COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Losartankalium Mylan 50 mg and 100 mg, film-coated tablets

(losartan potassium)

NL/H/4580/001-002/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Losartankalium Mylan 50 mg and 100 mg, film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/899/002-003/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Losartan 25 mg, 50 mg & 100 mg Film-coated Tablets
Losartan Potassium

UK/H/899/01-03/DC

UK licence no: PL 17871/0009-11

Applicant: Jenson Pharmaceutical Services Ltd.

LAY SUMMARY

The MHRA granted Jenson Pharmaceutical Services Ltd Marketing Authorisations (licences) for the medicinal products Losartan Potassium 25mg, 50mg & 100mg Film-coated Tablets (PL 17871/0009-11) on 6th June 2007. These are prescription-only medicines (POM) used to treat high blood pressure, reduce the risk of stroke in patients with high blood pressure and thickening of the heart muscle and to protect against kidney damage in diabetic patients with high blood pressure.

Losartan is effective in these conditions by its action on reducing blood pressure and making the blood vessels wider. This makes the blood flow more easily and reduces the effort needed for the heart to pump blood around the body.

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

TABLE OF CONTENTS

Module 1

Product Name	Losartan Potassium 25 mg, 50 mg & 100 mg Film-coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Losartan potassium
Form	Film-Coated Tablets
Strength	25mg, 50mg and 100mg Film-Coated Tablets
MA Holder	Jenson Pharmaceutical Services Ltd.
RMS	UK
CMS	NL
Procedure Number	UK/H/899/01-03/DC
Timetable	Day 150– 23rd April 2007

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium 25 mg Film Coated Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 25mg film-coated tablet contains 25mg of Losartan potassium.
(Equivalent to 22.88mg of lostartan and 2.12mg/ 0.054mmol potassium)
Also contains 12.75 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film Coated Tablet

25mg
Round, white film coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Losartan is indicated for the treatment of hypertension.

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

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

4.2 Posology and method of administration

Losartan may be administered with or without food.
Losartan may be administered with other antihypertensive agents. The concomitant use of Losartan and ACE inhibitors has not been adequately studied.

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

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

Renal protection in type 2 diabetic patients with nephropathy.
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily according to blood pressure response from one month after initiation of therapy onwards. Losartan may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).
Losartan was not studied in type 2 diabetic patients with severe renal impairment.

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

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

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

Use in 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

4.3 Contraindications

Losartan is contraindicated in pregnancy (see 4.6 'Pregnancy and lactation') and in patients who are hypersensitive to any component of this product.

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema. See 4.8 'Undesirable effects'.
The use of Losartan in patients with haemodynamically significant obstructive valvular disease or cardiomyopathy has not been adequately studied.

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

Liver function impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment (see 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').

Renal function impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin – angiotensin – aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction).
As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy.
Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with Losartan.

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

Surgery, anaesthesia:

Losartan blocks the effect of angiotensin II after compensatory renin secretion in patients that undergo major surgery or are treated during anaesthesia with substances that cause hypotension. If hypotension occurs and it may be attributed to this mechanism, it may be corrected by volume expansion.

Haemodialysis patients:
A lower dose must be considered in patients on haemodialysis. It appears from pharmacokinetic data that the plasma concentration of losartan is highly variable in this group of patients and is significantly higher on average than in other patients.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Other antihypertensive agents may increase the hypotensive effects of losartan. Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 in the active carboxy-acid metabolite. Fenobarbital, an inducer of metabolism enzymes has no influence on the metabolism of losartan. However, in a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50 %. It was found that concomitant treatment of losartan with rifampicine (inducer of metabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitantly treatment with fluconazole (weak inhibitor of CYP2C9). Losartan might increase the clearance of lithium (this is not specifically studied). Therefore, when lithium salts are administrated, lithium concentration in plasma should be checked regular.

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 fetal 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, fetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the fetus 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 fetus. 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

Losartan is not expected to affect the ability to drive or operate machinery. However, side effects such as dizziness and hypotension may influence ability to drive or operate machinery.

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.

Blood and lymphatic system disorders Rare (<1/1000)	Anaemia (see 4.4 'Special warnings and precautions for use)
Immune system disorders Rare (<1/1000)	Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue (some of these patients previously experienced angioedema with other drugs including ACE inhibitors). Vasculitis, including Henoch-Schlonlein purpura.
Metabolism and nutrition disorders Common (>1/100)	Hyperkalaemia (type II diabetic patients)
Nervous system/Psychiatric disorders Common (>1/100) Rare (<1/1000)	Dizziness, Vertigo (hypersensitive patients with left ventricular hypertrophy) Migraine
Cardiac disorders Common (>1/100) Uncommon (>1/1000, <1/100)	Hypotension (type II diabetic patients) Orthostatic effects (essential hypertension patients)
Respiratory, thoracic and mediastinal disorders Rare (<1/1000)	Cough
Gastrointestinal disorders Rare (<1/1000)	diarrhoea
Hepatobiliary disorders Rare (<1/1000)	Hepatitis, liver function abnormalities
Skin and subcutaneous tissue disorders Rare (<1/1000)	Urticaria, pruritus, rash
Musculoskeletal and connective tissue disorders Rare (<1/1000)	Myalgia, arthraigia
General Common (>1/100)	asthenia/fatigue (hypersensitive patients with left ventricular hypertrophy and type II diabetic patients)

Laboratory test findings

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

4.9 Overdose

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

Limited data are available in regard to 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: {group}, ATC code: CO9C A

Losartan is an oral, specific angiotensin-II receptor (type AT1) antagonist. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT1 receptor. In vitro and in vivo, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT1 receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.

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

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

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

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

Hypertension Studies:
In clinical studies, once-daily administration of 50 mg Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year.

Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours.

The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of Losartan had no clinically significant effect on heart rate.

