LOSARTAN POTASSIUM 12.5MG FILM-COATED TABLETS (PL 18110/0019)

LOSARTAN POTASSIUM 25MG FILM-COATED TABLETS (PL 18110/0002)

LOSARTAN POTASSIUM 50MG FILM-COATED TABLETS (PL 18110/0003)

LOSARTAN POTASSIUM 100MG FILM-COATED TABLETS (PL 18110/0004)

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TABLE OF CONTENTS

LOSARTAN POTASSIUM 12.5MG FILM-COATED TABLETS (PL 18110/0019)

LOSARTAN POTASSIUM 25MG FILM-COATED TABLETS (PL 18110/0002)

LOSARTAN POTASSIUM 50MG FILM-COATED TABLETS (PL 18110/0003)

LOSARTAN POTASSIUM 100MG FILM-COATED TABLETS (PL 18110/0004)

LAY SUMMARY

On 26th November 2009, the MHRA granted Chanelle Medical (UK) Limited Marketing Authorisations (licences) for the medicinal products Losartan Potassium 12.5mg, 25mg, 50mg and 100mg Film-Coated Tablets. These are prescription-only medicines that are used in the treatment of high blood pressure.

Losartan belongs to a group of medicines called angiotensin-receptor antagonists Angiotensin is a naturally occurring chemical in the body that binds to receptors in blood vessels, causing them to tighten and thus blood pressure to increase. Losartan blocks the effects of angiotensin, causing blood vessels to relax (which lowers blood pressure).

In patients with type 2 diabetes, where there has been damage to the kidneys, losartan can provide kidney protection by blocking the harmful effects of angiotensin II and slowing the worsening of kidney damage. Losartan potassium can also be used to treat chronic heart failure, if another medicine called an ACE inhibitor is not considered suitable. It can also be used to treat patients with high blood pressure and a thickening of the left ventricle of the heart, to reduce risk of stroke.

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

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LOSARTAN POTASSIUM 25MG FILM-COATED TABLETS (PL 18110/0002)

LOSARTAN POTASSIUM 50MG FILM-COATED TABLETS (PL 18110/0003)

LOSARTAN POTASSIUM 100MG FILM-COATED TABLETS (PL 18110/0004)

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Losartan Potassium 12.5mg, 25mg, 50mg and 100mg Film-Coated Tablets (PL 18110/0002-4 and 0019) to Chanelle Medical (UK) Limited on 26th November 2009. The products are prescription-only medicines for the:

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

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

The products contain the active ingredient losartan potassium, a competitive and selective angiotensin II (type AT_1) receptor antagonist that inhibits hypertensive effects, especially those related to vasoconstriction and aldosterone release.

PHARMACEUTICAL ASSESSMENT

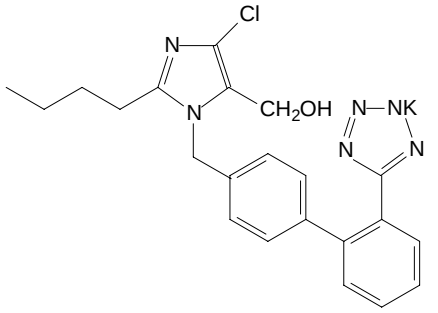
DRUG SUBSTANCE

INN: Losartan Potassium

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

Molecular Formula: $C_{22}H_{22}ClKN_6O$

Structure:



Molecular Weight: 461.01

Appearance: A white to off-white powder, freely soluble in water, soluble in ethanol and methanol, and practically insoluble in chloroform.

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

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

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

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

Based on stability data provided, a suitable retest period has been set for the active substance.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of pharmaceutical excipients microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, hypromellose (E464), polyoxyethylene stearate and titanium dioxide.

All excipients are controlled in-line with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph.

None of the excipients contain materials of animal or human origin. No genetically modified organisms were used in the production of any of the excipients.

Pharmaceutical development

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

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

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

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

Manufacturing Process

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

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

Finished Product Specification

The finished product specifications proposed for all strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System

Product is packaged in polyethylene/polyvinylchloride/aluminium/polyvinylidene chloride blisters in pack sizes of 28 tablets. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product

Stability studies were performed in accordance with current guidelines, using product manufactured by the proposed finished product manufacturer and in the packaging

proposed for marketing. The results support a shelf-life of 3 years, with no specific storage conditions.

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

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

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

Pharmaceutical Expert Report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

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.

A suitable justification has been provided for not submitting a risk management plan for these products.

CONCLUSION
It is recommended that marketing authorisations are granted for these applications.

PRECLINICAL ASSESSMENT

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

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

With the exception of the below bioequivalence study, no new pharmacokinetic data have been submitted and none are required for applications of this type.

Bioequivalence

A randomised, open label, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioequivalence study to compare Losartan Potassium 50mg Tablets (test) versus Cozaar 50mg Tablets (reference) in healthy fasted volunteers.

A single dose of test or reference study drug was administered with 240ml of water after an overnight fast. Blood samples were taken pre- and up to 36 hours post dose. Each treatment arm was separated by a 7-day washout period.

Results

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

Variable	Test	Reference	Point Estimate (test/reference) (%)	90 % C.I.
Losartan				
C_{max} (ng/ml)	212 ± 122	225 ± 118	94.9	83.4– 108.1
$AUC_{(0-t)}$ (ngh/ml)	443 ± 206	454 ± 211	98.0	95.3 – 100.8
$AUC_{(0-inf)}$ (ngh/ml)	453 ± 215	464 ± 218	98.0	95.2 – 100.7
T_{max} (h)	1.1 ± 0.7	1.3 ± 0.8	-	-
T_{el} (h)	2.8 ± 1.5	2.7 ± 1.2	-	-
[redacted]				
Carboxylosartan (active metabolite)				
C_{max} (ng/ml)	242 ± 105	235 ± 105	101.7	97.2 – 106.4
$AUC_{(0-t)}$ (ngh/ml)	1805 ± 642	1787 ± 643	99.9	97.1 – 102.8
$AUC_{(0-inf)}$ (ngh/ml)	1832 ± 650	1815 ± 650	100.0	97.4 – 102.8
T_{max} (h)	4.0 ± 1.0	4.0 ± 1.0	-	-
T_{el} (h)	6.3 ± 1.3	6.1 ± 1.0	-	-

Mean ± SD represented

Conclusions

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

As these products meet all the criteria as specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 50mg strength can be extrapolated to the 12.5mg, 25mg and 100mg strength tablets.

PHARMACODYNAMICS

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

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

SAFETY
No new or unexpected safety concerns were raised during the bioequivalence study.

EXPERT REPORTS
A clinical expert report is provided, written by an appropriately qualified physician. It is a satisfactory summary of the clinical aspects of the dossier.

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

PATIENT INFORMATION LEAFLET (PIL)
The PIL has been provided and is satisfactory.

LABELLING
All labelling provided is satisfactory.

APPLICATION FORM (MAA)
The MAA forms are satisfactory.

DISCUSSION
Bioequivalence has been satisfactorily demonstrated for the 50mg product in accordance with CPMP criteria. As these products meet all the criteria as specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 50mg strength can be extrapolated to the 12.5mg, 25mg and 100mg strength tablets.

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

MEDICAL CONCLUSION
The grant of marketing authorisations for these products is recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

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

PRECLINICAL

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

EFFICACY

Bioequivalence has been demonstrated between the applicant's Losartan Potassium 50mg Tablets and the originator product Cozaar 50mg Tablets. As these products meet all the criteria as specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 50mg strength can be extrapolated to the 12.5mg, 25mg and 100mg strengths also.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent.

BENEFIT-RISK ASSESSMENT

The quality of these products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with losartan potassium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

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LOSARTAN POTASSIUM 100MG FILM-COATED TABLETS (PL 18110/0004)

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 18th December 2007 (15th June 2009 for the 12.5mg strength)
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 13th January 2008 (30th June 2009 for the 12.5mg strength)
3	Following assessment of the applications the MHRA requested further information relating to the dossier on 17th April 2008 and 21st April 2009 for the 25, 50 and 100mg strengths, and 30th July 2009 for all four strengths
4	The applicant responded to the MHRA's requests, providing further information on 13th March 2009 and 11th May 2009 for the 25, 50 and 100mg strengths, and 23rd September 2009 for all four strengths
5	The applications were determined on 26th November 2009

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LOSARTAN POTASSIUM 25MG FILM-COATED TABLETS (PL 18110/0002)

LOSARTAN POTASSIUM 50MG FILM-COATED TABLETS (PL 18110/0003)

LOSARTAN POTASSIUM 100MG FILM-COATED TABLETS (PL 18110/0004)

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium 25 mg Film-Coated Tablets
Losartan Potassium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Losartan Potassium 25 mg Film-Coated Tablets
Each tablet contains 25 mg of losartan potassium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-Coated Tablet

Losartan Potassium 25 mg Film-Coated Tablet is supplied as white, oblong, biconvex, non-scored film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension

Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5g/day as part of an antihypertensive treatment.

Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, *especially cough*, or contraindication. Patients who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 *Pharmacodynamic studies, Hypertension studies, Race*)

4.2 Posology and method of administration

Losartan Potassium may be administered with or without food.
Losartan Tablets should be swallowed with a glass of water.

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

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).

