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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Limited Marketing Authorisations for the medicinal products Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets (PL 17907/0242-4) on 23 March 2011. Losartan Potassium Film-coated Tablets are only available on prescription from your doctor and are used:

- to treat patients with high blood pressure (hypertension) in adults and in children and adolescents 6-18 years of age
- to protect the kidney in hypertensive type 2 diabetic patients with laboratory evidence of impaired renal function and proteinuria > 0.5 g per day (a condition in which urine contains an abnormal amount of protein)
- to treat patients with chronic heart failure when therapy with specific medicines called angiotensin-converting-enzyme inhibitors (ACE inhibitors, medicines used to lower high blood pressure) is not considered suitable by your doctor. If your heart failure has been stabilised with an ACE inhibitor you should not be switched to losartan.
- in patients with high blood pressure and a thickening of the left ventricle, Losartan Potassium Film-coated Tablets have been shown to decrease the risk of stroke (“LIFE indication”).

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

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
**SCIENTIFIC DISCUSSION**

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bristol Laboratories Limited Marketing Authorisations for the medicinal products Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets (PL 17907/0242-4) on 23 March 2011. The products are prescription-only medicines used in the:

- treatment of essential hypertension in adults and in children and adolescents 6-18 years of age.
- treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment
- treatment of chronic heart failure in adult patients when treatment with Angiotensin Converting Enzyme (ACE) inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be clinically stable and on an established treatment regimen for chronic heart failure
- reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG.

These applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Cozaar 25 mg, 50 mg and 100 mg Film-coated Tablets (Merck Sharp & Dohme Limited, UK), which were first authorised on 15 December 1994.

The active ingredient losartan potassium is an angiotensin II (AT₁) receptor (type AT₁) blocker. Angiotensin II is a potent vasoconstritor and is the primary active hormone in the renin-angiotensin system, and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT₁ receptor found in many tissues and elicits several important biological actions, including vasoconstriction and the release of aldosterone. In vitro and in vivo losartan potassium, and its pharmacologically active carboxylic acid metabolite E-3174, block all physiologically relevant actions of angiotensin-II, regardless of the source or route of its synthesis.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

A single-dose, two-way crossover bioequivalence study was submitted to support these applications, comparing the test product Losartan Potassium 100 mg Film-coated Tablets (Bristol Laboratories Limited) with the reference product Cozaar 100 mg Film-coated Tablets (Merck Sharp & Dohme) under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.
No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Losartan potassium
Chemical Name: 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}ClKN_{6}O
Structure

Molecular weight: 461.01
Appearance: White to off-white crystalline powder, freely soluble in water and in methanol, slightly soluble in acetonitrile

Losartan potassium is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period for the active substance when stored in the proposed packaging.

DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients in the tablet core and film coating, namely maize starch, microcrystalline cellulose, purified talc, colloidal anhydrous silica, sodium starch glycollate (Type A), magnesium stearate,
hypromellose, macrogol 6000 and titanium dioxide E171. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Cozaar 25 mg, 50 mg and 100 mg Film-coated Tablets (Merck Sharp & Dohme Limited, UK).

Suitable pharmaceutical development data have been provided for these applications. Comparative in-vitro dissolution and impurity profiles have been provided for these products and their respective reference products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to submitting validation data performed on full-scale batches as soon as they are available.

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

Container Closure System
The tablets are packaged in aluminium/polyvinylchloride blisters. These are packed into cardboard cartons with patient information leaflets in pack sizes of 28, 56 and 84 tablets. Not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the packaging to MHRA for approval before marketing any pack size.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage conditions “Do not store above 25°C. Store in the original package.”
Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

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

**Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling**
The SmPCs, PIL and labelling are pharmaceutically satisfactory.

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, as amended. 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.

**MAA Forms**
The MAA forms are pharmaceutically satisfactory.

**Expert Report**
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of losartan potassium are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of losartan potassium is well-known. With the exception of data from the below bioequivalence study, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

Pharmacokinetics
In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, single-dose, open-label, two-treatment, two-sequence, two-period, two-way crossover study comparing the pharmacokinetics of the test product Losartan Potassium 100 mg Film-coated Tablets (Bristol Laboratories Limited) and the reference product Cozaar 100 mg Film-coated Tablets (Merck Sharp & Dohme) in healthy adult male subjects under fasting conditions

The subjects were administered one tablet of either the test or the reference product with 240 ml of water, after an overnight fast. Blood samples were collected before and up to 48 hours after each administration. The washout period between the treatment arms was 14 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (geometric means±standard deviation, ratios and confidence intervals [CI]) of losartan potassium (parent)</th>
<th>Losartan Potassium 100mg (Test)</th>
<th>Cozaar 100mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-ₜ (ng·h/ml)</td>
<td>1038±381</td>
<td>1000±436</td>
<td>103.8</td>
<td>99.1-108.3</td>
</tr>
<tr>
<td>AUC₀-∞ (ng·h/ml)</td>
<td>1049±386</td>
<td>1013±441</td>
<td>103.6</td>
<td>85.2-111.2</td>
</tr>
<tr>
<td>Cₘₙₜ (ng/ml)</td>
<td>564±298</td>
<td>579±403</td>
<td>97.3</td>
<td>99.2-108.5</td>
</tr>
</tbody>
</table>

AUC₀-ₜ area under the plasma concentration-time curve from time zero to t hours
AUC₀-∞ area under the plasma concentration-time curve from time zero to infinity
Cₘₙₜ maximum plasma concentration
Ratios and 90% geometric CI calculated from ln-transformed data