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

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

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

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

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

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

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

The results showed that treatment with Losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation),

or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary composite end point, the results also showed significant risk reduction in the group treated with Losartan: 25.3% risk reduction in doubling of serum creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease (p=0.002); 19.9% risk reduction in end-stage renal disease or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal disease (p=0.010). All-cause mortality alone was not significantly different between the two treatment groups.

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

5.2 Pharmacokinetic properties

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

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

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

Elimination
Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.
Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6 – 9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.
Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of 14C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

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

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenicity.

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium that provided exposures for losartan and its pharmacologically active metabolite that were 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 fetuses 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

Lactose monohydrate
Pregelatinised maize starch
Microcrystalline cellulose
Magnesium stearate
hyprolose
hypromellose
Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 Months

6.4 Special precautions for storage

Store in the original package

6.5 Nature and contents of container

Aluminium-PE/PVDC blisters

Packs of 10, 14, 20, 21, 28, 28 (cal), 30, 50x1, 56, 60, 98, 98 (cal), 100, 210, 280 tablets

Not all pack sizes may be marketed in all territories

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Ltd, 31 Bridgeland Street, Bideford, Devon, EX39 2PS, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/06/2007

10 DATE OF REVISION OF THE TEXT

06/06/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium 50 mg Film Coated Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50mg film-coated tablet contains 50mg of Losartan potassium.
(Equivalent to 45.76mg of lostartan and 4.24mg/ 0.108mmol potassium))
Also contains 25.50 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film Coated Tablet

50mg

Round, white film coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Losartan is indicated for the treatment of hypertension.

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

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

4.2 Posology and method of administration

Losartan may be administered with or without food.
Losartan may be administered with other antihypertensive agents. The concomitant use of Losartan and ACE inhibitors has not been adequately studied.

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

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

Renal protection in type 2 diabetic patients with nephropathy.
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily according to blood pressure response from one month after initiation of therapy onwards. Losartan may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).
Losartan was not studied in type 2 diabetic patients with severe renal impairment.

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

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

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

Use in 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

4.3 Contraindications

Losartan is contraindicated in pregnancy (see 4.6 'Pregnancy and lactation') and in patients who are hypersensitive to any component of this product.

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema. See 4.8 'Undesirable effects'.
The use of Losartan in patients with haemodynamically significant obstructive valvular disease or cardiomyopathy has not been adequately studied.

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

Liver function impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment (see 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').

Renal function impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin ‾ angiotensin ‾ aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction).
As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy.
Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with Losartan.

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

Surgery, anaesthesia:
Losartan blocks the effect of angiotensin II after compensatory renin secretion in patients that undergo major surgery or are treated during anaesthesia with substances that cause hypotension. If hypotension occurs and it may be attributed to this mechanism, it may be corrected by volume expansion.

Haemodialysis patients:

A lower dose must be considered in patients on haemodialysis. It appears from pharmacokinetic data that the plasma concentration of losartan is highly variable in this group of patients and is significantly higher on average than in other patients.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Other antihypertensive agents may increase the hypotensive effects of losartan. Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 in the active carboxy-acid metabolite. Fenobarbital, an inducer of metabolism enzymes has no influence on the metabolism of losartan. However, in a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50 %. It was found that concomitant treatment of losartan with rifampicine (inducer of metabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitantly treatment with fluconazole (weak inhibitor of CYP2C9). Losartan might increase the clearance of lithium (this is not specifically studied). Therefore, when lithium salts are administrated, lithium concentration in plasma should be checked regular.

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 fetal 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, fetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the fetus 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 fetus. 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

Losartan is not expected to affect the ability to drive or operate machinery. However, side effects such as dizziness and hypotension may influence ability to drive or operate machinery.

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.

Blood and lymphatic system disorders Rare (<1/1000)	Anaemia (see 4.4 'Special warnings and precautions for use)
Immune system disorders Rare (<1/1000)	Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue (some of these patients previously experienced angioedema with other drugs including ACE inhibitors). Vasculitis, including Henoch-Schlonlein purpura.
Metabolism and nutrition disorders Common (>1/100)	Hyperkalaemia (type II diabetic patients)
Nervous system/Psychiatric disorders Common (>1/100) Rare (<1/1000)	Dizziness, Vertigo (hypersensitive patients with left ventricular hypertrophy) Migraine
Cardiac disorders Common (>1/100) Uncommon (>1/1000, <1/100)	Hypotension (type II diabetic patients) Orthostatic effects (essential hypertension patients)
Respiratory, thoracic and mediastinal disorders Rare (<1/1000)	Cough
Gastrointestinal disorders Rare (<1/1000)	diarrhoea
Hepatobiliary disorders Rare (<1/1000)	Hepatitis, liver function abnormalities
Skin and subcutaneous tissue disorders Rare (<1/1000)	Urticaria, pruritus, rash
Musculoskeletal and connective tissue disorders Rare (<1/1000)	Myalgia, arthraigia
General Common (>1/100)	asthenia/fatigue (hypersensitive patients with left ventricular hypertrophy and type II diabetic patients)

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

4.9 Overdose

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

Limited data are available in regard to 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: {group}, ATC code: CO9C A

Losartan is an oral, specific angiotensin-II receptor (type AT1) antagonist. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT1 receptor. In vitro and in vivo, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT1 receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.

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

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

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

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

Hypertension Studies:
In clinical studies, once-daily administration of 50 mg Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours.

The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of Losartan had no clinically significant effect on heart rate.

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

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

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

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

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

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

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

The results showed that treatment with Losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary composite end point, the results also showed significant risk reduction in the group treated with Losartan: 25.3% risk reduction in doubling of serum

creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease (p=0.002); 19.9% risk reduction in end-stage renal disease or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal disease (p=0.010). All-cause mortality alone was not significantly different between the two treatment groups.

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

5.2 Pharmacokinetic properties

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

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

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

Elimination
Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.
Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6 – 9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.
Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of 14C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

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

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenicity.

