Public Assessment Report

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

Losartan potassium

PL 19364/0012-14

UK Regulatory Affairs Ltd

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Lay Summary

The MHRA has granted Marketing Authorisations (licences) for the medicinal products Losartan potassium 25mg Film-coated Tablets (Pl 19364/0012), Losartan potassium 50mg Film-coated Tablets (Pl 19364/0013) and Losartan potassium 100mg Film-coated Tablets (Pl 19364/0014) on 28th January 2008.

Losartan is used in the treatment of high blood pressure, high blood pressure with heart disease and in slowing the progression of kidney disease in diabetes.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Losartan Film-coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.

Scientific Discussion

INTRODUCTION

Based on a review of the data on quality, safety and efficacy, the MHRA granted marketing authorisations for the medicinal products Losartan potassium 25mg Film-coated Tablets (Pl 19364/0012), Losartan potassium 50mg Film-coated Tablets (Pl 19364/0013) and Losartan potassium 100mg Film-coated Tablets (Pl 19364/0014) on 28th January 2008. The products are prescription only medicines.

Losartan is an oral, specific angiotensin-II receptor (type AT_1) antagonist. Losartan is used in the treatment of the following conditions

- *Hypertension*

  Losartan is indicated for the treatment of hypertension.
- *Hypertensive patients with left ventricular hypertrophy*

  In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated. The data do not support the use of losartan for this indication in black patients (see Section 4.4, *Race* and Section 5.1, *LIFE Study*, *Race*).
- *Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)*

  Losartan is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

Losartan Film-coated tablets were considered to be generic medical products of Cozaar 50 mg Tablets (Merck Sharp and Dohme B.V., Netherlands, marketed in Denmark and Iceland, BN HJ33430).

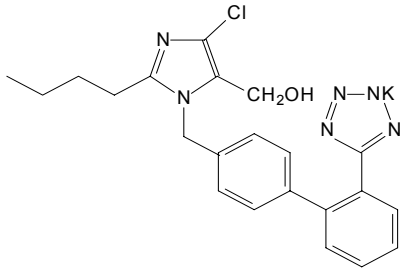
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

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

Structure



Molecular formula: $C_{22}H_{22}CLKN_6O$
Mr: 461.001 g/mol

General properties

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

An appropriate specification based on the USP has been provided.

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

Active losartan is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

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

Appropriate stability data have been generated. The finished product manufacture will confirm compliance with the approved specification immediately before manufacture of the finished product.

DRUG PRODUCT

Other Ingredients

The other ingredients of the drug product are listed below

Mannitol
Microcrystalline cellulose
Croscarmellose sodium,
Povidone K-30
Magnesium stearate

The film-coat contains
Hypromellose
Titanium dioxide (E171)
Talc
Propylene glycol

All excipients are controlled to the relevant Ph.Eur. Monographs. Specifications for the excipients from the finished product manufacturer are provided, together with satisfactory Certificates of Analysis. A declaration is provided from the supplier of magnesium stearate in the products, confirming that the magnesium stearate that they manufacture is not of animal origin

Dissolution and impurity profiles

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

Manufacture

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

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

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The tablets are packaged in transparent PVC/PVDC/Al heat-sealed blisters, formed by thermoforming the PVC/PVDC foil and then soldering it with the aluminium foil. Specifications for the PVC foil coated with PVDC and for the aluminium foil are acceptable.

The PVC is stated to comply with the Ph.Eur. monograph for materials based on non-plasticised poly(vinyl chloride) for containers for dry dosage forms for oral

administration and the composite PVC/PVDC material is stated to comply with 90/128/EC. A statement was provided from the supplier of the PVC/PVDC primary packaging to confirm that the material they supply complies with European food contact legislation. A declaration is provided from the manufacturer of the aluminium foil stating that the material complies with the EU resolution AP (96)-5.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and justify the declared shelf-life and storage conditions.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

The data provided support the suitability of drug substance and finished product for its intended use. The product is of equivalent qualitative and quantitative composition, the same pharmaceutical form and is bioequivalent to the reference product and therefore satisfies regulatory requirements for approval under Article 10.1 of the Directive.

PRECLINICAL ASSESSMENT

No preclinical data were submitted with these applications and none were required.

MEDICAL ASSESSMENT

Pharmcodynamics

Losartan is an oral, specific angiotensin-II receptor (type AT_1) antagonist. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone.

Pharmacokinetics

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

Bioequivalence study

A bioequivalence study was performed comparing the test product, Losartan potassium 50 mg Tablets with Cozaar 50 mg Tablets (Merck Sharp and Dohme B.V., Netherlands, marketed in Denmark and Iceland).

The study was a randomised, cross-over, open-label, single dose, fasting study in 20 healthy non-smoking adult male volunteers. The results from the first 18 subjects to complete the study were used (as per the protocol) to determine the statistical parameters of the study. Following a supervised overnight fast of at least 10 hours, one tablet of each product was given by oral administration with a washout period of 7 days between doses. Blood sampling was performed pre-dose and then over a 36 h period after each dosing.

The 90 % confidence intervals for Losartan potassium and losartan carboxy acid (active metabolite) from the bioequivalence study are:

Bioequivalence study parameter	90 % Confidence Interval (%)	
	Losartan potassium	Losartan carboxy acid
$AUC_{(0-\infty)}$	101.83-112.89	96.56-107.04
$AUC_{(0-t)}$	101.99-113.28	96.38-107.09
C_{max}	91.26-133.64	94.80-114.74

The upper limit of the 90 % confidence interval for the Cmax of the parent, losartan potassium, is outside the limits of 80-125 % and the wider limits of 75-133 %. This issue has previously been considered by the Commission on Human Medicines and it was decided that that a wider Cmax limit could be accepted for the parent molecule and that this would not result in any safety concerns.

Extrapolation of the results of this study to the other strengths submitted concurrently is justified considering relative composition, method of manufacture, in vitro data and pharmacokinetic characteristics of losartan.

Efficacy and Safety

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

Summary of Product Characteristics

This was satisfactory

Patient Information Leaflet

This was satisfactory

Conclusion

Market Authorisations may be granted.

Overall Conclusion and Risk/Benefit Analysis

Quality

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

Pre-Clinical

No new preclinical data were submitted and none were required.

Clinical

The clinical characteristics of Losartan potassium Film-coated tablets were found to be acceptable.