Paediatric hypertension:
There are limited data on the efficacy and safety of Losartan Potassium in children and adolescents aged 6-16 years for the treatment of hypertension (see 5.1 “Pharmacodynamic Properties”). Limited pharmacokinetic data are available in hypertensive children above one month of age (see 5.2 “Pharmacokinetic Properties”). For patients who are able to 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 50mg once daily. Dosage should be adjusted according to blood pressure response.

In patients >50 kg, the usual dose is 50mg once daily. In exceptional cases the dose can be increased 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 Potassium is not recommended for use in children under 6 years old as limited data are available in these patient groups.

Losartan Potassium is not recommended in children with glomerular filtration <30ml/min/1.73m^2 as no data are available (see also section 4.4).

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

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

Heart Failure:
The usual initial dose of Losartan Potassium in patients with heart failure is 12.5mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5mg daily, 25mg daily, 50mg daily) to the usual maintenance dose of 50mg 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 Potassium once daily. A low dose of hydrochlorothiazide may be added and/or the dose of Losartan Potassium may be increased to 100 mg once daily based on blood pressure response.

Use in the patients with intravascular volume depletion:
For patients who have 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 "Special warnings and precautions for use").

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

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

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

4.3 Contraindications

Hypersensitivity to any of the ingredients of this product (see section 4.4 and 6.1).

Losartan Potassium is contraindicated in the second and third trimesters of pregnancy (see section 4.4 and 4.6).

Lactation (see section 4.6).

Severe hepatic impairment.

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema. Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8 "Undesirable effects").

Hypotension and electrolyte/fluid imbalance:
Symptomatic hypotension, especially after the first dose and after increasing the dose, may occur in patients who are volume depleted and/or sodium depleted (e.g. by high dose diuretic therapy, dietary salt restriction, diarrhoea or vomiting). These conditions should be corrected prior to administration of Losartan Potassium, or a lower starting dose should be used (see section 4.2. "Posology and method of administration"). This also applies to children.

Electrolyte imbalances:
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with Losartan Potassium as compared to the placebo group (see section 4.8 "Undesirable effects" – Hypertension and type 2 diabetes with renal disease – investigations and Post-marketing experience – investigations). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially in patients with heart failure and a creatinine clearance between 30-50 ml/min.

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

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

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

Renal function impairment:
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan Potassium 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 function impairment:
Losartan is not recommended in children with a glomerular filtration rate < 30ml/min/1.73m^2 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 been shown to impair renal function. Concomitant use is therefore not recommended.

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

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

Coronary heart disease and cerebrovascular disease:
As with any anti-hypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

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

There is insufficient 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 and mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

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 other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in black hypertensive population.

4.5 Interaction with other medicinal products and other forms of interaction
Other antihypertensive agents may increase the hypotensive effect of losartan. Concomitant use with these drugs that lower blood pressure, as a main or side-effect, may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the acive 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 metabolic enzymes) resulted in a 40% reduction in plasma level of the active metabolite. The clinical relevance of this effect is not known. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).

As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium (e.g. potassium-sparing diuretics such as 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

Potassium should be undertaken with caution. If this combination is essential, serum lithium level monitoring is recommended during concomitant use.

Combination with NSAIDs: When angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory medicinal products (e.g. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the anti-hypertensive 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 second and third trimesters of pregnancy (see sections 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 are no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. 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 (see section 4.3).

Losartan exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia); please refer to section 5.3 ("Preclinical Safety Data").

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

Lactation:
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, losartan is contra-indicated during breast-feeding (see section 4.3).

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

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 dose is increased.

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data) including isolated reports.

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

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

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

Cardiac disorders:
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

Hypertensive patients with left ventricular hypertrophy
In controlled clinical trials in hypertensive patients 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 patients with cardiac insuficiency the following adverse events were reported:

Nervous system disorders:
Uncommon: dizziness, headache
Rare: paraesthesia

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

Vascular disorders:
Uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
Uncommon: dyspnoea

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

Skin and sub-cutaneous tissue disorders:
Uncommon: urticaria, pruritus, rash

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

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

Nervous system disorders:
Common: dizziness

Vascular disorders:
Common: hypotension

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

Investigations:
Common: hypoglycaemia, hyperkalaemia

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

Cardiac disorders:
Not known: syncope, palpitations

Vascular disorders:
Not known: orthostatic hypertension

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

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

Blood and lymphatic system disorders:
Not known: anaemia, thrombocytopenia

Immune system disorders:
Rare: hypersensitivity – anaphylactic reactions, angiooedema 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 angiooedema had been reported in the past in connection with 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

Hepatobiliary disorders:
Rare: hepatitis
Not known: liver function abnormalities

Skin and sub-cutaneous tissue disorders:
Not known: urticaria, pruritus, rash

Musculoskeletal and connective tissue disorders
Not known: myalgia, arthralgia.

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

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

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

The adverse experience profile for 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:
There is no experience with overdose in man so far. The most likely symptoms, depending on the extent of overdosage would be hypotension, tachycardia and possibly bradycardia.

Treatment of intoxication:
Measures should depend on the time of drug intake and kind and severity of symptoms. Stabilisation of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Thereafter, 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: CO9CA01. Pharmacotherapeutic Group: Angiotensin II Receptor Antagonists.

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 vitro, both losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.

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

Both Losartan and its principal active metabolite have a far greater affinity for the AT_1-receptor than for the AT_2-receptor. The active metabolite is 10 to 40 times more active than Losartan on a weight for weight basis.

Hypertension studies:
In controlled clinical studies, once daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurement 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 of blood pressure (rebound). Despite the significant decrease in blood pressure, administration of Losartan potassium had no clinically significant effect on heart rate.

Losartan is equally effective in males and females, and in younger (below 65 years of age) 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 50mg or once daily atenolol 50mg. If target blood pressure (< 140/90 mmHg) was not reached, hydrochlorothiazide 12.5mg was added first and, if needed, the dose of Losartan or atenolol was increased to 100 mg once daily. Other antihypertensives (excluding ACE-inhibitors), angiotensin II antagonists or beta-blockers were added if necessary to reach the target blood pressure.

The mean length of follow up was 4.8 years.

The primary end-point 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, an the black patients treated with atenonol. Therefore the results observed for losartan in comparison with atenolol, regarding 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 study, conducted worldwide, of 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 50mg once daily, titrated if necessary, to achieve blood pressure response, or to receive placebo, on a background of conventional hypertensive therapy (excluding ACE-inhibitors and angiotensin II antagonists). Investigators were instructed to titrate the study medication to 100mg daily as appropriate (72% of patients received 100mg daily the majority of the time). Other anti-hypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting anti-hypertensives) 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 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 end point, the results showed significant risk reduction in the group treated with losartan: 25.3% risk reduction for doubling of serum creatinine (p=0.006); 28.6% risk reduction for end-stage renal disease (p=0.002); 19.9% risk reduction for end-stage renal failure or death (p=0.009); 21.0% risk reduction for doubling of serum creatinine or end-stage renal failure (p=0.01).

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

ELITE I and ELITE II Study
In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between 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 which is described in the following -

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

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

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

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

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/1.73m2. 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 (2.5mg and 5mg), corresponding to an average daily dose of 0.07mg/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.

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 Potassium 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

Around 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 is attributed primarily 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 of up to 200 mg.

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

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of 14C-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 those seen in young male volunteers (see section 4.2 and 4.4).

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2 times higher than in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients >1 month to <16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg Losartan Potassium (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 pre-school 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 repeat dose toxicity studies, the administration of losartan induced a decrease in 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 histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse effects on late foetal development, resulting in foetal death and malformations.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Each Losartan Potassium 25 mg Film-Coated Tablet contains the following excipients:
microcrystalline cellulose (E460)
sodium stearyl fumarate
croscarmellose sodium
colloidal anhydrous silica
hypromellose (E464)
polyoxyethylene stearate
titanium dioxide (E171)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Three years.

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

6.5 Nature and contents of container

Losartan Potassium 25 mg Tablet is supplied in PVC/PE/PVDC aluminium blisters. Pack of 28 tablets.

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

Chanelle Medical U.K. Limited
Stanford Bridge Farm
Station Road
Pluckley
Ashford
Kent
TN27 0RU

8 MARKETING AUTHORISATION NUMBER(S)

PL 18110/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/11/2009

10 DATE OF REVISION OF THE TEXT

26/11/2009

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium 50 mg Film-Coated Tablets
Losartan Potassium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Losartan Potassium 50 mg Film-Coated Tablets
Each tablet contains 50 mg of losartan potassium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-Coated Tablet

Losartan Potassium 50 mg Film-Coated Tablet is supplied as white, oval, biconvex, non-scored film-coated tablet. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension

Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5g/day as part of an antihypertensive treatment.

Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, *especially cough*, or contraindication. Patients who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 *Pharmacodynamic studies, Hypertension studies, Race*)

4.2 Posology and method of administration

Losartan Potassium may be administered with or without food.
Losartan Tablets should be swallowed with a glass of water.

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

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).

Paediatric hypertension:
There are limited data on the efficacy and safety of Losartan Potassium in children and adolescents aged 6-16 years for the treatment of hypertension (see 5.1 “Pharmacodynamic Properties”). Limited pharmacokinetic data are available in hypertensive children above one month of age (see 5.2 “Pharmacokinetic Properties”). For patients who are able to 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 50mg once daily. Dosage should be adjusted according to blood pressure response.