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (geometric means±standard deviation, ratios and confidence intervals [CI]) of carboxylosartan (active metabolite)</th>
<th>Losartan Potassium 100mg (Test)</th>
<th>Cozaar 100mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-ₜ (ng·h/ml)</td>
<td>4887±1863</td>
<td>4893±1890</td>
<td>99.9</td>
<td>97.2-102.6</td>
</tr>
<tr>
<td>AUC₀-∞ (ng·h/ml)</td>
<td>4932±1864</td>
<td>4944±1889</td>
<td>99.8</td>
<td>97.2-102.5</td>
</tr>
<tr>
<td>Cₘₙₜ (ng/ml)</td>
<td>736±321</td>
<td>743±334</td>
<td>99.0</td>
<td>94.6-103.7</td>
</tr>
</tbody>
</table>

AUC₀-ₜ area under the plasma concentration-time curve from time zero to t hours
AUC₀-∞ area under the plasma concentration-time curve from time zero to infinity
Cₘₙₜ maximum plasma concentration
Ratios and 90% geometric CI calculated from ln-transformed data

The Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) defines the confidence limits as 80% to 125% for Cₘₙₜ and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for AUC₀-ₜ,
AUC₀-∞ and C_max lie within the acceptable limits. Thus, the data support the claim that the test product Losartan Potassium 100 mg Film-Coated Tablets (Bristol Laboratories Limited) is bioequivalent to the reference product Cozaar 100 mg Film-coated Tablets (Merck Sharp & Dohme).

As the 25 mg, 50 mg and 100 mg strength products meet the criteria specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions from the bioequivalence study with the 100 mg tablet strength can be extrapolated to the 25 mg and 50 mg tablet strengths.

Efficacy
The efficacy of losartan potassium is well-known. No new efficacy data have been submitted and none are required for applications of this type.

Safety
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues were raised by the bioequivalence data.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are clinically acceptable. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Expert Report
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

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

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of losartan potassium are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new efficacy data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 100 mg strength tablet and the reference product Cozaar 100 mg Film-coated Tablets (Merck Sharp & Dohme). As the 25 mg, 50 mg and 100 mg strengths of the product meet the criteria specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions from the bioequivalence study with the 100 mg tablet strength can be extrapolated to the 25 mg and 50 mg strengths.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are acceptable. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that these products are generic medicinal products of the reference products, Cozaar 25 mg, 50 mg and 100 mg Film-coated Tablets (Merck Sharp & Dohme Limited, UK). Extensive clinical experience with losartan potassium is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.
LOSARTAN POTASSIUM 25 MG FILM-COATED TABLETS
LOSARTAN POTASSIUM 50 MG FILM-COATED TABLETS
LOSARTAN POTASSIUM 100 MG FILM-COATED TABLETS
PL 17907/0242-4

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation applications on 21 July 2006.
2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 17 April 2007.
3. Following assessment of the applications the MHRA requested further information relating to the dossier on 04 May 2007 and 28 October 2009,
4. The applicant responded to the MHRA’s requests, providing further information on the dossier on 05 March 2009 and 19 February 2010.
5. The applications were determined on 01 February 2011 and granted on 23 March 2011.
SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Losartan Potassium 25 mg Film-coated Tablets contains 25 mg of losartan potassium. For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated Tablet
Losartan Potassium 25 mg Film-coated Tablet is white to off white, oval shaped, biconvex, film coated tablet embossed with “25” on one side and “BL” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
• Treatment of essential hypertension in adults and in children and adolescents 6-18 years of age.
• Treatment of renal disease in adults with hypertension and type 2 diabetes mellitus with proteinuria ≥0.5 g/day as part of an antihypertensive treatment.
• Treatment of chronic heart failure in adults when treatment with Angiotensin converting enzyme (ACE) inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤40% and should be clinically stable and on an established treatment regimen for chronic heart failure.
• Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

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

Hypertension
The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning).

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

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

Heart failure
The usual initial dose of losartan in patients with heart failure is 12.5 mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5 mg daily, 25 mg daily, 50 mg daily) to the usual maintenance dose of 50 mg once daily, as tolerated by the patient.
Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG

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

Special populations

Use in patients with intravascular volume depletion:

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

Use in patients with renal impairment and haemodialysis patients:

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

Use in patients with hepatic impairment:

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

Use in paediatric patients

There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-18 years old for the treatment of hypertension (see section 5.1). Limited pharmacokinetic data are available in hypertensive children above one month of age (see section 5.2).

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

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

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

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

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

Use in Elderly

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 4.4 and 6.1).

2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6).

Severe hepatic impairment.

4.4 Special warnings and precautions for use

Hypersensitivity

Angio-oedema. Patients with a history of angio-oedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8).

Hyptension and electrolyte/fluid imbalance

Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium- depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to
administration of losartan, or a lower starting dose should be used (see section 4.2). This also applies to children 6 to 18 years of age.

Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalemia was higher in the group treated with losartan as compared to the placebo group (see section 4.8). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a creatinine clearance between 30-50 ml/ min should be closely monitored.

The concomitant use of potassium-sparing diuretics, potassium supplements and potassium-containing salt substitutes with losartan is not recommended (see section 4.5).

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

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

Renal impairment
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other medicinal products that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

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

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

Concomitant use of losartan and ACE inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended (see section 4.5).

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

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of losartan is not recommended.

Coronary heart disease and cerebrovascular disease
As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.
Heart failure
In patients with heart failure, with or without renal impairment, there is-as with other medicinal products acting on the renin-angiotensin system—a risk of severe arterial hypotension, and (often acute) renal impairment.

There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life threatening cardiac arrhythmias. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution (see section 5.1).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

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

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

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

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

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

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

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

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

4.6 Pregnancy and lactation

Pregnancy
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 medicinal products. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3). Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Losartan has been evaluated in clinical studies as follows:
• in controlled clinical trials in approximately 3300 adult patients 18 years of age and older for essential hypertension,
• in a controlled clinical trial in 9193 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy
• in a controlled clinical trial in approximately 3900 patients 20 years of age and older with chronic heart failure
• in a controlled clinical trial in 1513 type 2 diabetic patients 31 years of age and older with proteinuria
• in a controlled clinical trial in 177 hypertensive paediatric patients 6 to 16 years of age

In these clinical trials, the most common adverse reaction was dizziness.
The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100, to < 1/10); uncommon (≥ 1/1000, to < 1/100); rare (≥ 1/10000, to < 1/1000); very rare (< 1/10000), not known (cannot be estimated from the available data).