No new or unexpected safety concerns arise from these applications.

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

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 27/04/2006.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 30/06/2006.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 06/07/2006 and 22/02/2007.
4	The applicant provided further information in regard to the quality assessment on and 04/11/2006 and 24/10/2007.
5	The application was determined on 28/01/2008.

Steps Taken after Assessment

None

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Losartan potassium 25 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg of losartan potassium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Losartan 25 mg Film-coated tablets are white, round (8 mm) and biconvex with no score.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- *Hypertension*

  Losartan is indicated for the treatment of hypertension.
- *Hypertensive patients with left ventricular hypertrophy*

  In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated. The data do not support the use of losartan for this indication in black patients (see Section 4.4 Special Warnings and precautions for use -, *Race* and Section 5.1, *LIFE Study*, *Race*).
- *Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)*

  Losartan is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

4.2 Posology and method of administration

Losartan may be administered with or without food.
Losartan may be administered with other antihypertensive agents. The concomitant use of losartan and ACE inhibitors has not been adequately studied.
Hypertension
The starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy
The usual starting dose is 50 mg of losartan once daily. A low dose of hydrochlorothiazide may be added and/or the dose of losartan may be increased to 100 mg once daily based on blood pressure.
Renal protection in type 2 diabetic patients with nephropathy
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily according to blood pressure response from one month after initiation of therapy onwards. Losartan may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).
Losartan was not studied in type 2 diabetic patients with severe renal impairment.
Use in patients with intravascular volume depletion: For the very small proportion of patients who have intravascular volume depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see Section 4.4).
Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.
Use in hepatic impairment: A lower dose should be considered for patients with a history of hepatic impairment (see Section 4.4).
Use in the elderly: Patients up to 75 years: No initial dosage adjustment is necessary for this group of patients.
Patients over 75 years: Presently there is limited clinical experience in this group; a lower starting dose of 25 mg once daily is recommended.
Use in children and adolescents: There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 years old for the treatment of hypertension (see Section 5.1). Limited pharmacokinetic data are available in hypertensive children above one month of age (see Section 5.2).
For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients > 20 to < 50 kg. The dose can be increased to a maximum of 50 mg once daily. In patients >50 kg, the starting dose is 50 mg once daily. The dose can be adjusted to a maximum of 100 mg once daily.
Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 m^2, as no data are available.
Losartan is also not recommended in children with hepatic impairment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Losartan is contraindicated in pregnancy (see Section 4.6).

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema. See Section 4.8.

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

Hypotension and electrolyte/fluid imbalance

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

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

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

Liver function impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment (see Section 4.2 and Section 5.2).

Renal function impairment

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

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

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

Race (Black patients)

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Combination with NSAIDs: When Angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid > 3 g / day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
As with ACE inhibitors, concomitant use of Angiotensin II antagonists 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.
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme (ACE) inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. I f this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

4.6 Pregnancy and lactation

Use during pregnancy

Although there is no experience with the use of losartan in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.
In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the foetus increases if losartan is administered during the second or third trimesters of pregnancy.
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing foetus. Losartan should not be used in pregnancy, and if pregnancy is detected losartan should be discontinued as soon as possible.

Use during lactation

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

4.7 Effects on ability to drive and use machines

There are no data to suggest that losartan affects the ability to drive and use machines.

4.8 Undesirable effects

Side effects have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with losartan was comparable to placebo.
In controlled clinical trials for essential hypertension, dizziness was the only side effect reported as drug related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan. In addition, dose-related orthostatic effects were seen in less than 1% of patients.
The adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.
Losartan was generally well tolerated in a controlled clinical trial in hypertensive patients with left ventricular hypertrophy. The most common drug-related side effects were dizziness, asthenia/fatigue and vertigo.
Losartan was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with nephropathy. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalaemia. In this study, few patients discontinued due to hyperkalaemia (see Section 4.4, *Hypotension and electrolyte/fluid imbalance*).
The following adverse reactions have been reported in post-marketing experience:

- *Hypersensitivity*: Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue have been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schonlein purpura, has been reported rarely.
- *Gastro-intestinal*: Hepatitis (reported rarely), diarrhoea, liver function abnormalities.
- *Haematologic*: Anaemia (see Section 4.4), thrombocytopenia (reported rarely).
- *Musculoskeletal*: Myalgia, arthralgia.
- *Nervous system/Psychiatric*: Migraine.
- *Respiratory*: Cough.
- *Skin*: Urticaria, pruritus, rash.

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

4.9 Overdose

Significant lethality was observed in mice and rats after oral administration of 1,000 mg/kg (3,000 mg/m^2) and 2,000 mg/kg (11,800 mg/m^2) (500 and 1,000 times the maximum recommended daily human dose*), respectively.
Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.
Neither losartan nor the active metabolite can be removed by haemodialysis.
*Based on a patient weight of 50 kg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain
ATC code: C09CA01
Losartan is an oral, specific angiotensin-II receptor (type AT_1) antagonist. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT_1 receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.
During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.
Losartan binds selectively to the AT_1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT_1 receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.
Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding that is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.
A study was carried out which was specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors. In this study and in the controlled clinical trials for hypertension, the incidence of cough reported by patients receiving losartan or an agent not associated with ACE-inhibitor-induced cough

(hydrochlorothiazide or placebo) was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4,131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.
In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually <24 micromol) that was persistent in chronic therapy.
Losartan has no effect on autonomic reflexes and no sustained effect on plasma noradrenaline.
Losartan potassium administered in doses of up to 150 mg once daily did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.
Hypertension Studies
In clinical studies, once-daily administration of 50 mg losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.
The antihypertensive effect of 50 mg of losartan is similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of 50-100 mg of losartan is comparable to once-daily administration of atenolol 50 – 100 mg. The effect of administration of 50-100 mg of losartan once daily also is equivalent to felodipine extended-release 5-10 mg in older hypertensives (>65 years) after 12 weeks of therapy.
Although losartan is antihypertensive in all races, as with other drugs that affect the renin-angiotensin-aldosterone system, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.
If losartan is given together with thiazide-type diuretics, the blood-pressure-lowering effects are approximately additive.
LIFE Study
The losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other

antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.
The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.
Race: There were 533 black patients in the study. In this group, treatment with losartan resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint (p=0.033, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke (p=0.030, 95% confidence interval 1.08-4.40).
RENAAL Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a multicentre, randomised, placebo-controlled, double‑blind study 1,513 type 2 diabetic patients with nephropathy (751 treated with losartan), with or without hypertension. Patients were recruited with proteinuria as defined by urinary albumin to creatinine ratio>25 mg/mmol or 24-hour urinary protein excretion>500 mg and a serum creatinine of 115-265 micromol/l (a lower limit of 133 micromol/l was used for patients weighing more than 60 kg). The patients were randomised to receive losartan 50 mg once daily, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg daily as appropriate after one month; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Patients were followed for 3.4 years on average.
The results showed that treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary composite end point, the results also showed significant risk reduction in the group treated with losartan: 25.3% risk reduction in doubling of serum creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease (p=0.002); 19.9% risk reduction in end-stage renal disease or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal disease (p=0.010). All-cause mortality alone was not significantly different between the two treatment groups.
For the secondary endpoints, the results showed an average reduction of 34.3% in the level of proteinuria in the group treated with losartan (p<0.001)

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

Paediatric Hypertension

The antihypertensive effect of losartan was established in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age, with a body weight > 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, the two higher doses reduced diastolic blood pressure by 5 to 6 mmHg more than the lowest dose used by each group. The dose response to losartan was observed across all subgroups (e.g. age, Tanner stage, gender, race). However, the lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/kg, did not appear to offer consistent antihypertensive efficacy. When patients were randomised to continue losartan or placebo, after three weeks of therapy, trough diastolic blood pressure rose in patients on placebo between 5 and 7 mmHg more than patients on losartan at the two higher doses. However, the rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

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

5.2 Pharmacokinetic properties

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardised meal.

Distribution

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

Biotransformation

About 14% of an intravenously or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite.
In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.
Elimination
Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.
Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6 – 9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.
Both biliary and urinary excretion contributes to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.
Characteristics in patients
Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.
Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.
Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients> 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The results showed that the active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

5.3 Preclinical safety data

The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.
Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline cellulose
Croscarmellose sodium,
Povidone K-30
Magnesium stearate

The film-coat contains
Hypromellose
Titanium dioxide (E171)
Talc
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Transparent PVC/PVdC/Aluminium blister strips containing 7 or 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER

UKR Regulatory Affairs Limited.
Chiltern House
Thame Road
Haddenham
Bucks.,
HP17 8BY
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 19364/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/01/2008

10 DATE OF REVISION OF THE TEXT

28/01/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Losartan potassium 50 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of losartan potassium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Losartan potassium 50 mg Film-coated tablets are white, round (10 mm) and biconvex with no score.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- *Hypertension*

  Losartan is indicated for the treatment of hypertension.
- *Hypertensive patients with left ventricular hypertrophy*

  In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated. The data do not support the use of losartan for this indication in black patients (see Section 4.4, *Race* and Section 5.1, *LIFE Study*, *Race*).
- *Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)*

  Losartan is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

4.2 Posology and method of administration

Losartan may be administered with or without food.
Losartan may be administered with other antihypertensive agents. The concomitant use of losartan and ACE inhibitors has not been adequately studied.
Hypertension
The starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy
The usual starting dose is 50 mg of losartan once daily. A low dose of hydrochlorothiazide may be added and/or the dose of losartan may be increased to 100 mg once daily based on blood pressure.
Renal protection in type 2 diabetic patients with nephropathy
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily according to blood pressure response from one month after initiation of therapy onwards. Losartan may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).
Losartan was not studied in type 2 diabetic patients with severe renal impairment.
Use in patients with intravascular volume depletion: For the very small proportion of patients who have intravascular volume depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see Section 4.4).
Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.
Use in hepatic impairment: A lower dose should be considered for patients with a history of hepatic impairment (see Section 4.4).
Use in the elderly: Patients up to 75 years: No initial dosage adjustment is necessary for this group of patients.
Patients over 75 years: Presently there is limited clinical experience in this group; a lower starting dose of 25 mg once daily is recommended.
Use in children and adolescents: There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 years old for the treatment of hypertension (see Section 5.1). Limited pharmacokinetic data are available in hypertensive children above one month of age (see Section 5.2).
For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients > 20 to < 50 kg. The dose can be increased to a maximum of 50 mg once daily. In patients >50 kg, the starting dose is 50 mg once daily. The dose can be adjusted to a maximum of 100 mg once daily.
Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 m^2, as no data are available.
Losartan is also not recommended in children with hepatic impairment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Losartan is contraindicated in pregnancy (see Section 4.6).

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema. See Section 4.8.

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

Hypotension and electrolyte/fluid imbalance

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

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

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

Liver function impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment (see Section 4.2 and Section 5.2).

Renal function impairment

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

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

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

Race (Black patients)

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Combination with NSAIDs: When Angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid > 3 g / day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
As with ACE inhibitors, concomitant use of Angiotensin II antagonists 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.
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme (ACE) inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

4.6 Pregnancy and lactation

Use during pregnancy

Although there is no experience with the use of losartan in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.
In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the foetus increases if losartan is administered during the second or third trimesters of pregnancy.
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing foetus. Losartan should not be used in pregnancy, and if pregnancy is detected losartan should be discontinued as soon as possible.

Use during lactation

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

4.7 Effects on ability to drive and use machines

There are no data to suggest that losartan affects the ability to drive and use machines.

4.8 Undesirable effects

Side effects have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with losartan was comparable to placebo.
In controlled clinical trials for essential hypertension, dizziness was the only side effect reported as drug related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan. In addition, dose-related orthostatic effects were seen in less than 1% of patients.
The adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.
Losartan was generally well tolerated in a controlled clinical trial in hypertensive patients with left ventricular hypertrophy. The most common drug-related side effects were dizziness, asthenia/fatigue and vertigo.
Losartan was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with nephropathy. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalaemia. In this study, few patients discontinued due to hyperkalaemia (see Section 4.4, *Hypotension and electrolyte/fluid imbalance*).
The following adverse reactions have been reported in post-marketing experience:

- *Hypersensitivity*: Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue have been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schonlein purpura, has been reported rarely.
- *Gastro-intestinal*: Hepatitis (reported rarely), diarrhoea, liver function abnormalities.
- *Haematologic*: Anaemia (see Section 4.4), thrombocytopenia (reported rarely).
- *Musculoskeletal*: Myalgia, arthralgia.
- *Nervous system/Psychiatric*: Migraine.
- *Respiratory*: Cough.
- *Skin*: Urticaria, pruritus, rash.