In patients >50 kg, the usual dose is 50mg once daily. In exceptional cases the dose can be increased 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 Potassium is not recommended for use in children under 6 years old as limited data are available in these patient groups.
Losartan Potassium is not recommended in children with glomerular filtration <30ml/min/1.73m^2 as no data are available (see also section 4.4).

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

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

Heart Failure:
The usual initial dose of Losartan Potassium in patients with heart failure is 12.5mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5mg daily, 25mg daily, 50mg daily) to the usual maintenance dose of 50mg 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 Potassium once daily. A low dose of hydrochlorothiazide may be added and/or the dose of Losartan Potassium may be increased to 100 mg once daily based on blood pressure response.

Use in the patients with intravascular volume depletion:
For patients who have 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 "Special warnings and precautions for use").

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

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

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

4.3 Contraindications

Hypersensitivity to any of the ingredients of this product (see section 4.4 and 6.1).

Losartan Potassium is contraindicated in the second and third trimesters of pregnancy (see section 4.4 and 4.6).

Lactation (see section 4.6).

Severe hepatic impairment.

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema. Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8 "Undesirable effects").

Hypotension and electrolyte/fluid imbalance:
Symptomatic hypotension, especially after the first dose and after increasing the dose, may occur in patients who are volume depleted and/or sodium depleted (e.g. by high dose diuretic therapy, dietary salt restriction, diarrhoea or vomiting). These conditions should be corrected prior to administration of Losartan Potassium, or a lower starting dose should be used (see section 4.2. "Posology and method of administration"). This also applies to children.

Electrolyte imbalances:
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with Losartan Potassium as compared to the placebo group (see section 4.8 "Undesirable effects" – Hypertension and type 2 diabetes with renal disease – investigations and Post-marketing experience – investigations). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially in patients with heart failure and a creatinine clearance between 30-50 ml/min.

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

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

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

Renal function impairment:
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan Potassium 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 function impairment:
Losartan is not recommended in children with a glomerular filtration rate < 30ml/min/1.73m^2 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 been shown to impair renal function. Concomitant use is therefore not recommended.

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

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

Coronary heart disease and cerebrovascular disease:
As with any anti-hypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

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

There is insufficient 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 and mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

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 other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in black hypertensive population.

4.5 Interaction with other medicinal products and other forms of interaction
Other antihypertensive agents may increase the hypotensive effect of losartan. Concomitant use with these drugs that lower blood pressure, as a main or side-effect, may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the acive 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 metabolic enzymes) resulted in a 40% reduction in plasma level of the active metabolite. The clinical relevance of this effect is not known. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).

As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium (e.g. potassium-sparing diuretics such as 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

Potassium should be undertaken with caution. If this combination is essential, serum lithium level monitoring is recommended during concomitant use.

Combination with NSAIDs: When angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory medicinal products (e.g. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the anti-hypertensive 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 second and third trimesters of pregnancy (see sections 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 are no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. 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 (see section 4.3).

Losartan exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia); please refer to section 5.3 ("Preclinical Safety Data").

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

Lactation:
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, losartan is contra-indicated during breast-feeding (see section 4.3).

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

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 dose is increased.

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data) including isolated reports.

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

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

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

Cardiac disorders:
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

Hypertensive patients with left ventricular hypertrophy
In controlled clinical trials in hypertensive patients 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 patients with cardiac insuficiency the following adverse events were reported:

Nervous system disorders:
Uncommon: dizziness, headache
Rare: paraesthesia

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

Vascular disorders:
Uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
Uncommon: dyspnoea

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

Skin and sub-cutaneous tissue disorders:
Uncommon: urticaria, pruritus, rash

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

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

Nervous system disorders:
Common: dizziness

Vascular disorders:
Common: hypotension

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

Investigations:
Common: hypoglycaemia, hyperkalaemia

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

Cardiac disorders:
Not known: syncope, palpitations

Vascular disorders:
Not known: orthostatic hypertension

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

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

Blood and lymphatic system disorders:
Not known: anaemia, thrombocytopenia

Immune system disorders:
Rare: hypersensitivity – anaphylactic reactions, angiooedema 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 angiooedema had been reported in the past in connection with 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

Hepatobiliary disorders:
Rare: hepatitis
Not known: liver function abnormalities

Skin and sub-cutaneous tissue disorders:
Not known: urticaria, pruritus, rash

Musculoskeletal and connective tissue disorders
Not known: myalgia, arthralgia.

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

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

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

The adverse experience profile for 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:
There is no experience with overdose in man so far. The most likely symptoms, depending on the extent of overdosage would be hypotension, tachycardia and possibly bradycardia.

Treatment of intoxication:
Measures should depend on the time of drug intake and kind and severity of symptoms. Stabilisation of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Thereafter, 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: CO9CA01. Pharmacotherapeutic Group: Angiotensin II Receptor Antagonists.

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 vitro, both losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.

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

Both Losartan and its principal active metabolite have a far greater affinity for the AT_1-receptor than for the AT_2-receptor. The active metabolite is 10 to 40 times more active than Losartan on a weight for weight basis.

Hypertension studies:
In controlled clinical studies, once daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurement 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 of blood pressure (rebound). Despite the significant decrease in blood pressure, administration of Losartan potassium had no clinically significant effect on heart rate.

Losartan is equally effective in males and females, and in younger (below 65 years of age) 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 50mg or once daily atenolol 50mg. If target blood pressure (< 140/90 mmHg) was not reached, hydrochlorothiazide 12.5mg was added first and, if needed, the dose of Losartan or atenolol was increased to 100 mg once daily. Other antihypertensives (excluding ACE-inhibitors), angiotensin II antagonists or beta-blockers were added if necessary to reach the target blood pressure.

The mean length of follow up was 4.8 years.

The primary end-point 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, an the black patients treated with atenonol. Therefore the results observed for losartan in comparison with atenolol, regarding 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 study, conducted worldwide, of 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 50mg once daily, titrated if necessary, to achieve blood pressure response, or to receive placebo, on a background of conventional hypertensive therapy (excluding ACE-inhibitors and angiotensin II antagonists). Investigators were instructed to titrate the study medication to 100mg daily as appropriate (72% of patients received 100mg daily the majority of the time). Other anti-hypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting anti-hypertensives) 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 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 end point, the results showed significant risk reduction in the group treated with losartan: 25.3% risk reduction for doubling of serum creatinine (p=0.006); 28.6% risk reduction for end-stage renal disease (p=0.002); 19.9% risk reduction for end-stage renal failure or death (p=0.009); 21.0% risk reduction for doubling of serum creatinine or end-stage renal failure (p=0.01).

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

ELITE I and ELITE II Study
In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between 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 which is described in the following -

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

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

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

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

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/1.73m^2. 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 (2.5mg and 5mg), corresponding to an average daily dose of 0.07mg/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.

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 Potassium 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

Around 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 is attributed primarily 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 of up to 200 mg.

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

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of 14C-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 those seen in young male volunteers (see section 4.2 and 4.4).

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2 times higher than in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients >1 month to <16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg Losartan Potassium (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 pre-school 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 repeat dose toxicity studies, the administration of losartan induced a decrease in 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 histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse effects on late foetal development, resulting in foetal death and malformations.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Each Losartan Potassium 50 mg Film-Coated Tablet contains the following excipients:
microcrystalline cellulose (E460)
sodium stearyl fumarate
croscarmellose sodium
colloidal anhydrous silica
hypromellose (E464)
polyoxyethylene stearate
titanium dioxide (E171)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Three years.

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

6.5 Nature and contents of container

Losartan Potassium 50 mg Tablet is supplied in PVC/PE/PVDC aluminium blisters. Pack of 28 tablets.

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

Chanelle Medical U.K. Limited
Stanford Bridge Farm
Station Road
Pluckley
Ashford
Kent
TN27 0RU

8 MARKETING AUTHORISATION NUMBER(S)

PL 18110/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/11/2009

10 DATE OF REVISION OF THE TEXT

26/11/2009

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium 100 mg Film-Coated Tablets
Losartan Potassium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Losartan Potassium 100 mg Film-Coated Tablets
Each tablet contains 100 mg of losartan potassium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-Coated Tablet

Losartan Potassium 100 mg Film-Coated Tablet is supplied as white, oblong, biconvex, non-scored film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension

Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5g/day as part of an antihypertensive treatment.

Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, *especially cough*, or contraindication. Patients who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 *Pharmacodynamic studies, Hypertension studies, Race*)

4.2 Posology and method of administration

Losartan Potassium may be administered with or without food.
Losartan Tablets should be swallowed with a glass of water.

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

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).

Paediatric hypertension:
There are limited data on the efficacy and safety of Losartan Potassium in children and adolescents aged 6-16 years for the treatment of hypertension (see 5.1 “Pharmacodynamic Properties”). Limited pharmacokinetic data are available in hypertensive children above one month of age (see 5.2 “Pharmacokinetic Properties”). For patients who are able to 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 50mg once daily. Dosage should be adjusted according to blood pressure response.

In patients >50 kg, the usual dose is 50mg once daily. In exceptional cases the dose can be increased 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 Potassium is not recommended for use in children under 6 years old as limited data are available in these patient groups.

Losartan Potassium is not recommended in children with glomerular filtration <30ml/min/1.73m^2 as no data are available (see also section 4.4).