Hypertension
In controlled clinical trials of approximately 3300 adult patients 18 years of age and older, for essential hypertension with losartan, the following adverse reactions were reported:

Nervous system disorders:
common: dizziness, vertigo
uncommon: somnolence, headache, sleep disorders

Cardiac disorder:
uncommon: palpitations, angina pectoris

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

Gastro-intestinal disorders:
uncommon: abdominal pain, obstipation

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

Investigations:
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan tablets. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium>5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials.

Hypertensive patients with left ventricular hypertrophy
In a controlled clinical trial in 9193 hypertensive patients 55 to 80 years of age, with left ventricular hypertrophy, the following adverse reactions were reported:

Nervous system disorders:
common: dizziness

Ear and labyrinth disorders:
common: vertigo

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

Chronic heart failure
In a controlled clinical trial in approximately 3900 patients 20 years of age and older, with cardiac insufficiency, the following adverse reactions were reported:

Nervous system disorders:
uncommon: dizziness, headache

rare: paraesthesia

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

Vascular disorders:
uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
uncommon: dyspnoea
Gastro-intestinal disorders:
uncommon: diarrhoea, nausea, vomiting

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

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

Investigations:
uncommon: increase in blood urea, serum creatinine and serum potassium has been reported.

Hypertension and type 2 diabetes with renal disease
In a controlled clinical trial in 1513 type 2 diabetic patients 31 years of age and older, with proteinuria (RENAAL study, see section 5.1), the most common drug-related adverse events which were reported for losartan are as follows:

Nervous system disorders:
common: dizziness

Vascular disorders:
common: hypotension

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

Investigations:
common: hypoglycaemia, hyperkalaemia

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

Blood and lymphatic system disorders:
not known: anaemia

Cardiac disorders:
not known: syncope, palpitations

Vascular disorders:
not known: orthostatic hypotension

Gastro-intestinal disorders:
not known: diarrhoea

Musculoskeletal and connective tissue disorders:
not known: back pain

Renal and urinary disorders:
not known: urinary tract infections

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

Investigations:
In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with losartan tablets developed hyperkalaemia >5.5 mEq/l and 3.4% of patients treated with placebo.

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

Blood and lymphatic system disorders:
not known: anaemia, thrombocytopenia
Ear and labyrinth disorders:
not known: tinnitus

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

Nervous system disorders:
not known: migraine

Respiratory, thoracic and mediastinal disorders:
not known: cough

Gastro-intestinal disorders:
not known: diarrhoea, pancreatitis

General disorders and administration site conditions:
not known: malaise

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

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

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

Reproductive system and breast disorders:
not known: erectile dysfunction/impotence

Renal and urinary disorders:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy (see section 4.4)

Psychiatric disorders:
not known: depression

Investigations:
not known: hyponatraemia

Paediatric population
The adverse reaction profile for paediatric patients appears to be similar to that seen in adult patients. Data in the paediatric population are limited.

4.9 Overdose

Symptoms of intoxication
No case of overdose has been reported. The most likely symptoms, depending on the extent of overdose, are hypotension, tachycardia, possibly bradycardia.

Treatment of intoxication
Measures are depending on the time of medicinal product intake and kind and severity of symptoms. Stabilisation of the cardiovascular system should be given priority. After oral intake, the administration of a sufficient dose of activated charcoal is indicated. Afterwards,
close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.

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

5  PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C09CA

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

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

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

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

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

Hypertension studies

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

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

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

LIFE Study

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

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

Race
In the LIFE Study black patients treated with losartan had a higher risk of suffering the primary combined endpoint, i.e. a cardiovascular event (e.g. cardiac infarction, cardiovascular death) and especially stroke, than the black patients treated with atenolol. Therefore the results observed with losartan in comparison with atenolol in the LIFE study with regard to cardiovascular morbidity/mortality do not apply for black patients with hypertension and left ventricular hypertrophy.

RENAAL Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist losartan (RENAAL) Study was a controlled clinical study conducted worldwide in 1513 Type 2 diabetic patients with proteinuria, with or without hypertension. 751 patients were treated with losartan. The objective of the study was to demonstrate a nephroprotective effect of losartan potassium over and above the benefit of lowering blood pressure.

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

Investigators were instructed to titrate the study medication to 100 mg daily as appropriate; 72% of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed up for up to 4.6 years (3.4 years on average).

The primary endpoint of the study was a composite endpoint of doubling of the serum creatinine end-stage renal failure (need for dialysis or transplantation) or death.

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

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

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

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

In this study, 3152 patients with heart failure (NYHA Class II-IV) were followed for almost two years (median: 1.5 years) in order to determine whether losartan is superior to captopril in reducing all cause mortality. The primary endpoint did not show any statistically significant difference between losartan and captopril in reducing all-cause mortality.

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

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

**Paediatric Population**

**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 > 20 kg and a glomerular filtration rate > 30 ml/ min/ 1.73 m². Patients who weighed > 20 kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

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

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

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

In hypertensive (N=60) and normotensive (N=246) children with proteinuria, the effect of losartan on proteinuria was evaluated in a 12-week placebo- and active-controlled (amlodipine) clinical study. Proteinuria was defined as urinary protein/creatinine ratio of ≥ 0.3. The hypertensive patients (ages 6 through 18 years) were randomised to receive either losartan (n=30) or amlodipine (n=30). The normotensive patients (ages 1 through 18 years) were randomised to receive either losartan (n=122) or placebo (n=124). Losartan was given at doses of 0.7 mg/kg to 1.4 mg/kg (up to maximum dose of 100 mg per day). Amlodipine was given at doses of 0.05 mg/kg to 0.2 mg/kg (up to a maximum dose of 5 mg per day).