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

4.9 Overdose

Significant lethality was observed in mice and rats after oral administration of 1,000 mg/kg (3,000 mg/m^2) and 2,000 mg/kg (11,800 mg/m^2) (500 and 1,000 times the maximum recommended daily human dose*), respectively.
Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.
Neither losartan nor the active metabolite can be removed by haemodialysis.
*Based on a patient weight of 50 kg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain
ATC code: C09CA01
Losartan is an oral, specific angiotensin-II receptor (type AT_1) antagonist. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT_1 receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.
During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.
Losartan binds selectively to the AT_1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT_1 receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.
Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding that is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.
A study was carried out which was specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors. In this study and in the controlled clinical trials for hypertension, the incidence of cough reported by patients receiving losartan or an agent not associated with ACE-inhibitor-induced cough

(hydrochlorothiazide or placebo) was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4,131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.
In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually <24 micromol) that was persistent in chronic therapy.
Losartan has no effect on autonomic reflexes and no sustained effect on plasma noradrenaline.
Losartan potassium administered in doses of up to 150 mg once daily did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.
Hypertension Studies
In clinical studies, once-daily administration of 50 mg losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.
The antihypertensive effect of 50 mg of losartan is similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of 50-100 mg of losartan is comparable to once-daily administration of atenolol 50 – 100 mg. The effect of administration of 50-100 mg of losartan once daily also is equivalent to felodipine extended-release 5-10 mg in older hypertensives (>65 years) after 12 weeks of therapy.
Although losartan is antihypertensive in all races, as with other drugs that affect the renin-angiotensin-aldosterone system, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.
If losartan is given together with thiazide-type diuretics, the blood-pressure-lowering effects are approximately additive.
LIFE Study
The losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other

antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.
The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.
Race: There were 533 black patients in the study. In this group, treatment with losartan resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint (p=0.033, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke (p=0.030, 95% confidence interval 1.08-4.40).
RENAAL Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a multicentre, randomised, placebo-controlled, double‑blind study 1,513 type 2 diabetic patients with nephropathy (751 treated with losartan), with or without hypertension. Patients were recruited with proteinuria as defined by urinary albumin to creatinine ratio>25 mg/mmol or 24-hour urinary protein excretion>500 mg and a serum creatinine of 115-265 micromol/l (a lower limit of 133 micromol/l was used for patients weighing more than 60 kg). The patients were randomised to receive losartan 50 mg once daily, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg daily as appropriate after one month; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Patients were followed for 3.4 years on average.
The results showed that treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary composite end point, the results also showed significant risk reduction in the group treated with losartan: 25.3% risk reduction in doubling of serum creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease (p=0.002); 19.9% risk reduction in end-stage renal disease or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal disease (p=0.010). All-cause mortality alone was not significantly different between the two treatment groups.
For the secondary endpoints, the results showed an average reduction of 34.3% in the level of proteinuria in the group treated with losartan (p<0.001)

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

Paediatric Hypertension

The antihypertensive effect of losartan was established in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age, with a body weight > 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, the two higher doses reduced diastolic blood pressure by 5 to 6 mmHg more than the lowest dose used by each group. The dose response to losartan was observed across all subgroups (e.g. age, Tanner stage, gender, race). However, the lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/kg, did not appear to offer consistent antihypertensive efficacy. When patients were randomised to continue losartan or placebo, after three weeks of therapy, trough diastolic blood pressure rose in patients on placebo between 5 and 7 mmHg more than patients on losartan at the two higher doses. However, the rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

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

5.2 Pharmacokinetic properties

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardised meal.

Distribution

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

Biotransformation

About 14% of an intravenously or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite.
In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.
Elimination
Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.
Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6 – 9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.
Both biliary and urinary excretion contributes to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.
Characteristics in patients
Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.
Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.
Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients> 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The results showed that the active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

5.3 Preclinical safety data

The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.
Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline cellulose
Croscarmellose sodium,
Povidone K-30
Magnesium stearate

The film-coat contains
Hypromellose
Titanium dioxide (E171)
Talc
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Transparent PVC/PVdC/Aluminium blister strips containing 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

UKR Regulatory Affairs Limited.
Chiltern House
Thame Road
Haddenham
Bucks.,
HP17 8BY
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 19364/0013

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/01/2008

10 DATE OF REVISION OF THE TEXT

28/01/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Losartan potassium 100 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of losartan potassium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Losartan 100 mg Film-coated tablets are white, oval and biconvex with no score.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- *Hypertension*

  Losartan is indicated for the treatment of hypertension.
- *Hypertensive patients with left ventricular hypertrophy*

  In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated. The data do not support the use of losartan for this indication in black patients (see Section 4.4, *Race* and Section 5.1, *LIFE Study*, *Race*).
- *Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)*

  Losartan is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

4.2 Posology and method of administration

Losartan may be administered with or without food.
Losartan may be administered with other antihypertensive agents. The concomitant use of losartan and ACE inhibitors has not been adequately studied.
Hypertension
The starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy
The usual starting dose is 50 mg of losartan once daily. A low dose of hydrochlorothiazide may be added and/or the dose of losartan may be increased to 100 mg once daily based on blood pressure.
Renal protection in type 2 diabetic patients with nephropathy
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily according to blood pressure response from one month after initiation of therapy onwards. Losartan may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).
Losartan was not studied in type 2 diabetic patients with severe renal impairment.
Use in patients with intravascular volume depletion: For the very small proportion of patients who have intravascular volume depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see Section 4.4).
Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.
Use in hepatic impairment: A lower dose should be considered for patients with a history of hepatic impairment (see Section 4.4).
Use in the elderly: Patients up to 75 years: No initial dosage adjustment is necessary for this group of patients.
Patients over 75 years: Presently there is limited clinical experience in this group; a lower starting dose of 25 mg once daily is recommended.
Use in children and adolescents: There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 years old for the treatment of hypertension (see Section 5.1). Limited pharmacokinetic data are available in hypertensive children above one month of age (see Section 5.2).
For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients > 20 to < 50 kg. The dose can be increased to a maximum of 50 mg once daily. In patients >50 kg, the starting dose is 50 mg once daily. The dose can be adjusted to a maximum of 100 mg once daily.
Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 m^2, as no data are available.
Losartan is also not recommended in children with hepatic impairment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Losartan is contraindicated in pregnancy (see Section 4.6).