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

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

Heart Failure:
The usual initial dose of Losartan Potassium in patients with heart failure is 12.5mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5mg daily, 25mg daily, 50mg daily) to the usual maintenance dose of 50mg 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 Potassium once daily. A low dose of hydrochlorothiazide may be added and/or the dose of Losartan Potassium may be increased to 100 mg once daily based on blood pressure response.

Use in the patients with intravascular volume depletion:
For patients who have 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 "Special warnings and precautions for use").

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

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

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

4.3 Contraindications

Hypersensitivity to any of the ingredients of this product (see section 4.4 and 6.1).

Losartan Potassium is contraindicated in the second and third trimesters of pregnancy (see section 4.4 and 4.6).

Lactation (see section 4.6).

Severe hepatic impairment.

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema. Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8 "Undesirable effects").

Hypotension and electrolyte/fluid imbalance:
Symptomatic hypotension, especially after the first dose and after increasing the dose, may occur in patients who are volume depleted and/or sodium depleted (e.g. by high dose diuretic therapy, dietary salt restriction, diarrhoea or vomiting). These conditions should be corrected prior to administration of Losartan Potassium, or a lower starting dose should be used (see section 4.2. "Posology and method of administration"). This also applies to children.

Electrolyte imbalances:
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with Losartan Potassium as compared to the placebo group (see section 4.8 "Undesirable effects" – Hypertension and type 2 diabetes with renal disease – investigations and Post-marketing experience – investigations). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially in patients with heart failure and a creatinine clearance between 30-50 ml/min.

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

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

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

Renal function impairment:
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan Potassium 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 function impairment:
Losartan is not recommended in children with a glomerular filtration rate < 30ml/min/1.73m^2 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 been shown to impair renal function. Concomitant use is therefore not recommended.

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

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

Coronary heart disease and cerebrovascular disease:
As with any anti-hypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

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

There is insufficient 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 and mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

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 other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in black hypertensive population.

4.5 Interaction with other medicinal products and other forms of interaction
Other antihypertensive agents may increase the hypotensive effect of losartan. Concomitant use with these drugs that lower blood pressure, as a main or side-effect, may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the acive 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 metabolic enzymes) resulted in a 40% reduction in plasma level of the active metabolite. The clinical relevance of this effect is not known. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).

As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium (e.g. potassium-sparing diuretics such as 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

Potassium should be undertaken with caution. If this combination is essential, serum lithium level monitoring is recommended during concomitant use.

Combination with NSAIDs: When angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory medicinal products (e.g. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the anti-hypertensive 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 second and third trimesters of pregnancy (see sections 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 are no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. 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 (see section 4.3).

Losartan exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia); please refer to section 5.3 ("Preclinical Safety Data").

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

Lactation:
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, losartan is contra-indicated during breast-feeding (see section 4.3).

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

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 dose is increased.

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data) including isolated reports.

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

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

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

Cardiac disorders:
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

Hypertensive patients with left ventricular hypertrophy
In controlled clinical trials in hypertensive patients 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 patients with cardiac insuficiency the following adverse events were reported:

Nervous system disorders:
Uncommon: dizziness, headache
Rare: paraesthesia

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

Vascular disorders:
Uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
Uncommon: dyspnoea

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

Skin and sub-cutaneous tissue disorders:
Uncommon: urticaria, pruritus, rash

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

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

Nervous system disorders:
Common: dizziness

Vascular disorders:
Common: hypotension

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

Investigations:
Common: hypoglycaemia, hyperkalaemia

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

Cardiac disorders:
Not known: syncope, palpitations

Vascular disorders:
Not known: orthostatic hypertension

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

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

Blood and lymphatic system disorders:
Not known: anaemia, thrombocytopenia

Immune system disorders:
Rare: hypersensitivity – anaphylactic reactions, angiooedema 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 angiooedema had been reported in the past in connection with 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

Hepatobiliary disorders:
Rare: hepatitis
Not known: liver function abnormalities

Skin and sub-cutaneous tissue disorders:
Not known: urticaria, pruritus, rash

Musculoskeletal and connective tissue disorders
Not known: myalgia, arthralgia.

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

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

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

The adverse experience profile for 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:
There is no experience with overdose in man so far. The most likely symptoms, depending on the extent of overdosage would be hypotension, tachycardia and possibly bradycardia.

Treatment of intoxication:
Measures should depend on the time of drug intake and kind and severity of symptoms. Stabilisation of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Thereafter, 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: CO9CA01. Pharmacotherapeutic Group: Angiotensin II Receptor Antagonists.

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 vitro, both losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.

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

Both Losartan and its principal active metabolite have a far greater affinity for the AT_1-receptor than for the AT_2-receptor. The active metabolite is 10 to 40 times more active than Losartan on a weight for weight basis.

Hypertension studies:
In controlled clinical studies, once daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurement 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 of blood pressure (rebound). Despite the significant decrease in blood pressure, administration of Losartan potassium had no clinically significant effect on heart rate.

Losartan is equally effective in males and females, and in younger (below 65 years of age) 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 50mg or once daily atenolol 50mg. If target blood pressure (< 140/90 mmHg) was not reached, hydrochlorothiazide 12.5mg was added first and, if needed, the dose of Losartan or atenolol was increased to 100 mg once daily. Other antihypertensives (excluding ACE-inhibitors), angiotensin II antagonists or beta-blockers were added if necessary to reach the target blood pressure.

The mean length of follow up was 4.8 years.

The primary end-point 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, an the black patients treated with atenonol. Therefore the results observed for losartan in comparison with atenolol, regarding 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 study, conducted worldwide, of 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 50mg once daily, titrated if necessary, to achieve blood pressure response, or to receive placebo, on a background of conventional hypertensive therapy (excluding ACE-inhibitors and angiotensin II antagonists). Investigators were instructed to titrate the study medication to 100mg daily as appropriate (72% of patients received 100mg daily the majority of the time). Other anti-hypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting anti-hypertensives) 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 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 end point, the results showed significant risk reduction in the group treated with losartan: 25.3% risk reduction for doubling of serum creatinine (p=0.006); 28.6% risk reduction for end-stage renal disease (p=0.002); 19.9% risk reduction for end-stage renal failure or death (p=0.009); 21.0% risk reduction for doubling of serum creatinine or end-stage renal failure (p=0.01).

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

ELITE I and ELITE II Study
In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between 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 which is described in the following -

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

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

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

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

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/1.73m2. 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 (2.5mg and 5mg), corresponding to an average daily dose of 0.07mg/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.

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 Potassium 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

Around 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 is attributed primarily 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 of up to 200 mg.

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

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of 14C-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 those seen in young male volunteers (see section 4.2 and 4.4).

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2 times higher than in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients >1 month to <16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg Losartan Potassium (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 pre-school 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 repeat dose toxicity studies, the administration of losartan induced a decrease in 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 histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse effects on late foetal development, resulting in foetal death and malformations.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Each Losartan Potassium 100 mg Film-Coated Tablet contains the following excipients:
microcrystalline cellulose (E460)
sodium stearyl fumarate
croscarmellose sodium
colloidal anhydrous silica
hypromellose (E464)
polyoxyethylene stearate
titanium dioxide (E171)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Three years.

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

6.5 Nature and contents of container

Losartan Potassium 100 mg Tablet is supplied in PVC/PE/PVDC aluminium blisters. Pack of 28 tablets.

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

Chanelle Medical U.K. Limited
Stanford Bridge Farm
Station Road
Pluckley
Ashford
Kent
TN27 0RU

8 MARKETING AUTHORISATION NUMBER(S)

PL 18110/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/11/2009

10 DATE OF REVISION OF THE TEXT

26/11/2009

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium 12.5 mg Film-Coated Tablets
Losartan Potassium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Losartan Potassium 12.5 mg Film-Coated Tablets
Each tablet contains 12.5 mg of losartan potassium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-Coated Tablet

Losartan Potassium 12.5 mg Film-Coated Tablet is supplied as white, oblong, biconvex, non-scored film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension

Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5g/day as part of an antihypertensive treatment.

Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, *especially cough*, or contraindication. Patients who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 *Pharmacodynamic studies, Hypertension studies, Race*)

4.2 Posology and method of administration

Losartan Potassium may be administered with or without food.
Losartan Tablets should be swallowed with a glass of water.

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

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).

Paediatric hypertension:
There are limited data on the efficacy and safety of Losartan Potassium in children and adolescents aged 6-16 years for the treatment of hypertension (see 5.1 “Pharmacodynamic Properties”). Limited pharmacokinetic data are available in hypertensive children above one month of age (see 5.2 “Pharmacokinetic Properties”). For patients who are able to 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 50mg once daily. Dosage should be adjusted according to blood pressure response.

In patients >50 kg, the usual dose is 50mg once daily. In exceptional cases the dose can be increased 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 Potassium is not recommended for use in children under 6 years old as limited data are available in these patient groups.

Losartan Potassium is not recommended in children with glomerular filtration <30ml/min/1.73m^2 as no data are available (see also section 4.4).

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

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

Heart Failure:
The usual initial dose of Losartan Potassium in patients with heart failure is 12.5mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5mg daily, 25mg daily, 50mg daily) to the usual maintenance dose of 50mg 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 Potassium once daily. A low dose of hydrochlorothiazide may be added and/or the dose of Losartan Potassium may be increased to 100 mg once daily based on blood pressure response.