Overall, after 12 weeks of treatment, patients receiving losartan experienced a statistically significant reduction from baseline in proteinuria of 36% versus 1% increase in placebo/amlodipine group (p < 0.001). Hypertensive patients receiving losartan experienced a
reduction from baseline proteinuria of -41.5% (95% CI -29.9; -51.1) versus +2.4% (95% CI -22.2; 14.1) in the amlodipine group. The decline in both systolic blood pressure and diastolic blood pressure was greater in the losartan group (-5.5/-3.8 mmHg) versus the amlodipine group (-0.1/+0.8 mmHg). In normotensive children a small decrease in blood pressure was observed in the losartan group (-3.7/-3.4 mm Hg) compared to placebo. No significant correlation between the decline in proteinuria and blood pressure was noted, however it is possible that the decline in blood pressure was responsible, in part, for the decline in proteinuria in the losartan treated group. Long-term effects of reduction of proteinuria in children have not been studied.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Biotransformation

About 14% of an intravenously- or orally administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about 1% of individuals studied.

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

Elimination

Plasma clearance of losartan and its active metabolite is 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 excretions contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of 14C-labelled losartan in man, about 35%/43% of radioactivity is recovered in the urine and 58%/50% in the faeces.

Characteristics in patients

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

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

In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma levels of losartan and its active metabolite after oral administration were respectively 5 and 1.7 times higher than in young male volunteers (see section 4.2 and 4.4).
Plasma concentrations of losartan are not altered in patients with a creatinine clearance above 10 ml/minute. Compared to patients with normal renal function, the AUC for losartan is about 2-times higher in haemodialysis dialysis patients.

The plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

Pharmacokinetics in paediatric patients

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

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

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Microcrystalline cellulose
Purified Talc
Colloidal Anhydrous Silica
Sodium Starch Glycollate (Type A)
Magnesium Stearate
Hypromellose
Macrogol 6000
Titanium dioxide E171

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Al / PVC Blister strip of 14 tablets.
Blister strips packaged in an outer carton to give pack sizes of 28, 56, and 84 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements
MARKETING AUTHORISATION HOLDER
Bristol Laboratories Limited
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom

MARKETING AUTHORIZATION NUMBER(S)
PL 17907/0242

DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
23/03/2011

DATE OF REVISION OF THE TEXT
23/03/2011
1 NAME OF THE MEDICINAL PRODUCT
Losartan Potassium 50 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Losartan Potassium 50 mg Film-coated Tablets contains 50 mg of losartan potassium. For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated Tablet
Losartan Potassium 50 mg Film-coated Tablet is white to off white, oval-shaped, biconvex, film coated tablet embossed with “50” on one side and “BL” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
• Treatment of essential hypertension in adults and in children and adolescents 6-18 years of age.
• Treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
• Treatment of chronic heart failure in adult patients when treatment with Angiotensin converting enzyme (ACE) inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be clinically stable and on an established treatment regimen for chronic heart failure.
• Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

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

Hypertension
The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3 – 6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning). Losartan may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

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

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

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

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

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

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

Use in paediatric patients
There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-18 years old for the treatment of hypertension (see section 5.1). Limited pharmacokinetic data are available in hypertensive children above one month of age (see section 5.2).

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

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

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

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

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

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

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

4.4 Special warnings and precautions for use

Hypersensitivity
Angio-oedema. Patients with a history of angio-oedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8).

Hypotension and electrolyte/fluid imbalance
Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium- depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used (see section 4.2). This also applies to children 6 to 18 years of age.

Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalemia was higher in the group treated with losartan.
as compared to the placebo group (see section 4.8). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a creatinine clearance between 30-50 ml/ min should be closely monitored.

The concomitant use of potassium-sparing diuretics, potassium supplements and potassium-containing salt substitutes with losartan is not recommended (see section 4.5).

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

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

Renal impairment
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin- angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other medicinal products that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

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

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

Concomitant use of losartan and ACE inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended (see section 4.5).

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

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of losartan is not recommended.

Coronary heart disease and cerebrovascular disease
As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure
In patients with heart failure, with or without renal impairment, there is, - as with other medicinal products acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life threatening cardiac arrhythmias.
Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution (see section 5.1).

**Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy**
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

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

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

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

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

Other antihypertensive agents may increase the hypotensive action of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension. Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan with rifampicin (inducer of metabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).

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

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

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

Pregnancy

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 medicinal products. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3). Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

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

Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Losartan has been evaluated in clinical studies as follows:
• in controlled clinical trials in approximately 3300 adult patients 18 years of age and older for essential hypertension,
• in a controlled clinical trial in 9193 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy
• in a controlled clinical trial in approximately 3900 patients 20 years of age and older with chronic heart failure
• in a controlled clinical trial in 1513 type 2 diabetic patients 31 years of age and older with proteinuria
• in a controlled clinical trial in 177 hypertensive paediatric patients 6 to 16 years of age

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

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

Hypertension

In controlled clinical trials of approximately 3300 adult patients 18 years of age and older, for essential hypertension with losartan, the following adverse reactions were reported
Nervous system disorders:
common: dizziness, vertigo
uncommon: somnolence, headache, sleep disorders

Cardiac disorder:
uncommon: palpitations, angina pectoris

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

Gastro-intestinal disorders:
uncommon: abdominal pain, obstipation

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

Investigations:
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan tablets. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium>5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials.