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema. See Section 4.8.

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

Hypotension and electrolyte/fluid imbalance

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

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

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

Liver function impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment (see Section 4.2 and Section 5.2).

Renal function impairment

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

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

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

Race (Black patients)

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Combination with NSAIDs: When Angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid > 3 g / day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
As with ACE inhibitors, concomitant use of Angiotensin II antagonists 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.
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme (ACE) inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

4.6 Pregnancy and lactation

Use during pregnancy

Although there is no experience with the use of losartan in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.
In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the foetus increases if losartan is administered during the second or third trimesters of pregnancy.
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing foetus. Losartan should not be used in pregnancy, and if pregnancy is detected losartan should be discontinued as soon as possible.

Use during lactation

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

4.7 Effects on ability to drive and use machines

There are no data to suggest that losartan affects the ability to drive and use machines.

4.8 Undesirable effects

Side effects have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with losartan was comparable to placebo.
In controlled clinical trials for essential hypertension, dizziness was the only side effect reported as drug related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan. In addition, dose-related orthostatic effects were seen in less than 1% of patients.
The adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.
Losartan was generally well tolerated in a controlled clinical trial in hypertensive patients with left ventricular hypertrophy. The most common drug-related side effects were dizziness, asthenia/fatigue and vertigo.
Losartan was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with nephropathy. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalaemia. In this study, few patients discontinued due to hyperkalaemia (see Section 4.4, *Hypotension and electrolyte/fluid imbalance*).
The following adverse reactions have been reported in post-marketing experience:

- *Hypersensitivity*: Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue have been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schonlein purpura, has been reported rarely.
- *Gastro-intestinal*: Hepatitis (reported rarely), diarrhoea, liver function abnormalities.
- *Haematologic*: Anaemia (see Section 4.4), thrombocytopenia (reported rarely).
- *Musculoskeletal*: Myalgia, arthralgia.
- *Nervous system/Psychiatric*: Migraine.
- *Respiratory*: Cough.
- *Skin*: Urticaria, pruritus, rash.

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

4.9 Overdose

Significant lethality was observed in mice and rats after oral administration of 1,000 mg/kg (3,000 mg/m^2) and 2,000 mg/kg (11,800 mg/m^2) (500 and 1,000 times the maximum recommended daily human dose*), respectively.
Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.
Neither losartan nor the active metabolite can be removed by haemodialysis.
*Based on a patient weight of 50 kg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain
ATC code: C09CA01
Losartan is an oral, specific angiotensin-II receptor (type AT_1) antagonist. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT_1 receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.
During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.
Losartan binds selectively to the AT_1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT_1 receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.
Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding that is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.
A study was carried out which was specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors. In this study and in the controlled clinical trials for hypertension, the incidence of cough reported by patients receiving losartan or an agent not associated with ACE-inhibitor-induced cough

(hydrochlorothiazide or placebo) was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4,131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.
In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually <24 micromol) that was persistent in chronic therapy.
Losartan has no effect on autonomic reflexes and no sustained effect on plasma noradrenaline.
Losartan potassium administered in doses of up to 150 mg once daily did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.
Hypertension Studies
In clinical studies, once-daily administration of 50 mg losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.
The antihypertensive effect of 50 mg of losartan is similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of 50-100 mg of losartan is comparable to once-daily administration of atenolol 50 – 100 mg. The effect of administration of 50-100 mg of losartan once daily also is equivalent to felodipine extended-release 5-10 mg in older hypertensives (>65 years) after 12 weeks of therapy.
Although losartan is antihypertensive in all races, as with other drugs that affect the renin-angiotensin-aldosterone system, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.
If losartan is given together with thiazide-type diuretics, the blood-pressure-lowering effects are approximately additive.
LIFE Study
The losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other

antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.
The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.
Race: There were 533 black patients in the study. In this group, treatment with losartan resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint (p=0.033, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke (p=0.030, 95% confidence interval 1.08-4.40).
RENAAL Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a multicentre, randomised, placebo-controlled, double‑blind study 1,513 type 2 diabetic patients with nephropathy (751 treated with losartan), with or without hypertension. Patients were recruited with proteinuria as defined by urinary albumin to creatinine ratio>25 mg/mmol or 24-hour urinary protein excretion>500 mg and a serum creatinine of 115-265 micromol/l (a lower limit of 133 micromol/l was used for patients weighing more than 60 kg). The patients were randomised to receive losartan 50 mg once daily, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg daily as appropriate after one month; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Patients were followed for 3.4 years on average.
The results showed that treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary composite end point, the results also showed significant risk reduction in the group treated with losartan: 25.3% risk reduction in doubling of serum creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease (p=0.002); 19.9% risk reduction in end-stage renal disease or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal disease (p=0.010). All-cause mortality alone was not significantly different between the two treatment groups.
For the secondary endpoints, the results showed an average reduction of 34.3% in the level of proteinuria in the group treated with losartan (p<0.001)

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

Paediatric Hypertension

The antihypertensive effect of losartan was established in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age, with a body weight > 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, the two higher doses reduced diastolic blood pressure by 5 to 6 mmHg more than the lowest dose used by each group. The dose response to losartan was observed across all subgroups (e.g. age, Tanner stage, gender, race). However, the lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/kg, did not appear to offer consistent antihypertensive efficacy. When patients were randomised to continue losartan or placebo, after three weeks of therapy, trough diastolic blood pressure rose in patients on placebo between 5 and 7 mmHg more than patients on losartan at the two higher doses. However, the rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

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

5.2 Pharmacokinetic properties

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardised meal.

Distribution

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

Biotransformation

About 14% of an intravenously or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite.
In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.
Elimination
Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.
Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6 – 9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.
Both biliary and urinary excretion contributes to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.
Characteristics in patients
Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.
Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.
Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients> 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The results showed that the active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

5.3 Preclinical safety data

The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.
Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline cellulose
Croscarmellose sodium,
Povidone K-30
Magnesium stearate

The film-coat contains
Hypromellose
Titanium dioxide (E171)
Talc
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30^{o}C. Store in the original package.