Use in the patients with intravascular volume depletion:
For patients who have 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 "Special warnings and precautions for use").

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

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

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

4.3 Contraindications

Hypersensitivity to any of the ingredients of this product (see section 4.4 and 6.1).

Losartan Potassium is contraindicated in the second and third trimesters of pregnancy (see section 4.4 and 4.6).

Lactation (see section 4.6).

Severe hepatic impairment.

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema. Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8 "Undesirable effects").

Hypotension and electrolyte/fluid imbalance:
Symptomatic hypotension, especially after the first dose and after increasing the dose, may occur in patients who are volume depleted and/or sodium depleted (e.g. by high dose diuretic therapy, dietary salt restriction, diarrhoea or vomiting). These conditions should be corrected prior to administration of Losartan Potassium, or a lower starting dose should be used (see section 4.2. "Posology and method of administration"). This also applies to children.

Electrolyte imbalances:
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with Losartan Potassium as compared to the placebo group (see section 4.8 "Undesirable effects" – Hypertension and type 2 diabetes with renal disease – investigations and Post-marketing experience – investigations). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially in patients with heart failure and a creatinine clearance between 30-50 ml/min.

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

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

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

Renal function impairment:
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan Potassium 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 function impairment:
Losartan is not recommended in children with a glomerular filtration rate < 30ml/min/1.73m^2 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 been shown to impair renal function. Concomitant use is therefore not recommended.

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

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

Coronary heart disease and cerebrovascular disease:
As with any anti-hypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

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

There is insufficient 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 and mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

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 other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in black hypertensive population.

4.5 Interaction with other medicinal products and other forms of interaction
Other antihypertensive agents may increase the hypotensive effect of losartan. Concomitant use with these drugs that lower blood pressure, as a main or side-effect, may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the acive 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 metabolic enzymes) resulted in a 40% reduction in plasma level of the active metabolite. The clinical relevance of this effect is not known. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).

As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium (e.g. potassium-sparing diuretics such as 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

Potassium should be undertaken with caution. If this combination is essential, serum lithium level monitoring is recommended during concomitant use.

Combination with NSAIDs: When angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory medicinal products (e.g. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the anti-hypertensive 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 second and third trimesters of pregnancy (see sections 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 are no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. 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 (see section 4.3).

Losartan exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia); please refer to section 5.3 ("Preclinical Safety Data").

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

Lactation:
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, losartan is contra-indicated during breast-feeding (see section 4.3).

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

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 dose is increased.

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data) including isolated reports.

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

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

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

Cardiac disorders:
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

Hypertensive patients with left ventricular hypertrophy
In controlled clinical trials in hypertensive patients 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 patients with cardiac insuficiency the following adverse events were reported:

Nervous system disorders:
Uncommon: dizziness, headache
Rare: paraesthesia

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

Vascular disorders:
Uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
Uncommon: dyspnoea

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

Skin and sub-cutaneous tissue disorders:
Uncommon: urticaria, pruritus, rash

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

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

Nervous system disorders:
Common: dizziness

Vascular disorders:
Common: hypotension

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

Investigations:
Common: hypoglycaemia, hyperkalaemia

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

Cardiac disorders:
Not known: syncope, palpitations

Vascular disorders:
Not known: orthostatic hypertension

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

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

Blood and lymphatic system disorders:
Not known: anaemia, thrombocytopenia

Immune system disorders:
Rare: hypersensitivity – anaphylactic reactions, angiooedema 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 angiooedema had been reported in the past in connection with 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

Hepatobiliary disorders:
Rare: hepatitis
Not known: liver function abnormalities

Skin and sub-cutaneous tissue disorders:
Not known: urticaria, pruritus, rash

Musculoskeletal and connective tissue disorders
Not known: myalgia, arthralgia.

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

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

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

The adverse experience profile for 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:
There is no experience with overdose in man so far. The most likely symptoms, depending on the extent of overdosage would be hypotension, tachycardia and possibly bradycardia.

Treatment of intoxication:
Measures should depend on the time of drug intake and kind and severity of symptoms. Stabilisation of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Thereafter, 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: CO9CA01. Pharmacotherapeutic Group: Angiotensin II Receptor Antagonists.

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 vitro, both losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.

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

Both Losartan and its principal active metabolite have a far greater affinity for the AT_1-receptor than for the AT_2-receptor. The active metabolite is 10 to 40 times more active than Losartan on a weight for weight basis.

Hypertension studies:
In controlled clinical studies, once daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurement 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 of blood pressure (rebound). Despite the significant decrease in blood pressure, administration of Losartan potassium had no clinically significant effect on heart rate.

Losartan is equally effective in males and females, and in younger (below 65 years of age) 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 50mg or once daily atenolol 50mg. If target blood pressure (< 140/90 mmHg) was not reached, hydrochlorothiazide 12.5mg was added first and, if needed, the dose of Losartan or atenolol was increased to 100 mg once daily. Other antihypertensives (excluding ACE-inhibitors), angiotensin II antagonists or beta-blockers were added if necessary to reach the target blood pressure.

The mean length of follow up was 4.8 years.

The primary end-point 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, an the black patients treated with atenonol. Therefore the results observed for losartan in comparison with atenolol, regarding 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 study, conducted worldwide, of 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 50mg once daily, titrated if necessary, to achieve blood pressure response, or to receive placebo, on a background of conventional hypertensive therapy (excluding ACE-inhibitors and angiotensin II antagonists). Investigators were instructed to titrate the study medication to 100mg daily as appropriate (72% of patients received 100mg daily the majority of the time). Other anti-hypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting anti-hypertensives) 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 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 end point, the results showed significant risk reduction in the group treated with losartan: 25.3% risk reduction for doubling of serum creatinine (p=0.006); 28.6% risk reduction for end-stage renal disease (p=0.002); 19.9% risk reduction for end-stage renal failure or death (p=0.009); 21.0% risk reduction for doubling of serum creatinine or end-stage renal failure (p=0.01).

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

ELITE I and ELITE II Study
In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between 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 which is described in the following -

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

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

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

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

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/1.73m2. 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 (2.5mg and 5mg), corresponding to an average daily dose of 0.07mg/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.

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 Potassium 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

Around 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 is attributed primarily 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 of up to 200 mg.

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

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of 14C-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 those seen in young male volunteers (see section 4.2 and 4.4).

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2 times higher than in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients >1 month to <16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg Losartan Potassium (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 pre-school 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 repeat dose toxicity studies, the administration of losartan induced a decrease in 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 histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse effects on late foetal development, resulting in foetal death and malformations.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Each Losartan Potassium 12.5 mg Film-Coated Tablet contains the following excipients:
microcrystalline cellulose (E460)
sodium stearyl fumarate
croscarmellose sodium
colloidal anhydrous silica
hypromellose (E464)
polyoxyethylene stearate
titanium dioxide (E171)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Three years.

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

6.5 Nature and contents of container

Losartan Potassium 12.5 mg Tablet is supplied in PVC/PE/PVDC aluminium blisters. Pack of 28 tablets.

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

Chanelle Medical U.K. Limited
Stanford Bridge Farm
Station Road
Pluckley
Ashford
Kent
TN27 0RU

8 MARKETING AUTHORISATION NUMBER(S)

PL 18110/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/11/2009

10 DATE OF REVISION OF THE TEXT

26/11/2009

PACKAGE LEAFLET: INFORMATION FOR THE USER

LOSARTAN POTASSIUM 12.5 MG FILM-COATED TABLET
LOSARTAN POTASSIUM 25 MG FILM-COATED TABLET
LOSARTAN POTASSIUM 50 MG FILM-COATED TABLET
LOSARTAN POTASSIUM 100 MG FILM-COATED TABLET

Read all of this leaflet carefully before you start using this medicine.

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

In this leaflet:

1. What Losartan Potassium Tablets are and what they are used for
The name of your medicine is Losartan Potassium 12.5mg Film-Coated Tablets, Losartan Potassium 25mg Film-Coated Tablets, Losartan Potassium 50mg Film-Coated Tablets or Losartan Potassium 100mg Film-Coated Tablets.
They are prescribed for the treatment of high blood pressure.

Losartan Potassium belongs to a group of medicines known as angiotensin-II antagonists.

In patients with type 2 diabetes, where there has been damage to the kidneys (shown by the presence of protein in the urine), Losartan Potassium (can provide kidney protection by blocking the harmful effects of angiotensin II (a chemical in the body which tightens blood vessels causing blood pressure to increase) and slowing the worsening of kidney damage.

Losartan Potassium is also used to treat chronic heart failure if another medicine, called an ACE inhibitor, is not considered to be suitable by your doctor. If your heart failure has been stabilised with an ACE inhibitor, you should not be switched to losartan potassium.

Losartan potassium is also used to treat patients with high blood pressure and a thickening of the left ventricle of the heart, to reduce the risk of a stroke.

Your doctor may have given you this medicine before from another company and it may have looked slightly different. Either brand will have the same effect.

2. Before you use Losartan Potassium Tablets

Do not take Losartan Potassium Tablets if
- you are or think you may be pregnant
- you are planning to become pregnant
- you are breast-feeding
- you have a liver disorder
- you are allergic to losartan potassium or any of the other ingredients (see section 6 of this leaflet)

Tell your doctor if any of the above conditions apply to you, before you take Losartan Potassium Tablets.