Hypertensive patients with left ventricular hypertrophy
In a controlled clinical trial in 9193 hypertensive patients 55 to 80 years of age, with left ventricular hypertrophy, the following adverse reactions were reported:

Nervous system disorders:
common: dizziness

Ear and labyrinth disorders:
common: vertigo

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

Chronic heart failure
In a controlled clinical trial in approximately 3900 patients 20 years of age and older, with cardiac insufficiency, the following adverse reactions were reported:

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

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

Vascular disorders:
uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
uncommon: dyspnoea

Gastro-intestinal disorders:
uncommon: diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders:
uncommon: urticaria, pruritus, rash
**General disorders and administration site conditions:**
uncommon: asthenia/fatigue

**Investigations:**
uncommon: increase in blood urea, serum creatinine and serum potassium has been reported

**Hypertension and type 2 diabetes with renal disease**
In a controlled clinical trial in 1513 type 2 diabetic patients 31 years of age and older, with proteinuria (RENAAL study, see section 5.1), the most common drug-related adverse events which were reported for losartan are as follows:

**Nervous system disorders:**
common: dizziness

**Vascular disorders:**
common: hypotension

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

**Investigations:**
common: hypoglycaemia, hyperkalaemia

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

**Blood and lymphatic system disorders:**
not known: anaemia

**Cardiac disorders:**
not known: syncope, palpitations

**Vascular disorders:**
not known: orthostatic hypotension

**Gastro-intestinal disorders:**
not known: diarrhoea

**Musculoskeletal and connective tissue disorders:**
not known: back pain

**Renal and urinary disorders:**
not known: urinary tract infections

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

**Investigations:**
In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with losartan tablets developed hyperkalaemia > 5.5 mEq/l and 3.4% of patients treated with placebo.

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

**Blood and lymphatic system disorders:**
not known: anaemia, thrombocytopenia

**Ear and labyrinth disorders:**
not known: tinnitus
Immune system disorders:
rare: hypersensitivity: anaphylactic reactions, angio-oedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angio-oedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors; vasculitis, including Henoch-Schonlein purpura.

Nervous system disorders:
not known: migraine

Respiratory, thoracic and mediastinal disorders:
not known: cough

Gastro-intestinal disorders:
not known: diarrhoea, pancreatitis

General disorders and administration site conditions:
not known: malaise

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

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

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

Reproductive system and breast disorders:
not known: erectile dysfunction/impotence

Renal and urinary disorders:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy (see section 4.4)

Psychiatric disorders:
not known: depression

Investigations:
not known: hyponatraemia

Paediatric population
The adverse reaction profile for paediatric patients appears to be similar to that seen in adult patients. Data in the paediatric population are limited.

4.9 Overdose
Symptoms of intoxication
No case of overdose has been reported. The most likely symptoms, depending on the extent of overdose, are hypotension, tachycardia, possibly bradycardia.

Treatment of intoxication
Measures are depending on the time of medicinal product intake and kind and severity of symptoms. Stabilisation of the cardiovascular system should be given priority. After oral intake, the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.

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

5.1 Pharmacodynamic properties

ATC code: C09C A

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

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

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

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

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

Hypertension studies

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

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

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

LIFE Study

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

The mean length of follow up was 4.8 years.

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

Race
In the LIFE Study black patients treated with losartan had a higher risk of suffering the primary combined endpoint, i.e. a cardiovascular event (e.g. cardiac infarction, cardiovascular death) and especially stroke, than the black patients treated with atenolol. Therefore the results observed with losartan in comparison with atenolol in the LIFE Study with regard to cardiovascular morbidity/mortality do not apply for black patients with hypertension and left ventricular hypertrophy.

RENAAL Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist losartan RENAAL Study was a controlled clinical study conducted worldwide in 1513 Type 2 diabetic patients with proteinuria, with or without hypertension. 751 patients were treated with losartan. The objective of the study was to demonstrate a nephroprotective effect of losartan potassium over and above the benefit of lowering blood pressure.

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

Investigators were instructed to titrate the study medication to 100 mg daily as appropriate; 72% of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed up for up to 4.6 years (3.4 years on average).

The primary endpoint of the study was a composite endpoint of doubling of the serum creatinine end-stage renal failure (need for dialysis or transplantation) or death.

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

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

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

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

In this study, 3152 patients with heart failure (NYHA Class II-IV) were followed for almost two years (median: 1.5 years) in order to determine whether losartan is superior to captopril in reducing all cause mortality. The primary endpoint did not show any statistically significant difference between losartan and captopril in reducing all-cause mortality.

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

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

Paediatric Population

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 > 20 kg and a glomerular filtration rate > 30 ml/min/1.73 m². Patients who weighed > 20 kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

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

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

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

In hypertensive (N=60) and normotensive (N=246) children with proteinuria, the effect of losartan on proteinuria was evaluated in a 12-week placebo- and active-controlled (amlodipine) clinical study. Proteinuria was defined as urinary protein/creatinine ratio of ≥ 0.3. The hypertensive patients (ages 6 through 18 years) were randomised to receive either losartan (n=30) or amlodipine (n=30). The normotensive patients (ages 1 through 18 years) were randomised to receive either losartan (n=122) or placebo (n=124). Losartan was given at doses of 0.7 mg/kg to 1.4 mg/kg (up to maximum dose of 100 mg per day). Amlodipine was given at doses of 0.05 mg/kg to 0.2 mg/kg (up to a maximum dose of 5 mg per day).

Overall, after 12 weeks of treatment, patients receiving losartan experienced a statistically significant reduction from baseline in proteinuria of 36% versus 1% increase in placebo/amlodipine group (p < 0.001). Hypertensive patients receiving losartan experienced a reduction from baseline proteinuria of -41.5% (95% CI -29.9; -51.1) versus +2.4% (95% CI -22.2; 14.1) in the amlodipine group. The decline in both systolic blood pressure and diastolic blood pressure was greater in the losartan group (-5.5/-3.8 mmHg) versus the amlodipine group (-0.1/+0.8 mm Hg). In normotensive children a small decrease in blood pressure was observed in the losartan group (-3.7/-3.4 mm Hg) compared to placebo. No
significant correlation between the decline in proteinuria and blood pressure was noted, however it is possible that the decline in blood pressure was responsible, in part, for the decline in proteinuria in the losartan treated group. Long-term effects of reduction of proteinuria in children have not been studied.

