction and may be life threatening. You must seek urgent medical attention if you experience any of the following symptoms:
  - swelling of the face, lips, tongue or throat
  - breathlessness
  - rash
  - vasculitis (inflammation of blood vessel)

Other side effects:
- diarrhoea
- hepatitis, liver problems
- anaemia (drop in white blood cells)
- thrombocytopenia (drop in some other types of blood cells needed for blood clotting)
- increased levels of potassium
- decrease in blood pressure
- muscle and joint pain
- weakness, fatigue
- dizziness, migraine, vertigo (spinning feeling)
- cough
- rashes, hives, itching

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

How to store Losartan Tablets
Do not store above 25°C.
Store in the original package.
Keep out of the reach and sight of children.

The end of the carton is printed with 'Use by', followed by a date. The expiry date refers to the last day of that month. Do not use these tablets after this date.

Further information
What Losartan Tablets contain
- The active substance is losartan potassium
- The other ingredients are microcrystalline cellulose, calcium hydrogen phosphate dihydrate, colloidal anhydrous silica, croscarmellose sodium, talc and magnesium stearate.
- The tablet coating for the 25mg tablets consists of hypromellose, lactose monohydrate, titanium dioxide (E171), glycerol triacetate and indigo carmine lake (E132).
- The tablet coating for the 50mg tablets consists of hypromellose, lactose monohydrate, titanium dioxide (E171), glycerol triacetate and iron oxide red (E172).
- The tablet coating for the 100mg tablets consists of hypromellose, lactose monohydrate, titanium dioxide (E171) and glycerol tricetate.

What Losartan Tablets look like and contents of pack
Losartan potassium 25mg film-coated Tablets are light blue, round biconvex, film-coated tablet with a score line on one side and debossed LS 25 on the other side. They are available in packs of 28 tablets. Each carton contains four strips of seven tablets.

Losartan potassium 50mg film-coated Tablets are light pink, round, biconvex film-coated tablet with a score line on one side and debossed LS 50 on the other side. They are available in packs of 28 tablets. Each carton contains two strips of 14 tablets.

Losartan potassium 100mg film-coated Tablets are white, round, biconvex film-coated tablets with a score line on one side. They are available in packs of 28 tablets. Each carton contains two strips of 14 tablets.

The scoreline on the tablets is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Marketing Authorisation Holder and Manufacturer:
Marketing Authorisation Holder:
TechnoPharm Limited,
Fannin House, South County Business Park,
Leopardstown, Dublin 18, Ireland.

Manufacturer:
PLIVA Krakow S.A.,
80 Mogiliska Str., 31 546 Krakow, Poland

These medicinal products are authorised in the Member States of the EEA under the following names:
United Kingdom:
Losartan potassium 25mg film-coated Tablets
Losartan potassium 50mg film-coated Tablets
Losartan potassium 100mg film-coated Tablets

This leaflet was last approved in
(MM/YYYY):
25mg PL 20176/0053
50mg PL 20176/0054
100mg PL 20176/0055

xxxxx-P1
Losartan potassium 25mg film-coated Tablets

Each film-coated tablet contains 25mg losartan (as losartan potassium).

Use by:

Read the package leaflet before use.
Contains lactose.
See enclosed leaflet for further information.
For oral use.
Do not store above 25°C.
Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

POM PL 20176/0053 xxxx-C1

MA Holder:
TechnoPharm Ltd,
Chapelizod, Dublin 20, Ireland

Distributed by:
PLIVA Pharma Ltd,
Vision House, Bedford Road,
Petersfield, Hampshire
GU32 3QB, United Kingdom
Losartan potassium 50mg film-coated Tablets

Each film-coated tablet contains 50mg losartan (as losartan potassium)

Use of

POM PL 20176/0054: xxxx-C1

MA Holder: TechnoPharm Ltd, Chapelizod, Dublin 20, Ireland
Distributed by: PLIVA Pharma Ltd, Vision House, Bedford Road, Petersfield, Hampshire GU32 3QB, United Kingdom
Losartan potassium
100mg film-coated Tablets

Losartan potassium
100mg film-coated Tablets

Each film-coated tablet contains 100mg losartan (as losartan potassium)

Use by:
Read the package leaflet before use.
Contains lactose.
See enclosed leaflet for further information.
For oral use.
Do not store above 25°C.
Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

MA Holder:
TechnoPharm Ltd,
Chapelizod, Dublin 20,
Ireland

Distributed by:
PLIVA Pharma Ltd,
Vision House, Bedford Road,
Petersfield,
Hampshire GU32 3QG,
United Kingdom

POM PL 20176/0055 xxxxx-C1

Bar code