Take Special Care (check with your doctor) with Losartan Potassium Tablets if
- you suffer from liver problems (see section 2 of this leaflet "Do not take Losartan Potassium Tablets if " and section 3 "Dosage in special patient groups")
- you suffer from heart disease (caused by a reduced blood flow in the blood vessels of the heart), or problems with your heart valves or heart muscle
- you suffer from heart failure; special caution is necessary if you are being treated with beta-blockers (medicines used to treat some heart problems or to reduce blood pressure)
- you have a reduced blood flow to the brain (cerebrovascular disease)
- you have received a kidney transplant
- you suffer from excessive vomiting and/or diarrhoea leading to an extreme loss of fluid and/or salt from your body
- you are known to have narrowing or blockage of the blood vessels leading to your kidneys
- you know that you have high levels of potassium in your blood (hyperkalaemia) or you are on a low potassium diet.
- you have a history of angiooedema (swelling of the face, lips, throat, and/or tongue); see also section 4 of this leaflet ("Possible Side Effects")
- you are taking diuretics (medicines used to increase the amount of water that you pass out through your kidneys) or if you are under a special diet to reduce your salt intake (see section 3 of this leaflet; "Dosage in special patient groups")
- you have a disorder of the adrenal gland (a condition known as hyperaldosteronism caused by increase in secretion of the hormone aldosterone by the adrenal gland)

Taking other medicines
Tell your doctor if you are taking any of the following medicines:
- other medicines which can lower blood pressure (as they may additionally reduce your blood pressure), e.g. tricyclic antidepressants, baclofen, amifostine, antipsychotics (for the treatment of mental disorders)
- lithium, a medicine used to treat certain mental disorders; if you are taking lithium as well as losartan, your doctor will need to supervise you carefully and you may need regular blood tests.
- non-steroidal anti-inflammatory painkillers (such as indometacin) and COX-2 inhibitors (such as celecoxib, etoricoxib or lumiracoxib) as they may reduce the effect of losartan potassium tablets
- medicines which retain potassium or which may increase potassium levels, such as potassium supplements, potassium sparing medicines (e.g. heparin or certain diuretics like amiloride, triamterene and spironolactone) or potassium-containing salt substitutes.

If your kidney function is reduced and you take any of the above medicines together with Losartan Potassium Tablets, it may make your kidney problem worse.
You should also tell your doctor about all medicines that you are taking or plan to take. This includes any medicines obtained without a prescription, herbal medicines or natural health products.

Taking Losartan Potassium Tablets with Food and Drink
Losartan Potassium Tablets may be taken with or without food.

Pregnancy and breast-feeding:
You should not take Losartan Potassium Tablets in the first 12 weeks of pregnancy, and you must not take them at all after the 13th week, as this may be possibly harmful to the baby. If you become pregnant while on Losartan Potassium Tablets, tell your doctor immediately. If you are planning to become pregnant, tell your doctor; you will need to be switched to a different medicine.
Do not take Losartan Potassium Tablets if you are breast feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Use in children and adolescents:
Ask your doctor for information about the use of Losartan Potassium Tablets in children.

Driving and using machines
Losartan Potassium Tablets are unlikely to affect your ability to drive or use machines. However, Losartan Potassium Tablets may cause dizziness or drowsiness in some people. If you experience dizziness or drowsiness, consult your doctor before attempting such activities.

Important information about some of the ingredients of Losartan Potassium Tablets Tablets
If you have an allergy to any of the ingredients of Losartan Potassium Tablets (see "Further Information" below), contact your doctor before taking this medicine.

3. How to take Losartan Potassium Tablets
You must take your tablets as instructed by your doctor who will decide on the appropriate dose depending on your condition and whether you are taking other medicines. Losartan Potassium Tablets should be taken by mouth with a drink of water. You must keep taking Losartan Potassium Tablets every day and exactly as your doctor has told you. It is important that you take Losartan Potassium Tablets for as long as your doctor prescribes it, in order to keep your blood pressure controlled and/or protect your kidneys from worsening damage. You can take the tablets with or without food. It is recommended that you take your tablets at the same time each day.
Patients with High Blood Pressure
The usual dose of Losartan Potassium Tablets for most patients is one 50 mg tablet once a day. The maximal reduction in blood pressure should be reached 3-6 weeks after starting treatment. In some patients, the doctor may prescribe a higher dose (such as 100 mg). Follow your doctor's instructions exactly. If you have the impression that the effect of Losartan Potassium Tablets is too strong or too weak, tell your doctor or pharmacist.

Patients with High Blood Pressure and Type 2 diabetes
The usual starting dose of Losartan Potassium Tablets is 50 mg once daily. The dose may be increased to 100 mg once daily depending on your blood pressure response.
Losartan Potassium Tablets may be given with other medicines used to lower blood pressure, as well as insulin and other medicines which decrease the level of glucose in the blood.

Patients with Heart Failure
Treatment usually starts with 12.5mg of losartan once a day. Generally, the dose is increased gradually (i.e. 12.5mg daily during the first week, 25mg daily during the second week and 50mg daily during the third week).

In the treatment of heart failure, losartan is usually given with a diuretic (medicine that increases the amount of water which you pass through your kidneys) and/or digitalis (medicine that helps to make the heart stronger and more efficient) and/or a beta blocker.

Dosage in special patient groups
In patients over 75 years of age, the doctor may prescribe a lower dose.
A lower dose may also be prescribed in patients given high doses of diuretics or in patients with liver disorders. The use of losartan should not be given to patients with severe liver problems (see section 2, "Do not take Losartan Potassium Tablets if..")

Keep taking the medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop taking them your condition may get worse.

If you take more Losartan Potassium Tablets than you should
Contact your nearest hospital casualty department or your doctor ***immediately*** for advice if you have swallowed too many tablets or if you think a child has swallowed any.
Take this leaflet, and any tablets that you still have to show the doctor.
An overdose of this medicine may be dangerous; the symptoms of overdose are low blood pressure, increased heartbeat or possibly a decreased heartbeat.

If you forget to take Losartan Potassium Tablets
Try to take Losartan Potassium Tablets daily as prescribed. However, if you miss a dose, just carry on with the next dose as normal. Do not take an extra tablet to make up for a forgotten tablet.

4. Possible side effects
Like all medicines Losartan Potassium may cause side effects. They are generally mild and do not normally need treatment. **Stop taking Losartan Potassium and contact your doctor or pharmacist immediately if you develop any of these symptoms:**
- an allergic reaction, causing swelling of the face, lips, throat which may cause difficulty in breathing or swallowing

This is a serious but rare side effect, which affects more than 1 in 10,000 patients but fewer than 1 in1,000 patients. You may need urgent medical attention or hospitalisation.

The side effects of medicines are classified as follows:

very common:	happening in more than 1 in 10 patients
common:	happening in 1 in 100 to 1 in 10 patients
uncommon:	happening in 1 in 1,000 to 1 in 100 patients
rare:	happening in 1 in 10,000 to 1 in 1,000 patients
very rare:	happening in less than 1 in 10,000 patients
not known:	(cannot be estimated from the available data)

The following side effects have been reported with Losartan Potassium:-

Common:
- spinning sensation
- feeling dizzy
- low blood pressure (due to excessive loss of water from the body)
- weakness or feeling very tired
- too little sugar in the blood (hypoglycaemia)
- too much potassium in the blood (hyperkalaemia)
  – Your doctor will take regular blood samples to monitor the levels of potassium in your blood

Uncommon:
- drowsiness
- shortness of breath
- headache
- abdominal pain
- severe constipation
- nausea (feeling sick), vomiting (being sick)
- sleep problems
- localised swelling (oedema)
- diarrhoea
- feeling of increased heart rate (palpitations)
- hives, itching or rash
- severe chest pain (angina)
- a rapid drop in blood pressure (symptoms of which may be feeling light-headed or dizzy, particularly when standing up)

Rare:
- Inflammation of the blood vessels including inflammation of small veins, causing hard, purple blotches on the skin
- numbness or tingling sensation (paraesthesia)
- fainting
- irregular or rapid heartbeat
- stroke
- inflammation of the liver (hepatitis)
- elevated blood enzyme levels (can be reversible upon stopping treatment)

Frequency not known:
- anaemia - symptoms may be feeling tired or short of breath (a blood test will confirm this)
- a cough
- migraine
- muscle and joint pains
- liver problems (yellowing of the eyes and skin and flu-like symptoms)
- flu like symptoms
- back pain and urinary tract infection
- increase in blood urea, serum creatinine and serum potassium in patients with heart failure
- changes in kidney function including kidney failure (may be reversible upon stopping treatment)
- a reduction in the number of platelets in the blood. This may occasionally lead to abnormal (unexpected) bruising or bleeding

If any of the above side effects gets 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 Tablets
Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.

On the label you will find the letters "EXP" followed by some numbers. These numbers are the date when the medicine is no longer fit for use. Do not use this medicine after this date.

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

6. Further information

What Losartan Potassium Tablets contain
The active substance is losartan potassium. Each 12.5mg, 25mg, 50mg or 100mg film-coated tablet contains 12.5mg, 25 mg, 50mg or 100mg of losartan potassium respectively.

The other ingredients are:
microcrystalline cellulose (E460), sodium stearyl fumarate, croscarmellose sodium, colloidal anhydrous silica, hypromellose (E464), polyoxyethylene stearate, titanium dioxide (E171).