5.2 Pharmacokinetic properties

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

Distribution
Both losartan and its active metabolite are ≥ 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Biotransformation
About 14% of an intravenously- or orally- administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about 1% of individuals studied.

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

Elimination
Plasma clearance of losartan and its active metabolite is 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 excretions contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of 14C-labelled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58% / 50% in the faeces.

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

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

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

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

The plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients.
Neither losartan nor the active metabolite can be removed by haemodialysis.

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

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

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

6 **PHARMACEUTICAL PARTICULARS**
6.1 **List of excipients**
- Maize starch
- Microcrystalline cellulose
- Purified Talc
- Colloidal Anhydrous Silica
- Sodium Starch Glycollate (Type A)
- Magnesium Stearate
- Hypromellose
- Macrogol 6000
- Titanium dioxide E171

6.2 **Incompatibilities**
Not Applicable.

6.3 **Shelf life**
2 years

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

6.5 **Nature and contents of container**
Al/PVC Blister strip of 14 tablets.
Blister strips packaged in an outer carton to give pack sizes of 28, 56, and 84 tablets. Not all pack sizes may be marketed.

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

7 **MARKETING AUTHORISATION HOLDER**
Bristol Laboratories Limited
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom
MARKETING AUTHORISATION NUMBER(S)
PL 17907/0243

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/03/2011

DATE OF REVISION OF THE TEXT
23/03/2011
1 NAME OF THE MEDICINAL PRODUCT
Losartan Potassium 100 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Losartan Potassium 100 mg Film-coated Tablets contains 100 mg of losartan potassium.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated Tablet
Losartan Potassium 100 mg Film-coated Tablet is white to off white, oval shaped, biconvex, film coated tablet embossed with “100” on one side and “BL” on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
• Treatment of essential hypertension in adults and in children and adolescents 6-18 years of age.
• Treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
• Treatment of chronic heart failure in adult patients when treatment with Angiotensin Converting Enzyme (ACE) inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be clinically stable and on an established treatment regimen for chronic heart failure.
• Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

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

Hypertension
The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning).

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

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

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

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

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

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

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

Use in paediatric patients
There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-18 years old for the treatment of hypertension (see section 5.1). Limited pharmacokinetic data are available in hypertensive children above one month of age (see section 5.2).

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

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

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

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

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

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

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

4.4 Special warnings and precautions for use
Hypersensitivity
Angio-oedema. Patients with a history of angio-oedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8).

Hypotension and electrolyte/fluid imbalance
Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium- depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used (see section 4.2). This also applies to children 6 to 18 years of age.

Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalemia was higher in the group treated with losartan.
as compared to the placebo group (see section 4.8). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a creatinine clearance between 30-50 ml/ min should be closely monitored.

The concomitant use of potassium-sparing diuretics, potassium supplements and potassium-containing salt substitutes with losartan is not recommended (see section 4.5).

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

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

**Renal impairment**
As a consequence of inhibiting the renin–angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other medicinal products that affect the renin–angiotensin–aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

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

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

Concomitant use of losartan and ACE inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended (see section 4.5).

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

**Primary hyperaldosteronism**
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of losartan is not recommended.

**Coronary heart disease and cerebrovascular disease**
As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

**Heart failure**
In patients with heart failure, with or without renal impairment, there is- s with other medicinal products acting on the renin-angiotensin system-a risk of severe arterial hypotension, and (often acute) renal impairment.

There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life threatening cardiac arrhythmias.
Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution (see section 5.1).

**Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy**

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

**Excipients**

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

**Pregnancy**

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

**Other warnings and precautions**

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

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

Other antihypertensive agents may increase the hypotensive action of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension. Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan with rifampicin (inducer of metabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).

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

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

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

Pregnancy

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 medicinal products. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3). Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

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

Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Losartan has been evaluated in clinical studies as follows:
• in controlled clinical trials in approximately 3300 adult patients 18 years of age and older for essential hypertension,
• in a controlled clinical trial in 9193 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy
• in a controlled clinical trial in approximately 3900 patients 20 years of age and older with chronic heart failure
• in a controlled clinical trial in 1513 type 2 diabetic patients 31 years of age and older with proteinuria
• in a controlled clinical trial in 177 hypertensive paediatric patients 6 to 16 years of age

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

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

Hypertension

In controlled clinical trials of approximately 3300 adult patients 18 years of age and older, for essential hypertension with losartan, the following adverse reactions were reported
Nervous system disorders:
common: dizziness, vertigo
uncommon: somnolence, headache, sleep disorders

Cardiac disorder:
uncommon: palpitations, angina pectoris

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

Gastro-intestinal disorders:
uncommon: abdominal pain, obstipation

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

Investigations:
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan tablets. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium>5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials.

Hypertensive patients with left ventricular hypertrophy
In a controlled clinical trial in 9193 hypertensive patients 55 to 80 years of age, with left ventricular hypertrophy, the following adverse reactions were reported:
Nervous system disorders:
common: dizziness

Ear and labyrinth disorders:
common: vertigo

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

Chronic heart failure
In a controlled clinical trial in approximately 3900 patients 20 years of age and older, with cardiac insufficiency, the following adverse reactions were reported:
Nervous system disorders:
uncommon: dizziness, headache
rare: paraesthesia

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

Vascular disorders:
uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
uncommon: dyspnoea

Gastro-intestinal disorders:
uncommon: diarrhoea, nausea, vomiting

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

General disorders and administration site conditions:
uncommon: asthenia/fatigue
Investigations:
uncommon: increase in blood urea, serum creatinine and serum potassium has been reported.