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium that provided exposures for losartan and its pharmacologically active metabolite that were 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 fetuses 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

Lactose monohydrate
Pregelatinised maize starch
Microcrystalline cellulose
Magnesium stearate
hyprolose
hypromellose
Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 Months

6.4 Special precautions for storage

Store in the original package

6.5 Nature and contents of container

Aluminium-PE/PVDC blisters

Packs of 10, 14, 20, 21, 28, 28 (cal), 30, 50x1, 56, 60, 98, 98 (cal), 100, 210, 280 tablets

Not all pack sizes may be marketed in all territories

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Ltd, 31 Bridgeland Street, Bideford, Devon, EX39 2PS, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/06/2007

10 DATE OF REVISION OF THE TEXT

06/06/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium 100 mg Film Coated Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100mg film-coated tablet contains 100mg of Losartan potassium.
(Equivalent to 91.52mg of lostartan and 8.48mg/ 0.216mmol potassium)
Also contains 51.00 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film Coated Tablet

100mg
Round, white film coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Losartan is indicated for the treatment of hypertension.

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

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

4.2 Posology and method of administration

Losartan may be administered with or without food.
Losartan may be administered with other antihypertensive agents. The concomitant use of Losartan and ACE inhibitors has not been adequately studied.

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

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

Renal protection in type 2 diabetic patients with nephropathy.
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily according to blood pressure response from one month after initiation of therapy onwards. Losartan may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).
Losartan was not studied in type 2 diabetic patients with severe renal impairment.

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

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

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

Use in 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

4.3 Contraindications

Losartan is contraindicated in pregnancy (see 4.6 'Pregnancy and lactation') and in patients who are hypersensitive to any component of this product.

4.4 Special warnings and precautions for use

Hypersensitivity:
Angioedema. See 4.8 'Undesirable effects'.
The use of Losartan in patients with haemodynamically significant obstructive valvular disease or cardiomyopathy has not been adequately studied.

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

Liver function impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment (see 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').

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

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy.
Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with Losartan.

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

Surgery, anaesthesia:
Losartan blocks the effect of angiotensin II after compensatory renin secretion in patients that undergo major surgery or are treated during anaesthesia with substances that cause hypotension. If hypotension occurs and it may be attributed to this mechanism, it may be corrected by volume expansion.

Haemodialysis patients:

A lower dose must be considered in patients on haemodialysis. It appears from pharmacokinetic data that the plasma concentration of losartan is highly variable in this group of patients and is significantly higher on average than in other patients.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Other antihypertensive agents may increase the hypotensive effects of losartan. Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 in the active carboxy-acid metabolite. Fenobarbital, an inducer of metabolism enzymes has no influence on the metabolism of losartan. However, in a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50 %. It was found that concomitant treatment of losartan with rifampicine (inducer of metabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitantly treatment with fluconazole (weak inhibitor of CYP2C9). Losartan might increase the clearance of lithium (this is not specifically studied). Therefore, when lithium salts are administrated, lithium concentration in plasma should be checked regular.

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 fetal 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, fetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the fetus 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 fetus. 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

Losartan is not expected to affect the ability to drive or operate machinery. However, side effects such as dizziness and hypotension may influence ability to drive or operate machinery.

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.

Blood and lymphatic system disorders	

Rare (<1/1000)	Anaemia (see 4.4 'Special warnings and precautions for use)
Immune system disorders Rare (<1/1000)	Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue (some of these patients previously experienced angioedema with other drugs including ACE inhibitors). Vasculitis, including Henoch-Schlonlein purpura.
Metabolism and nutrition disorders Common (>1/100)	Hyperkalaemia (type II diabetic patients)
Nervous system/Psychiatric disorders Common (>1/100) Rare (<1/1000)	Dizziness, Vertigo (hypersensitive patients with left ventricular hypertrophy) Migraine
Cardiac disorders Common (>1/100) Uncommon (>1/1000, <1/100)	Hypotension (type II diabetic patients) Orthostatic effects (essential hypertension patients)
Respiratory, thoracic and mediastinal disorders Rare (<1/1000)	Cough
Gastrointestinal disorders Rare (<1/1000)	diarrhoea
Hepatobiliary disorders Rare (<1/1000)	Hepatitis, liver function abnormalities
Skin and subcutaneous tissue disorders Rare (<1/1000)	Urticaria, pruritus, rash
Musculoskeletal and connective tissue disorders Rare (<1/1000)	Myalgia, arthraigia
General Common (>1/100)	asthenia/fatigue (hypersensitive patients with left ventricular hypertrophy and type II diabetic patients)

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

4.9 Overdose

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

Limited data are available in regard to 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: {group}, ATC code: CO9C A

Losartan is an oral, specific angiotensin-II receptor (type AT1) antagonist. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT1 receptor. In vitro and in vivo, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT1 receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.

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

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

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

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

Hypertension Studies:
In clinical studies, once-daily administration of 50 mg Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours.

The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of Losartan had no clinically significant effect on heart rate.

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

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

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

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

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

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

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

The results showed that treatment with Losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary composite end point, the results also showed significant risk reduction in the group treated with Losartan: 25.3% risk reduction in doubling of serum

creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease (p=0.002); 19.9% risk reduction in end-stage renal disease or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal disease (p=0.010). All-cause mortality alone was not significantly different between the two treatment groups.

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

5.2 Pharmacokinetic properties

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

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

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

Elimination
Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.
Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6 – 9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.
Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of 14C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

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

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenicity.