6.5 Nature and contents of container

Transparent PVC/PVdC/Aluminium blister strips containing 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER

UKR Regulatory Affairs Limited.
Chiltern House
Thame Road
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Bucks.,
HP17 8BY
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8 MARKETING AUTHORISATION NUMBER(S)

PL 19364/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/01/2008

10 DATE OF REVISION OF THE TEXT

28/01/2008

Labels and Leaflet

Patient Information Leaflet

Losartan potassium 25 mg, 50 mg and 100 mg Film-coated Tablets

ratiopharm

Losartan Potassium

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have 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 get 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
2. Before you take Losartan potassium Tablets
3. How to take Losartan potassium Tablets
4. Possible side effects
5. How to store Losartan potassium Tablets
6. Further information

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

Losartan potassium Tablets belong to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin II is a chemical occurring in the body, which tightens your blood vessels making it harder for the blood to pass through them and causing your blood pressure to increase. Losartan potassium Tablets block this effect of angiotensin II, causing the blood vessels to relax and so lowers your blood pressure.

Your doctor has prescribed Losartan potassium Tablets because:
- You have high blood pressure. In patients with high blood pressure, who have developed thickening of the heart muscles, Losartan potassium Tablets can help lower the risk of a stroke. There is, however, no data to support this effect in black patients.

and/or
- You have type 2 diabetes with damage to your kidneys (shown by protein in the urine). If this is the case, taking Losartan potassium Tablets can slow down the worsening of the kidney damage.

2. BEFORE YOU TAKE LOSARTAN POTASSIUM TABLETS

Do not take this medicine if:
- you are allergic (hypersensitive) to losartan or to any of the ingredients in the tablet (see section 6, FURTHER INFORMATION)
- you are pregnant, you think you may be pregnant or you are planning to become pregnant

Take special care with Losartan potassium Tablets and tell your doctor or pharmacist before taking this medicine if:
- you have liver or kidney problems
- you have received a kidney transplant
- you have recently suffered from excessive vomiting and/or diarrhoea
- you have a condition called aortic stenosis or outflow obstruction to the main vessel leaving the heart
- you are known to have narrowing or blockage of the blood vessels leading to your kidneys
- you know you have high levels of potassium in your blood (hyperkalaemia) or you are on a low potassium diet

Taking other medicines
Please talk to your doctor or pharmacist if you are taking, or have recently taken, any other medicines; including any you have bought without prescription
Especially:
- rifampicin (used in the treatment of tuberculosis (TB))
- fluconazole (used to treat fungal infections such as thrush)
- lithium, a drug used to treat certain mental disorders
- non-steroidal, anti-inflammatory pain killers (such as ibuprofen, naproxen or diclofenac), COX-2 inhibitors (such as celecoxib, etoricoxib or lumiracoxib) or more than 3g of aspirin per day
- high doses of water tablets (diuretics)

You should also tell your doctor if you are taking potassium supplements, potassium sparing agents, or potassium-containing salt substitutes. Your doctor will decide whether you should take these medicines with Losartan potassium Tablets.

Pregnancy and breast-feeding
Losartan potassium Tablets should not be taken if you are pregnant. Talk to your doctor before taking these tablets if you are breast-feeding.

Driving and using machines
There is no evidence that losartan has any effect on the ability to drive and or use machines. However, if you experience dizziness as a side effect, do not continue to drive or use machinery.

3. HOW TO TAKE YOUR LOSARTAN POTASSIUM TABLETS

Always take Losartan potassium Tablets exactly as your doctor has told you. The label on the carton will tell you how many tablets you should take and when. You should check with your doctor or pharmacist if you are not sure.
- You should take your tablets by mouth with a glass of water. It is recommended that you take your tablets at the same time each day. You can take your tablets either with or without food.

Adults:
The usual starting dose for adults up to 75 years of age is one 50 mg tablet a day. Depending on how your blood pressure changes your doctor may increase your dose to one 100 mg tablet a day.
- If you have high blood pressure with a thickening of the heart muscle your doctor may also prescribe a low dose of diuretic (water tablet) and/or increase your dose of Losartan potassium Tablets to one 100 mg tablet a day.
- If you have Type II diabetes with kidney disease (protein in the urine), the usual starting dose is one 50mg tablet a day. This dose may be increased to one 100mg tablet a day based on your blood pressure response.

Elderly (over 75 years):
The recommended starting dose is one 25 mg tablet a day.

Patients with kidney or liver problems:
The doctor may prescribe a starting dose of one 25mg tablet a day.

Infants and children:
Losartan potassium Tablets are not recommended for infants or for children with liver or serious kidney problems.
- For children weighing between 20 and 50 kg the recommended starting dose is one 25 mg tablet a day. This dose may be increased to one 50 mg tablet a day.
- For children weighing more than 50 kg the recommended starting dose is one 50 mg tablet a day. This dose may be increased to one 100 mg tablet a day.

What if you miss a dose?
If you forget to take a dose at the right time, take it as soon as you remember. Then go on as before. **Do not** take two doses at the same time.

What if you have taken more losartan than you should?
If you have accidentally taken more than the prescribed dose, contact your nearest casualty department or tell your doctor/pharmacist **immediately**.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Losartan potassium Tablets can cause side effects, although not everybody gets them. The side effects are generally mild and do not normally mean that you have to stop taking the tablets.

Rarely patients have had a serious allergic reaction to Losartan potassium Tablets which caused:
- difficulty in breathing or dizziness, swelling of the face, throat, lips and/or tongue and/or inflammation of blood vessels, often with skin rash.

If you develop any of these symptoms you should stop taking your tablets and contact your doctor **immediately**.

The most commonly reported side effect in patients with high blood pressure and thickening of the heart muscle were:
- weakness/fatigue and a feeling of dizziness or 'spinning'.

The most commonly reported side effect in patients with type 2 diabetes with kidney disease were:
- weakness/fatigue, dizziness, a fall in blood pressure on standing up which caused dizziness, light-headedness or fainting and high blood levels of potassium which can cause abnormal heart rhythm.
- Your doctor will take regular blood samples to monitor the levels of potassium in your blood especially if you are elderly or have kidney problems.