Hypertension and type 2 diabetes with renal disease
In a controlled clinical trial in 1513 type 2 diabetic patients 31 years of age and older, with
proteinuria (RENAAL study, see section 5.1), the most common drug-related adverse events
which were reported for losartan are as follows:

Nervous system disorders:
common: dizziness

Vascular disorders:
common: hypotension

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

Investigations:
common: hypoglycaemia, hyperkalaemia

The following adverse reactions occurred more often in patients receiving losartan than
placebo:
Blood and lymphatic system disorders:
not known: anaemia

Cardiac disorders:
not known: syncope, palpitations

Vascular disorders:
not known: orthostatic hypotension

Gastro-intestinal disorders:
not known: diarrhoea

Musculoskeletal and connective tissue disorders:
not known: back pain

Renal and urinary disorders:
not known: urinary tract infections

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

Investigations:
In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients
treated with losartan tablets developed hyperkalaemia>5.5 mEq/l and 3.4% of patients treated
with placebo.

Post-marketing experience
The following adverse reactions have been reported in post-marketing experience:
Blood and lymphatic system disorders:
not known: anaemia, thrombocytopenia

Ear and labyrinth disorders:
not known: tinnitus

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

Nervous system disorders:
not known: migraine

Respiratory, thoracic and mediastinal disorders:
not known: cough

Gastro-intestinal disorders:
not known: diarrhoea, pancreatitis

General disorders and administration site conditions:
not known: malaise

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

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

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

Reproductive system and breast disorders:
not known: erectile dysfunction/impotence

Renal and urinary disorders:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal
function including renal failure have been reported in patients at risk; these changes in renal
function may be reversible upon discontinuation of therapy (see section 4.4)

Psychiatric disorders:
not known: depression

Investigations:
not known: hyponatraemia

Paediatric population
The adverse reaction profile for paediatric patients appears to be similar to that seen in adult
patients. Data in the paediatric population are limited.

4.9 Overdose

Symptoms of intoxication
No case of overdose has been reported. The most likely symptoms, depending on the extent of
overdose, are hypotension, tachycardia, possibly bradycardia.

Treatment of intoxication
Measures are depending on the time of medicinal product intake and kind and severity of
symptoms. Stabilisation of the cardiovascular system should be given priority. After oral
intake, the administration of a sufficient dose of activated charcoal is indicated. Afterwards,
close monitoring of the vital parameters should be performed. Vital parameters should be
corrected if necessary.

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
ATC code: C09C A
Losartan is a synthetic oral angiotensin II receptor (type AT₁) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT₁ receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

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

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

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

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

**Hypertension studies**

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

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

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

**LIFE Study**

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

The mean length of follow up was 4.8 years.

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

Race
In the LIFE Study black patients treated with losartan had a higher risk of suffering the primary combined endpoint, i.e. a cardiovascular event (e.g. cardiac infarction, cardiovascular death) and especially stroke, than the black patients treated with atenolol. Therefore the results observed with losartan in comparison with atenolol in the LIFE study with regard to cardiovascular morbidity/mortality do not apply for black patients with hypertension and left ventricular hypertrophy.

RENAAL study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist losartan RENAAL study was a controlled clinical study conducted worldwide in 1513 Type 2 diabetic patients with proteinuria, with or without hypertension. 751 patients were treated with losartan. The objective of the study was to demonstrate a nephroprotective effect of losartan potassium over and above the benefit of lowering blood pressure.

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

Investigators were instructed to titrate the study medication to 100 mg daily as appropriate; 72 % of patients were taking the100 mg daily dose for the majority of the time. Other antihypertensive agents (diuretics, calcium antagonists, alpha- and beta- receptor blockers and also centrally acting antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed up for up to 4.6 years (3.4 years on average).

The primary endpoint of the study was a composite endpoint of doubling of the serum creatinine end-stage renal failure (need for dialysis or transplantation) or death.

The results showed that the treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 6.1% risk reduction (p = 0.022) in the number of patients reaching the primary composite endpoint. For the following individual and combined components of the primary endpoint, the results showed a significant risk reduction in the group treated with losartan: 25.3% risk reduction for doubling of the serum creatinine (p = 0.006); 28.6% risk reduction for end-stage renal failure (p = 0.002); 19.9% risk reduction for end-stage renal failure or death (p = 0.009); 21.0% risk reduction for doubling of serum creatinine or end-stage renal failure (p = 0.01).

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

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

In the ELITE II Study losartan 50 mg once daily (starting dose 12.5 mg, increased to 25 mg, then 50 mg once daily) was compared with captopril 50 mg three times daily (starting dose 12.5 mg, increased to 25 mg and then to 50 mg three times daily). The primary endpoint of this prospective study was the all-cause mortality.
In this study, 3152 patients with heart failure (NYHA Class II-IV) were followed for almost two years (median: 1.5 years) in order to determine whether losartan is superior to captopril in reducing all cause mortality. The primary endpoint did not show any statistically significant difference between losartan and captopril in reducing all cause mortality.

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

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

Paediatric Population

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> 20 kg and a glomerular filtration rate> 30 ml/ min/ 1.73 m². Patients who weighed> 20kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed> 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

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

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

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

In hypertensive (N=60) and normotensive (N=246) children with proteinuria, the effect of losartan on proteinuria was evaluated in a 12-week placebo- and active-controlled (amlodipine) clinical study. Proteinuria was defined as urinary protein/creatinine ratio of ≥ 0.3. The hypertensive patients (ages 6 through 18 years) were randomised to receive either losartan (n=30) or amlodipine (n=30). The normotensive patients (ages 1 through 18 years) were randomised to receive either losartan (n=122) or placebo (n=124). Losartan was given at doses of 0.7 mg/kg to 1.4 mg/kg (up to maximum dose of 100 mg per day). Amlodipine was given at doses of 0.05 mg/kg to 0.2 mg/kg (up to a maximum dose of 5 mg per day).