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium that provided exposures for losartan and its pharmacologically active metabolite that were 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 fetuses 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

Lactose monohydrate
Pregelatinised maize starch
Microcrystalline cellulose
Magnesium stearate
hyprolose
hypromellose
Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 Months

6.4 Special precautions for storage

Store in the original package

6.5 Nature and contents of container

Aluminium-PE/PVDC blisters

Packs of 10, 14, 20, 21, 28, 28 (cal), 30, 50x1, 56, 60, 98, 98 (cal), 100, 210, 280 tablets

Not all pack sizes may be marketed in all territories

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Ltd, 31 Bridgeland Street, Bideford, Devon, EX39 2PS, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/06/2007

10 DATE OF REVISION OF THE TEXT

06/06/2007

MODULE 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

LOSARTAN POTASSIUM 25 mg FILM-COATED TABLETS
LOSARTAN POTASSIUM 50 mg FILM-COATED TABLETS
LOSARTAN POTASSIUM 100 mg FILM-COATED TABLETS
(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 further questions, ask your doctor or pharmacist • This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours • If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

The name of your medicine is Losartan Potassium 25 mg, 50 mg or 100 mg Film-Coated Tablets (referred to as Losartan Tablets in this leaflet).

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

Your medicine comes as a film coated tablet containing the active ingredient losartan potassium. The other ingredients are listed in section 6 of this leaflet. Losartan belongs to a family of medicines known as angiotensin II receptor antagonists which reduce blood pressure and make the blood vessels wider. This makes the blood flow more easily and reduces the effort needed for the heart to pump blood around the body.

Losartan Tablets are used:

* to treat high blood pressure (hypertension)
* to reduce the risk of stroke in patients with hypertension and thickening of the heart muscle (ventricular hypertrophy)
* to slow the worsening of kidney damage in type 2 diabetic patients with hypertension.

Check with your doctor if you are unsure why you are taking this medicine.

2. BEFORE YOU TAKE LOSARTAN TABLETS

Do not take Losartan Tablets:

- if you are allergic (hypersensitive) to Losartan or any of the tablets ingredients
- if you are pregnant.

Take special care with Losartan Tablets:

- if you have had an allergic reaction with swelling of the face, lips, tongue and/or difficulty swallowing or breathing (angioedema) or you have suffered a similar allergic reaction for any reason in the past
- if you have recently suffered from severe diarrhoea and/or being sick leading to an extreme loss of fluid and/or salt from your body
- if you know you have abnormal salt (potassium, sodium) levels in your blood
- if you suffer from heart disease eg. heart valve disease, blood vessel disease or an enlarged heart disease, or an enlarged heart
- if you suffer from low blood pressure
- if you have severe kidney problems, narrowing of the blood vessels to the kidney or have had a kidney transplant
- if you need dialysis
- if you have a history of liver problems
- if you need surgery and a general anaesthetic.

Taking other medicines

Tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or the following:

* high doses of a diuretic ("water tablet") eg. Amiloride, Spironolactone, Triamterene
* medicine to treat blood clots eg. Heparin
* potassium supplements or salt substitutes containing potassium
* anti-inflammatory painkillers (NSAIDs) eg. Ibuprofen
* antifungal medicine called Fluconazole
* Rifampicin, an antibiotic.

Taking Losartan Tablets with food and drink:

This medicine can be taken before or after food. Alcohol may increase the effects of Losartan causing side effects such as dizziness.

Pregnancy and breast-feeding: You must **not** take Losartan Tablets if you are pregnant as Losartan may affect the growth of your unborn baby. If you become pregnant while on Losartan treatment, tell your doctor imediately. Your doctor will change your medicine. You must **not** take Losartan Tablets if you are breast-feeding.

Driving and using machines: No studies on the effects on the ability to drive and use machines have been performed. Losartan Tablets may cause side effects in some patients such as feeling light-headed or dizzy. **Do not** drive or operate machines if your ability to drive or use machines is affected.

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

3. HOW TO TAKE LOSARTAN TABLETS

Always take Losartan Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure • Swallow the tablets with a glass of water • Take as a single daily dose, at the same time each day • **Do not** stop taking this medicine unless your doctor tells you to. At the start of treatment your doctor will monitor your condition closely.

Adults (including the elderly up to 75 years old):
To treat high blood pressure - Treatment usually starts with 50 mg of Losartan once a day. The maximum blood pressure lowering effect will be reached within 3-6 weeks after beginning treatment. Your doctor will increase this to a dose which best controls your blood pressure. In some patients the dose may later be increased to 100 mg once daily.

To reduce the risk of stroke in patients with high blood pressure and thickened heart muscle - The dose is as above. You may also be given a diuretic ("water" tablet) eg. Hydrochlorothiazide to take. Losartan Tablets do not reduce the risk of stroke in black patients. Speak to your doctor or pharmacist for advice.

To treat diabetic patients with high blood pressure and kidney disease - The usual dose is 50 mg taken once a day. After a month, your doctor may need to increase this dose to 100 mg a day. You may also be taking other medicine to lower blood pressure as well as your diabetic medicine.

If you have liver or kidney problems, need dialysis treatment or are taking high doses of diuretic medicine, your doctor is likely to start you on a lower dose of 25 mg Losartan once daily.

Use in the Elderly - The doctor may advise a lower dose, especially when starting treatment in certain patients, such as those treated with high doses of diuretics, in patients with liver problems, or in patients over the age of 75 years. The use of Losartan is not recommended in patients with severe liver problems.

Children -Losartan Tablets should not be given to children under 18 years old.

If you take more Losartan Tablets than you should - Contact your doctor or hospital emergency department immediately. Remember to take the container and any remaining tablets with you.

If you forget to take a dose of Losartan Tablets - Take it as soon as you remember. However, if it is almost time for your next dose, **do not** take the missed dose, take the next dose on time. **Do not** take a double dose to make up for a forgotten dose. If you miss several doses, contact your doctor.

If you suddenly stop taking Losartan Tablets - Your blood pressure may increase. Speak to your doctor before stopping this medicine. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Losartan Tablets can cause side effects, although not everybody gets them.

It is vital to stop taking Losartan Tablets and seek medical attention immediately, if you begin to itch, get short of breath or wheezy, and develop swelling of the mouth, throat or face, as you may be allergic to Losartan. Patients who have experienced these effects before with other medicines are more likely to suffer these effects with Losartan Tablets.