What Losartan Potassium Tablets look like and contents of the pack
Losartan Potassium 12.5mg Tablet is a white, round, biconvex, film-coated tablet.
Losartan Potassium 25 mg Tablet is a white, oblong, biconvex, non-scored film-coated tablet.
Losartan Potassium 50 mg Tablet is a white, oval, biconvex, scored film-coated tablet (the tablets can be divided into two equal halves).
Losartan Potassium 100 mg Tablet is a white, oblong, biconvex, non-scored film-coated tablet.

Losartan Potassium Tablets are available in packs containing 28 tablets in blister strips.

Marketing Authorisation Holder
Chanelle Medical UK Limited, The Lodge, Stanford Bridge Farm, Station Road, Pluckley, Ashford, Kent, TN27 0RU, United Kingdom

Manufacturer:
Sofarimex Industria Quimica e Farmaceutica Lda.,
Av. Industrias,
Alto do Colaride
Agualva 2735-213
Cacem
Portugal

This leaflet was prepared in May 2009


Losartan Potassium 25 mg Film-Coated Tablets
Each film-coated tablet contains 25 mg Losartan Potassium
MA Holder & Distributor:
Chanelle Medical U.K.Limited
The Lodge,
Stanford Bridge Farm,
Station Road,Pluckley,
Ashford,Kent
TN27 0RU, U.K.
00000000
Losartan Potassium
25 mg Film-Coated Tablets
Losartan Potassium
28 Tablets
Losartan Potassium
25 mg Film-Coated Tablets
28 Tablets
Losartan Potassium 25 mg Film-Coated Tablets
Each film-coated tablet contains 25 mg Losartan Potassium
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RG 0000
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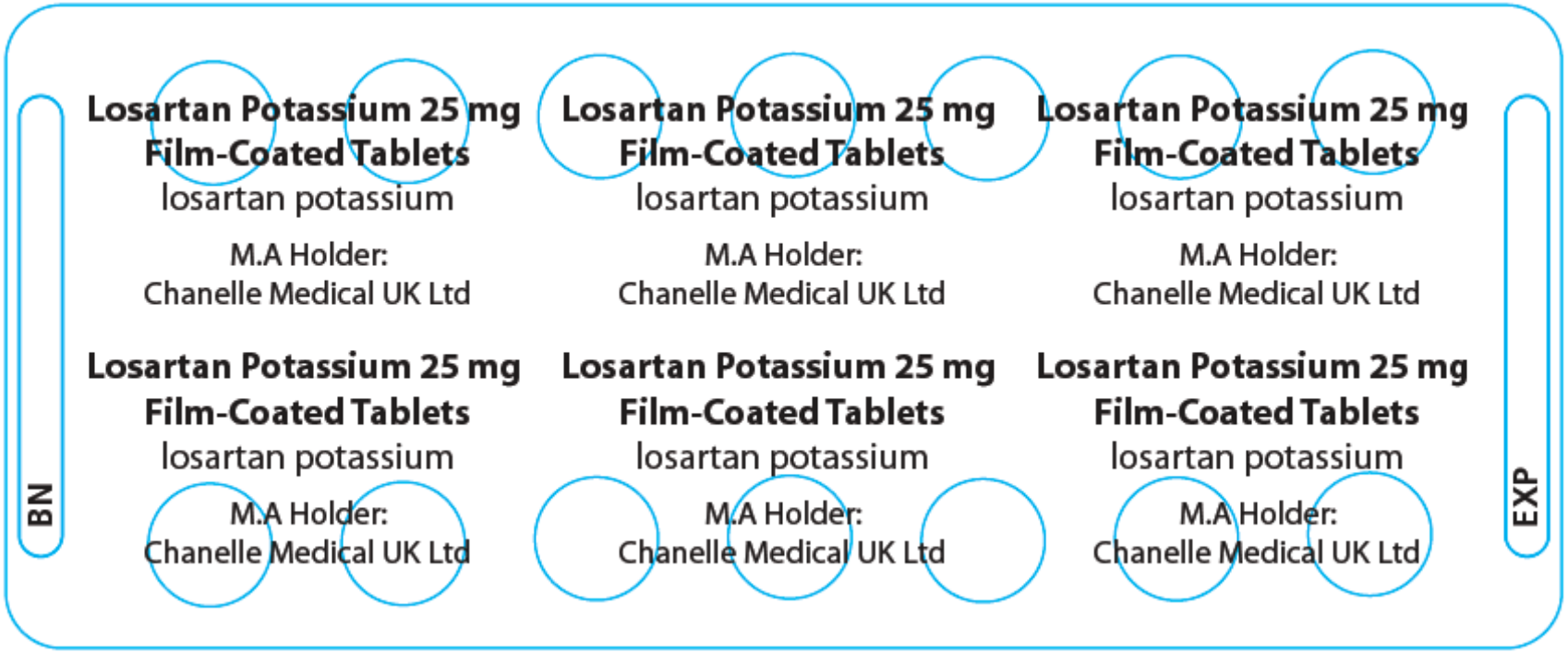
Lot
Exp.
Losartan Potassium 25 mg Film-Coated Tablets
Each film-coated tablet contains 25 mg Losartan Potassium
Read the package leaflet before use.
KEEP ALL MEDICINES OUT OF THE REACH
AND SIGHT OF CHILDREN.


Losartan Potassium 25 mg
Film-Coated Tablets
losartan potassium
M.A Holder:
Chanelle Medical UK Ltd
Losartan Potassium 25 mg
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Chanelle Medical UK Ltd
Losartan Potassium 25 mg
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M.A Holder:
Chanelle Medical UK Ltd
EXP


Losartan Potassium 50 mg Film-Coated Tablets
Each film-coated tablet contains 50 mg Losartan Potassium
MA Holder & Distributor:
Chanelle Medical U.K.Limited
The Lodge,
Stanford Bridge Farm,
Station Road, Pluckley,
Ashford, Kent
TN27 0RU, U.K.
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Losartan Potassium
50 mg Film-Coated Tablets
Losartan Potassium
28 Tablets
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28 Tablets
Losartan Potassium 50 mg Film-Coated Tablets
Each film-coated tablet contains 50 mg Losartan Potassium
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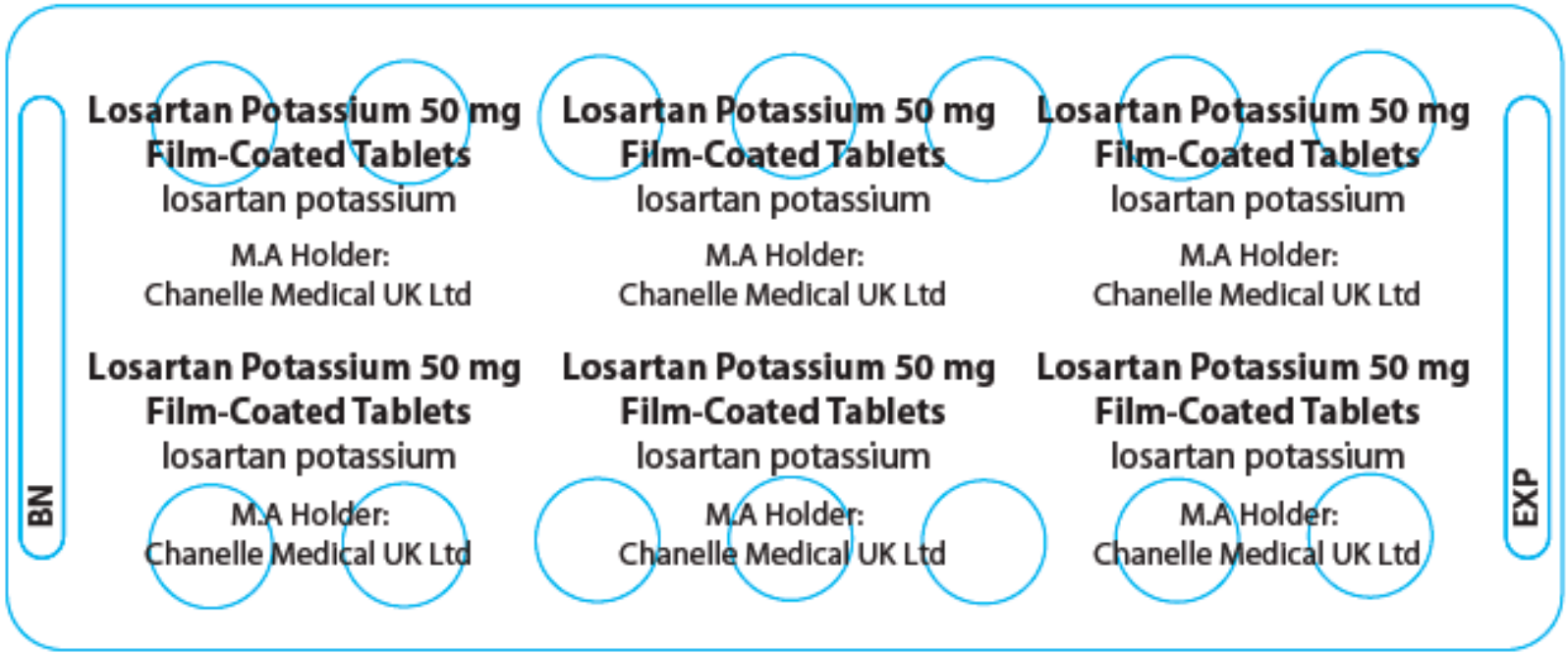
Losartan Potassium 50 mg Film-Coated Tablets
Each film-coated tablet contains 50 mg Losartan Potassium
Read the package leaflet before use.
KEEP ALL MEDICINES OUT OF THE REACH
AND SIGHT OF CHILDREN.