Overall, after 12 weeks of treatment, patients receiving losartan experienced a statistically significant reduction from baseline in proteinuria of 36% versus 1% increase in placebo/amlodipine group (p<0.001). Hypertensive patients receiving losartan experienced a reduction from baseline proteinuria of -41.5% (95% CI -29.9; -51.1) versus +2.4% (95% CI -22.2; 14.1) in the amlodipine group. The decline in both systolic blood pressure and diastolic blood pressure was greater in the losartan group (-5.5/-3.8 mmHg) versus the amlodipine group (-0.1/+0.8 mm Hg). In normotensive children a small decrease in blood pressure was observed in the losartan group (-3.7/-3.4 mm Hg) compared to placebo. No significant correlation between the decline in proteinuria and blood pressure was noted, however it is possible that the decline in blood pressure was responsible, in part, for the
decline in proteinuria in the losartan treated group. Long-term effects of reduction of proteinuria in children have not been studied.

5.2 Pharmacokinetic properties

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

Distribution
Both losartan and its active metabolite are ≥ 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Biotransformation
About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about 1% of individuals studied.

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

Elimination
Plasma clearance of losartan and its active metabolite is 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 excretions contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of 14C-labelled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58%/ 50% in the faeces.

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

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

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

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

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

Neither losartan nor the active metabolite can be removed by haemodialysis.
Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses).

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

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Maize starch
Microcrystalline cellulose
Purified Talc
Colloidal Anhydrous Silica
Sodium Starch Glycollate (Type A)
Magnesium Stearate
Hypermellose
Macrogol 6000
Titanium dioxide E171

6.2 Incompatibilities
Not Applicable.

6.3 Shelf life
2 years

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

6.5 Nature and contents of container
Al/PVC Blister strip of 14 tablets.
Blister strips packaged in an outer carton to give pack sizes of 28, 56, and 84 tablets.
Not all pack sizes may be marketed.

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

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Limited
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0244
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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10 DATE OF REVISION OF THE TEXT
23/03/2011
UKPAR Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets

PL 17907/0242-4

PATIENT INFORMATION LEAFLET

1. WHAT LOSARTAN POTASSIUM TABLETS ARE AND WHAT IT IS USED FOR

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

Losartan Potassium Tablets are used:

- in patients with high blood pressure (hypertension) in adults and in children and adolescents 6-15 years of age
- to protect the kidneys in hypertension type 2 diabetic patients with microalbuminuria who are on treatment with an ACE inhibitor
- in patients with chronic heart failure when therapy with specific medicines (angiotensin-receptor blockers, agent-induced enzyme inhibitors (ACE inhibitors, medicines used to lower blood pressure) is not considered suitable by your doctor. If your heart failure has been stabilised with an ACE inhibitor, you should not be switched to Losartan.
- in patients with high blood pressure and a thickening of the left ventricle. Losartan potassium has been shown to decrease the risk of stroke (CLUE Indications).
UKPAR Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets

If you take more Losartan Potassium Film-coated Tablets than you should

If you accidentally take too many tablets, contact your doctor immediately.

Symptoms of overdose are low blood pressure, increased heart rate, possibly decreased heart rate.

If you forget to take Losartan Potassium Film-coated Tablets

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

4. POSSIBLE SIDE EFFECTS

Use of medicines, Losartan Potassium Film-coated Tablets can cause side effects, although not everybody will have them.

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

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

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

The side effects of medicines are classified as follows:

Very common:
- affects more than 1 in 10
- common:
- affects 1 to 10 in 100
- uncommon:
- affects 1 to 10 in 1,000
- rare:
- affects less than 1 in 10,000
- very rare:
- affects less than 1 in 10,000 patients
- not known:
- frequency cannot be estimated from the available data.

The following side effects have been reported with Losartan:

Common:
- dizziness
- low blood pressure
- palpitations
- nausea
- headache
- sleep disorders
- feeling of increased heart rate (palpitations)
- severe chest pain (angina pectoris).

- low blood pressure (especially after excessive loss of water from the body within 8 to 12 hours and if less than 1 in 10,000 patients
- dizziness, feeling faint, dizziness, dizziness
- palpitations, heart rate
- headache, dizziness
- severe heart rate (angina pectoris)
- shortness of breath (frequent
- abdominal pain
- constipation
- diarrhoea
- nausea
- vomiting
- heartburn
- urinary incontinence
- weight loss
- sleep disorders
- palpitations
- feeling of increased heart rate (palpitations)
- severe chest pain (angina pectoris).

- ringing, buzzing, hearing, or holding in the ears (dizziness).

Side effects in children are similar to those seen in adults.

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

5. HOW TO STORE LOSARTAN POTASSIUM FILM-COATED TABLETS

- Keep out of the reach of children.

- Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

- Do not use Losartan Potassium after the expiry date which is marked on the container. The expiry date refers to the last day of that month. Do not take tablets in the original packaging.

- Do not open the tablet pack until you are ready to take the medication.

- Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Losartan Potassium Film-coated Tablets contains

The active substance is Losartan potassium.

Each Losartan potassium Film-coated Tablet contains 25 mg of Losartan potassium.

Each Losartan Potassium 50 mg Film-coated Tablet contains 50 mg of Losartan potassium.

Each Losartan Potassium Tablet contains 100 mg of Losartan potassium.

The other ingredients are maize starch, microcrystalline cellulose, purified talc, colloidal anhydrous silica, sodium starch glycolate, magnesium stearate, hypromellose, croscarmellose sodium, hydroxypropyl cellulose.

What Losartan Potassium Bombs like and contents of the pack

- 25 mg Film-coated Tablets in blister packs of 10, 20, 30, 60, 90, 120.

- 50 mg Film-coated Tablets in blister packs of 10, 20, 30, 60, 90, 120.

- 100 mg Film-coated Tablets in blister packs of 10, 20, 30, 60, 90, 120.

The tablets are packed in packs of 3, 6, 9, 12, 18, 27, 36, 72, and 108 tablets.

Not all pack sizes may be available.

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Losartan Potassium 25 mg Film-coated Tablet, PL 17907/0242
Losartan Potassium 50 mg Film-coated Tablet, PL 17907/0243
Losartan Potassium 100 mg Film-coated Tablet, PL 17907/0244

To request a copy of this booklet in Braille, large print or audio format, please contact the Product Manager at the address or telephone, fax, email above.

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