Common side effects (seen in more than 1 in 100 patients but less than 1 in 10) include:
- low potassium levels in the blood (hyperkalaemia)
- low blood pressure in diabetic patients
- dizziness
- vertigo
- feeling weak
- unusually tired

Rare side effects (seen in less than 1 in 1,000 patients) include:
- anaemia
- migraine
- severe inflamed red skin (vasculitis)
- cough
- diarrhoea
- skin rash, swollen itchy skin
- muscle or joint pain
- abnormal liver enzyme levels in the blood
- hepatitis, liver problems

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

5. HOW TO STORE LOSARTAN TABLETS

Keep all medicines out of the reach and sight of children. Do not use Losartan Tablets after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month. Store in the original pack.

6. FURTHER INFORMATION

What Losartan Tablets contain - Each tablet contains either 25 mg, 50 mg or 100 mg of the active ingredient Losartan potassium. The other ingredients are lactose monohydrate, pregelatinised starch, microcrystalline cellulose, magnesium stearate, hyprolose, hypromellose and titanium dioxide (E171).

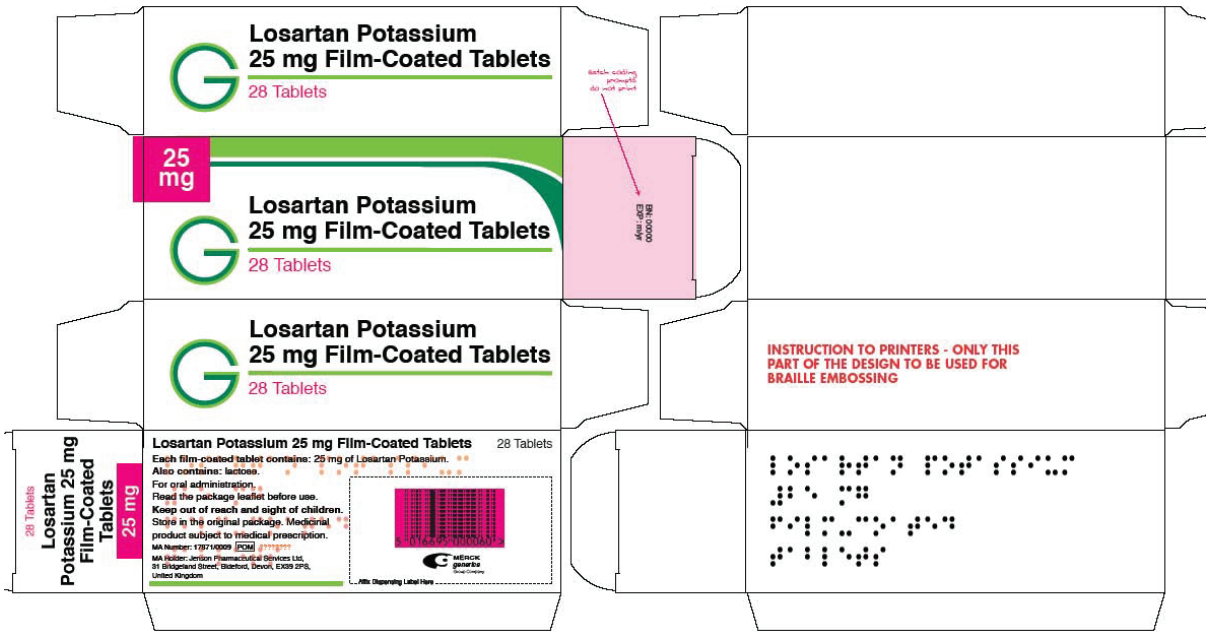
What Losartan Tablets look like and contents of the pack - The film-coated tablets are round and white. Losartan Tablets are available in blister packs of 28 tablets.

Marketing Authorisation Holder:
Jenson Pharmaceutical Services Ltd, 31 Bridgeland Street, Bideford, Devon, EX39 2PS, United Kingdom.

Manufacturers:
McDermott Laboratories t/a Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.
Generics [UK] Limited, Station Close, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom.