Other side effects that have been reported are:
- liver problems (signs of which may be yellowing of the skin and whites of the eyes and flu like symptoms), diarrhoea, muscle or joint pain, anaemia (reduction in red blood cells which can make the skin pale or yellow and cause weakness or breathlessness), migraine, cough, hives (itchy skin reaction), itchy rash.
- Rarely patients have developed thrombocytopenia - a reduction in blood platelets, which increases the risk of bleeding or bruising.

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 **immediately**.

5. HOW TO STORE LOSARTAN POTASSIUM TABLETS

Keep Losartan potassium Tablets out of reach and sight of children

Losartan potassium Tabets should be stored in the original package. Losartan potassium 100 mg Tablets should be stored below 30°C.

Do not take this medicine after the expiry date printed on the carton and blister.
Any out of date or unused medicines should be returned to your pharmacy for disposal. If you notice any visible signs of deterioration in the tablets, show them to your pharmacist for advice before taking them.

6. FURTHER INFORMATION

What Losartan potassium Tablets contain:
Each 25 mg tablet contains 25 mg of losartan potassium.
Each 50 mg tablet contains 50 mg of losartan potassium.
Each 100 mg tablet contains 100 mg of losartan potassium.

The other ingredients are: mannitol, microcrystalline cellulose, croscarmellose sodium, povidone K-30, magnesium stearate, hypromellose, titanium dioxide (E171), talc and propylene glycol.

What Losartan potassium Tablets look like and contents of the pack:
Losartan 25 mg Tablets are white, round, film-coated, marked 2L on one side and plain on the other.
Losartan 50 mg Tablets are white, round, film-coated, marked 3L on one side and scored on the other.
Losartan 100 mg Tablets are white, oval, film-coated, marked 4L on one side and plain on the other.

Each pack of Losartan potassium 25 mg Tablets contains 7 or 28 tablets.
Each pack of Losartan potassium 50 mg or 100 mg Tablets contains 28 tablets.

Marketing Authorisation Holder:
UKR Regulatory Affairs Ltd, Chiltern House, Thame Road, Haddenham, Bucks, HP17 8BY, United Kingdom.

Manufacturer:
Actavis hf, Reykjavikurvegur 78, 220 Hafnarfjordur, Iceland.
or
Actavis hf, Karnesbraut 108, 200 Kopavogur, Iceland.
or
Merckle GmbH, Blaubeuren, Germany.

For a large print, audio, Braille or CD-rom version of this patient information leaflet, phone XXXXXXXXXX.

This leaflet was last updated in January 2008.

Losartan 25 mg Film-coated Tablets	UKR Regulatory Affairs Limited	Losartan potassium
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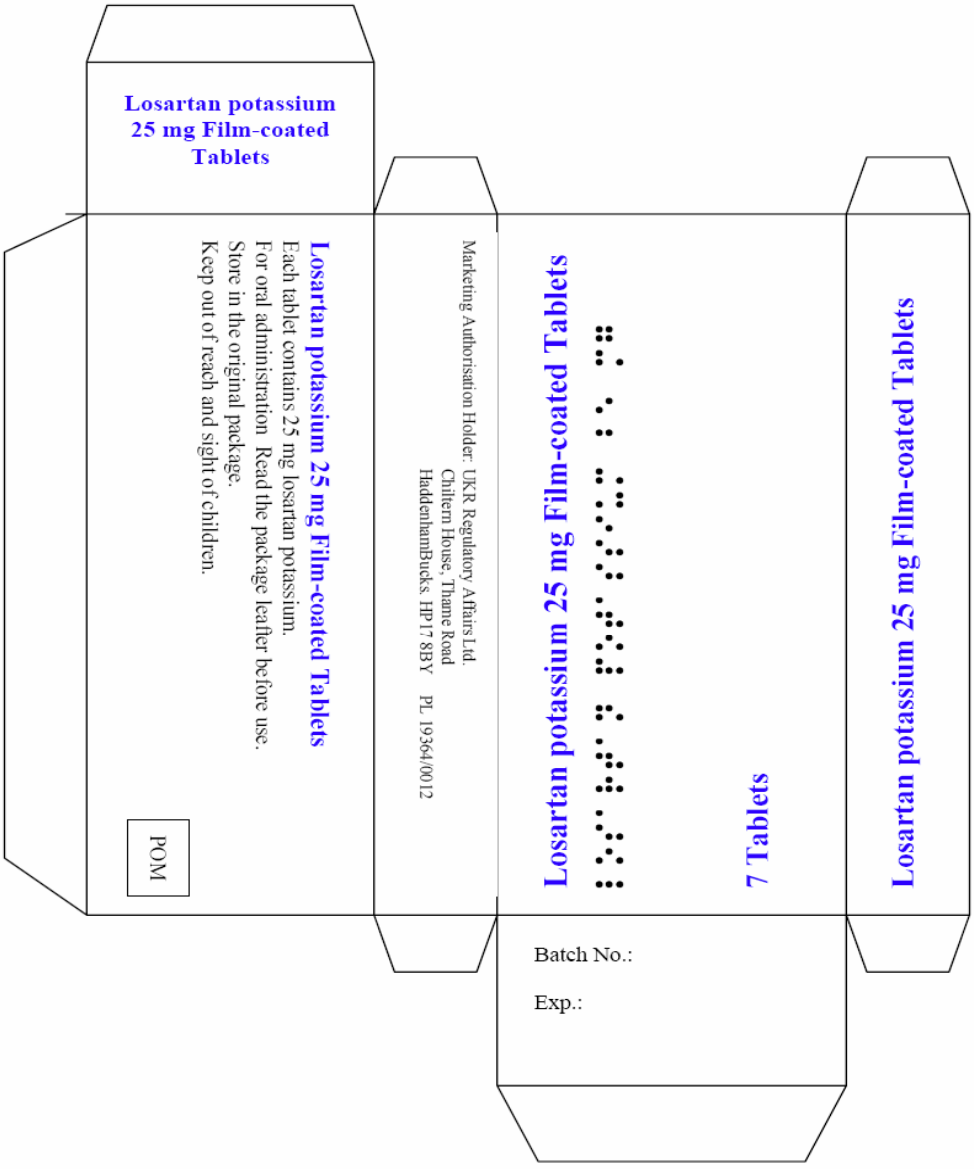