Losartan Potassium 50 mg
Film-Coated Tablets
losartan potassium
M.A Holder:
Chanelle Medical UK Ltd
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Chanelle Medical UK Ltd
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Film-Coated Tablets
losartan potassium
M.A Holder:
Chanelle Medical UK Ltd
EXP


Losartan Potassium 100 mg Film-Coated Tablets
Each film-coated tablet contains 100 mg Losartan Potassium
MA Holder & Distributor:
Chanelle Medical U.K. Limited
The Lodge,
Stanford Bridge Farm,
Station Road, Pluckley,
Ashford, Kent
TN27 0RU, U.K.
00000000
Losartan Potassium
100 mg Film-Coated Tablets
Losartan Potassium
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100 mg Film-Coated Tablets
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Losartan Potassium 100 mg Film-Coated Tablets
Each film-coated tablet contains 100 mg Losartan Potassium
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Losartan Potassium 100 mg Film-Coated Tablets
Each film-coated tablet contains 100 mg Losartan Potassium
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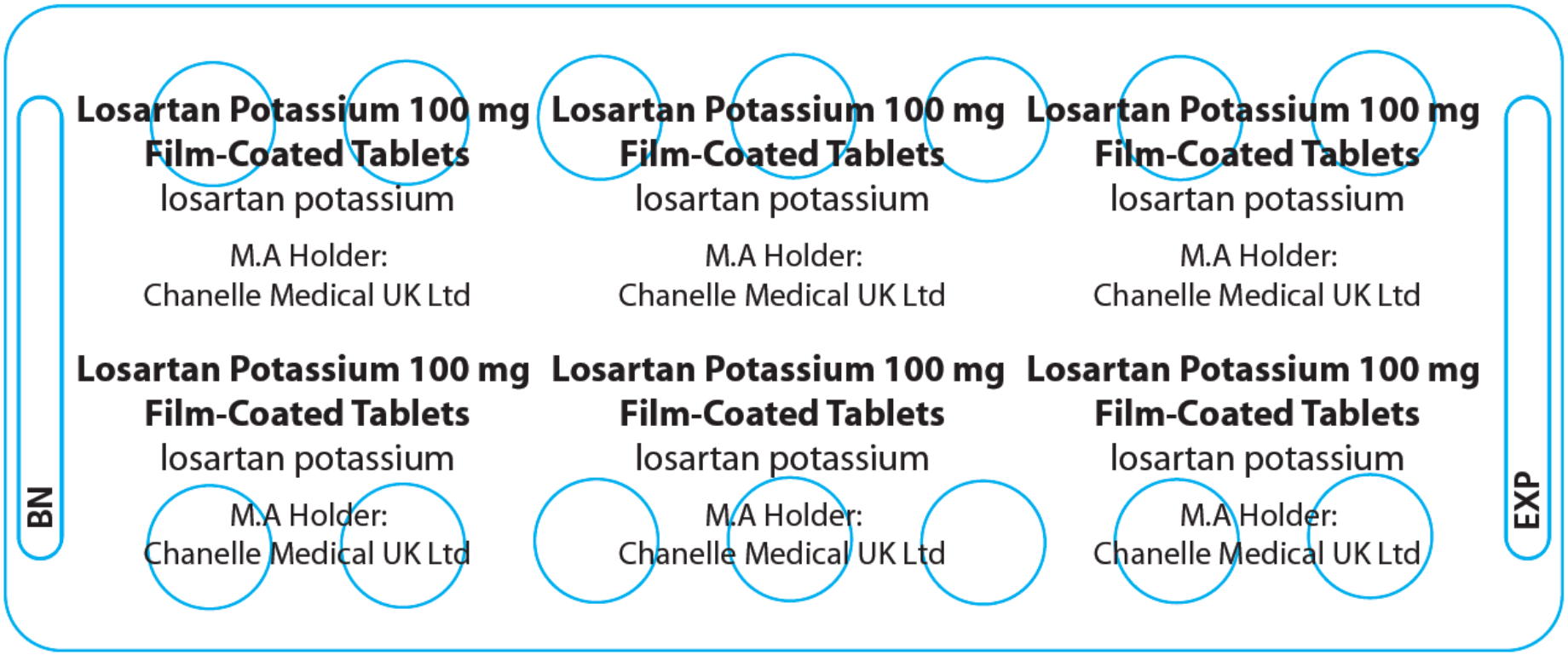
Losartan Potassium 100 mg
Film-Coated Tablets
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M.A Holder:
Chanelle Medical UK Ltd
Losartan Potassium 100 mg
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Losartan Potassium 100 mg
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M.A Holder:
Chanelle Medical UK Ltd
EXP


Losartan Potassium 12.5 mg Film-Coated Tablets
Each film-coated tablet contains 12.5 mg Losartan Potassium
MA Holder & Distributor:
Chanelle Medical U.K. Limited
The Lodge,
Stanford Bridge Farm,
Station Road, Pluckley,
Ashford, Kent
TN27 0RU, U.K.
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Losartan Potassium
12.5 mg Film-Coated Tablets
Losartan Potassium
28 Tablets
Losartan Potassium
12.5 mg Film-Coated Tablets
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Losartan Potassium 12.5 mg Film-Coated Tablets
Each film-coated tablet contains 12.5 mg Losartan Potassium
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Losartan Potassium 12.5 mg Film-Coated Tablets
Each film-coated tablet contains 12.5 mg Losartan Potassium
read the package leaflet before use.
KEEP ALL MEDICINES OUT OF THE REACH
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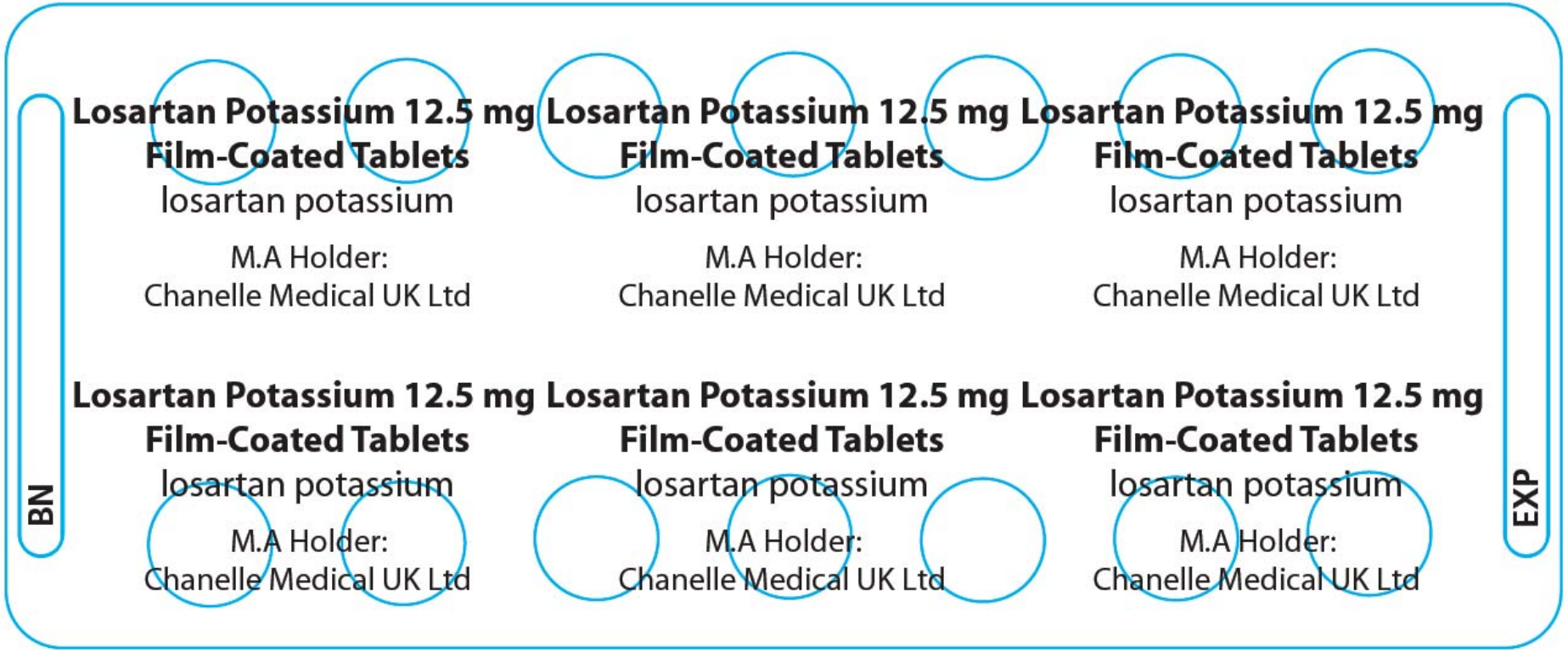
Losartan Potassium 12.5 mg
Film-Coated Tablets
losartan potassium
M.A Holder:
Chanelle Medical UK Ltd
Losartan Potassium 12.5 mg
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