Date of leaflet preparation: May 2007 99999999

Module 4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25 mg Film-Coated Tablets
28 Tablets
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Losartan Potassium 25 mg Film-Coated Tablets
25 mg
Losartan Potassium 25 mg Film-Coated Tablets
28 Tablets
Each film-coated tablet contains: 25 mg of Losartan Potassium.
Also contains: lactose.
For oral administration.
Read the package leaflet before use.
Keep out of reach and sight of children.
Store in the original package. Medicinal product subject to medical prescription.
MA Number: 17871/0009
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MA Holder: Jenson Pharmaceutical Services Ltd,
81 Bridgeland Street, Bideford, Devon, EX39 2PS,
United Kingdom
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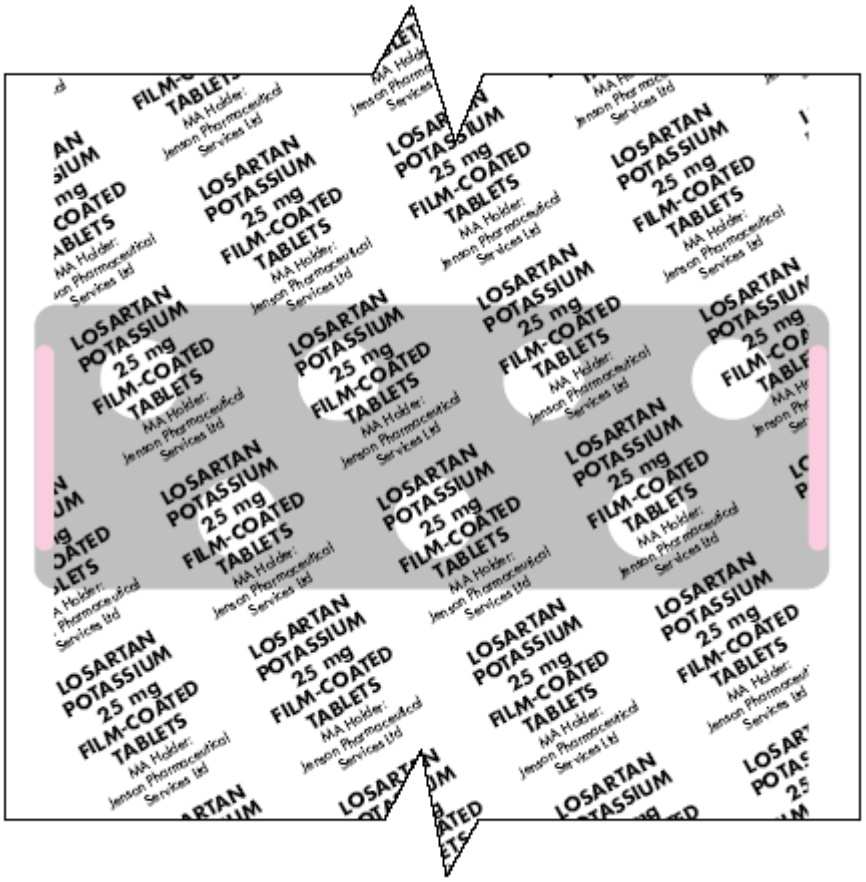
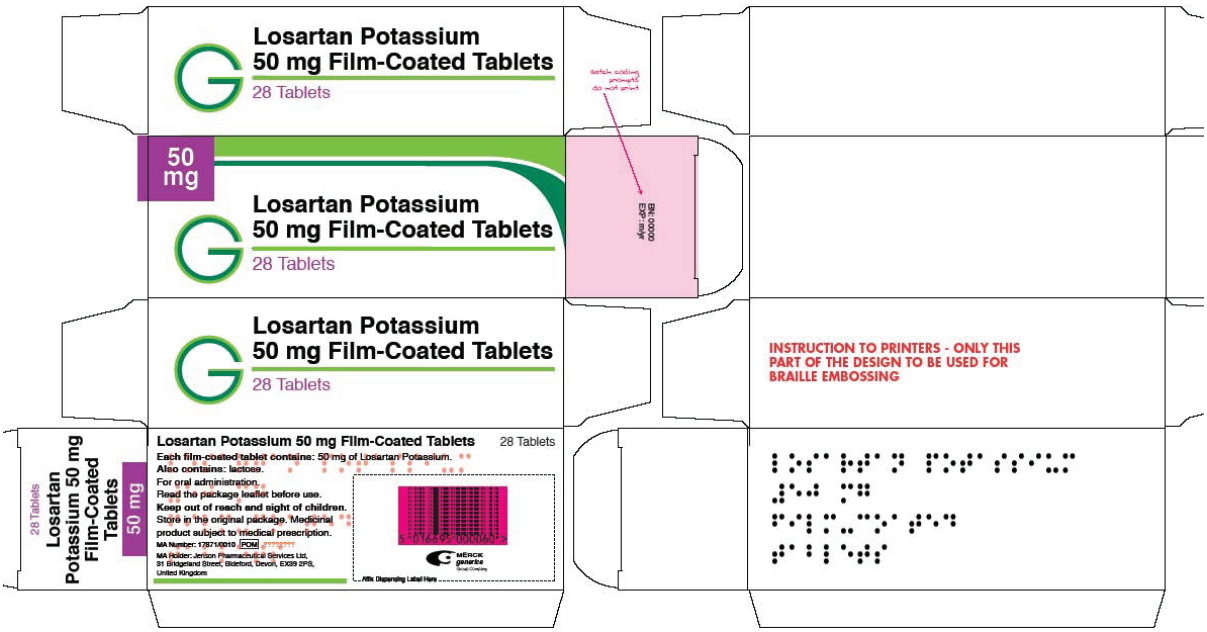