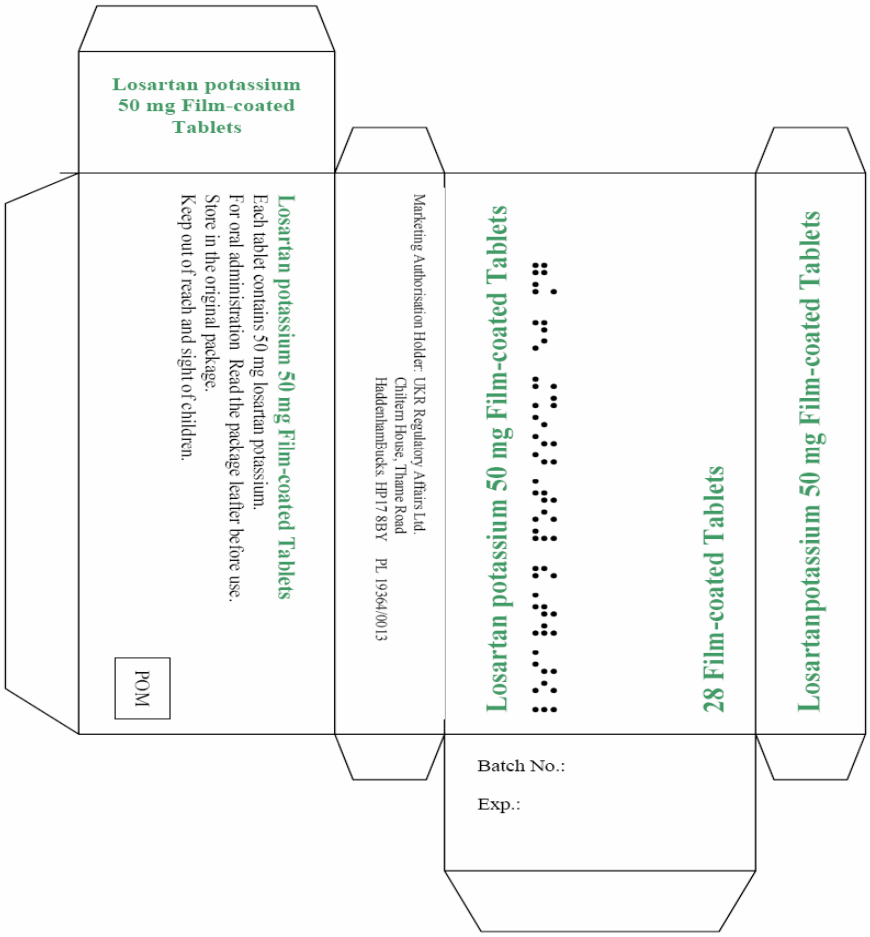

Losartan 50 mg Film-coated Tablets	UKR Regulatory Affairs Limited	Losartan potassium
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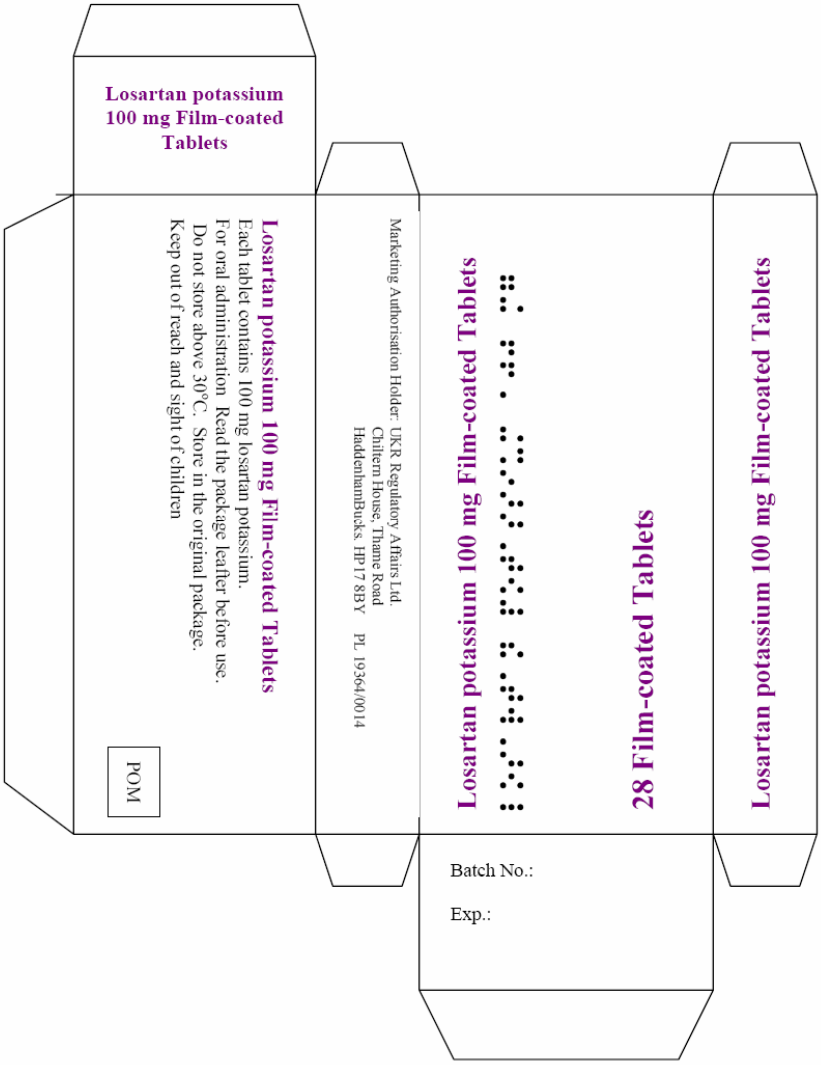
Losartan potassium 100 mg Film-coated Tablets
Losartan potassium 100 mg Film-coated Tablets
Each tablet contains 100 mg losartan potassium.
For oral administration. Read the package leaflet before use.
Do not store above 30°C. Store in the original package.
Keep out of reach and sight of children
POM
Marketing Authorisation Holder: UKR Regulatory Affairs Ltd.
Chiltern House, Thame Road
Haddenham Bucks. HP17 8BY PL 19364/0014
Losartan potassium 100 mg Film-coated Tablets
28 Film-coated Tablets
Batch No.:
Exp.:
Losartan potassium 100 mg Film-coated Tablets