LOSARTAN POTASSIUM 25 mg FILM-COATED TABLETS
MA Holder: Jenson Pharmaceutical Services Ltd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MA Holder: Jenson Pharmaceutical Services Ltd, 31 Bridgeland Street, Bideford, Devon, EX39 2PS, United Kingdom
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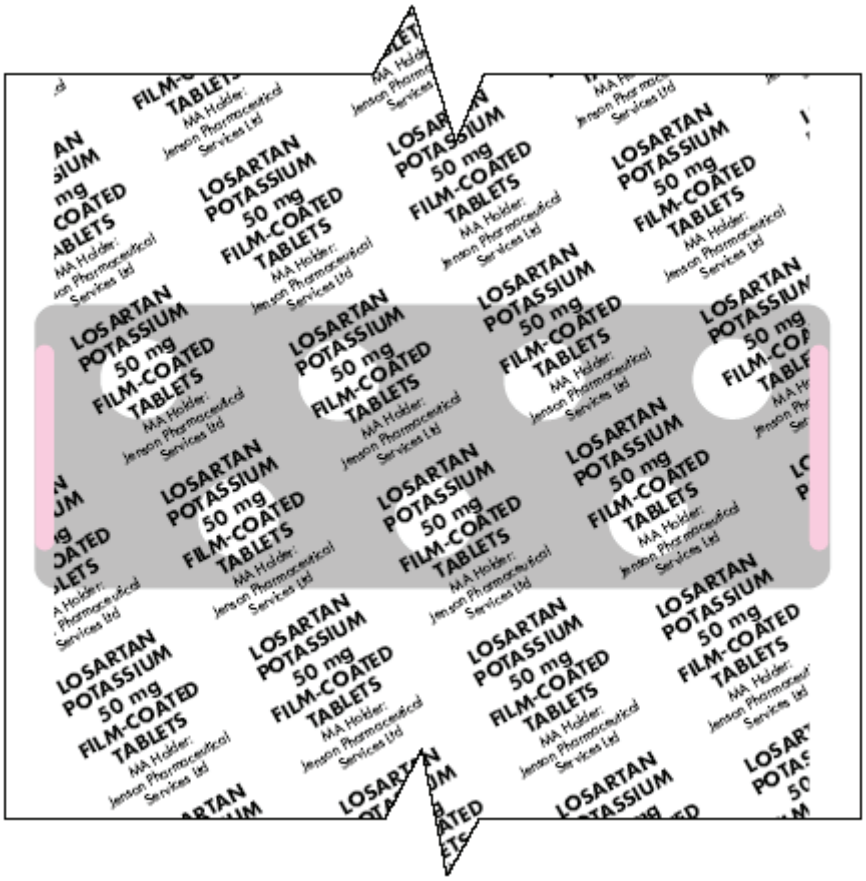
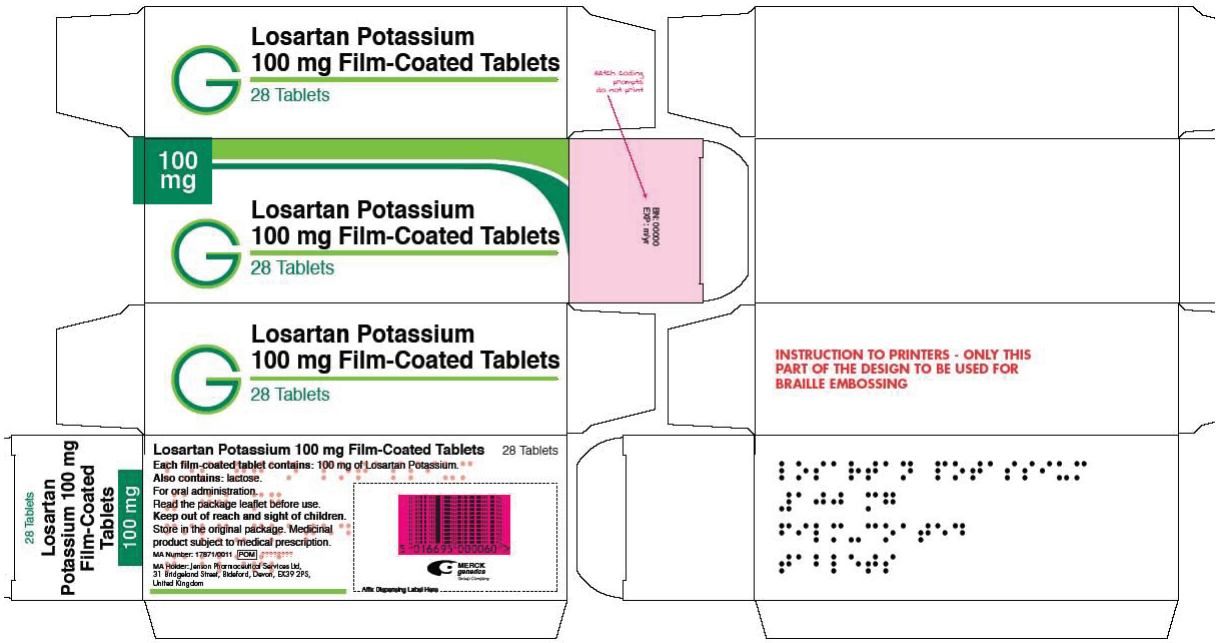

LOSARTAN POTASSIUM 50 mg FILM-COATED TABLETS
MA Holder: Jenson Pharmaceutical Services Ltd


Losartan Potassium
100 mg Film-Coated Tablets
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Losartan Potassium 100 mg Film-Coated Tablets
100 mg
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Each film-coated tablet contains: 100 mg of Losartan Potassium.
Also contains: lactose.
For oral administration.
Read the package leaflet before use.
Keep out of reach and sight of children.
Store in the original package. Medicinal product subject to medical prescription.
MA Number: 17871/0011 POM
MA Holder: Jenson Pharmaceutical Services Ltd, 31 Bridgeland Street, Bideford, Devon, EX39 2PS, United Kingdom
MERCK generics
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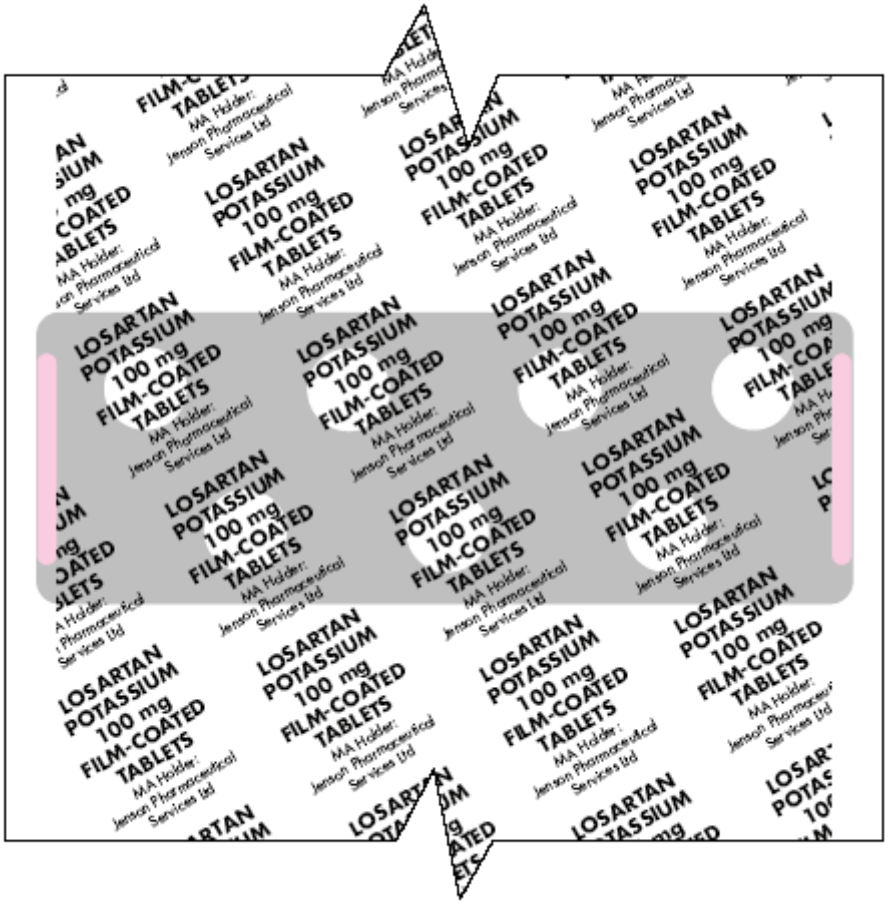

LOSARTAN POTASSIUM 100 mg FILM-COATED TABLETS
MA Holder: Jenson Pharmaceutical Services Ltd

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Losartan Potassium Film coated tablets, in the treatment of hypertension, reduction of stroke in those with left ventricular hypertrophy and renal protection, is approvable.

- The applicant has provided reasons by stating that the study results (Life study) supported the wording only for reduction of stroke. The RMS is in agreement with this.

Hypertension is a chronic disorder and a major risk factor for cardiovascular morbidity and mortality. The treatment of hypertension is complex with various classes of drugs available with variable benefits. These include diuretics, calcium channel blockers, beta- blockers, ACE inhibitors and angiotensin receptor blockers. In this application, authorisation is sought for a generic form of Losartan, an angiotensin receptor blocker for the following indications;

- Hypertension
- Reduction of risk of stroke in those hypertensives with left ventricular hypertrophy
- Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)

Losartan is the prototype angiotensin receptor blocker that was first authorised in several EU member states in 1994 for the treatment of hypertension. Since then several other indications have been added based on large clinical trial data that include the indications stated above.
The current formulation under discussion, Losartan Potassium film coated Tablets (25mg, 50mg, and 100mg) are a generic preparation manufactured by Liconsa SA. These are immediate release formulations to be marketed in the UK and the Netherlands by Jenson Pharmaceuticals. The applications are considered to be generic medicinal products of Cosaar Tablets and the applicant has provided the required bioavailability/bioequivalence studies.

The dossier is of acceptable quality. The Quality and non-clinical expert reports are of adequate standard and acceptable.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II. ABOUT THE PRODUCT

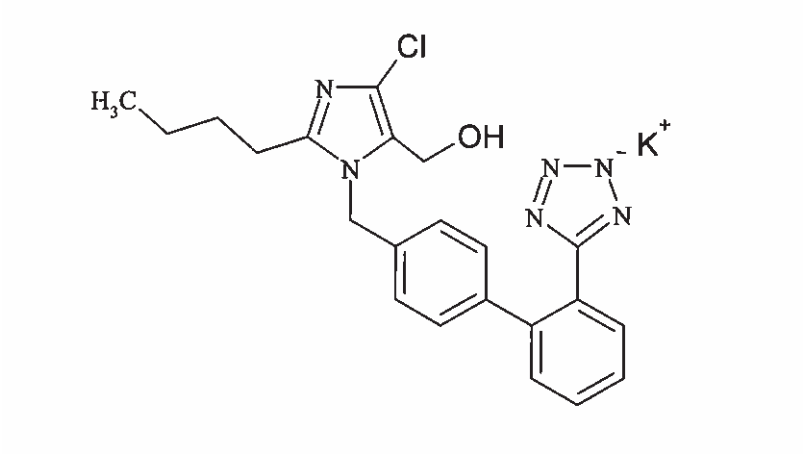
Name of the product in the Reference Member State	Losartan Potassium 25 mg, 50 mg & 100 mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Losartan potassium
Pharmacotherapeutic classification (ATC code)	Angiotensin II antagonists (C09 CA01)
Pharmaceutical form and strength(s)	25 mg, 50 mg & 100 mg Film-coated Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/899/01-03/DC
Reference Member State	United Kingdom
Member States Concerned	NL
Marketing Authorisation Number(s)	PL 17871/0009-11
Name and address of the authorisation holder	Jenson Pharmaceutical Services Ltd. 31 Bridgeland Street, Bideford, Devon, EX39 2PS, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug Substance

Nomenclature and structure



rINN: Losartan potassium

Chemical name:
2-Butyl-4chloro-1-[[(2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-imidazole-5-methanol, potassium salt
2-Butyl-4chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-imidazole-5-methanol, monopotassium salt
Chemical Abstracts Service (CAS) number:
[124750-99-8]

Physical form: White or almost white, crystalline powder, practically insoluble in water, freely soluble in ethanol and methylene chloride.

Molecular formula: $C_{22}H_{22}C_lKN_6O$

Relative molecular mass: 461.0

Losartan potassium is white to off-white crystalline powder freely soluble in water and in alcohol.

This is subject to DMF. A letter of access has been provided

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

An appropriate specification based on the European Pharmacopoeia has been provided.

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

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

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

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

Stability studies have been performed with the drug substance the proposed retest period of 15 months is justified.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, maize starch pregelatinised, microcrystalline cellulose, magnesium stearate, hydroxypropylcellulose, hydroxypropylmethylcellulose and titanium dioxide. All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients.

The only excipient used that contains material of animal origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce Losartan Potassium Film-coated Tablets that could be considered as generic products to the originator product Cozaar Tablets.

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

Dissolution and impurity profiles

Dissolution and impurity profiles for the drug product were found to be similar to that for the reference product.

Manufacture

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

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

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
Product is packaged in to PVDC/PE/Aluminium blisters. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 30 months with storage condition of store in the original package has been set. This is acceptable.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Satisfactory bioequivalence is seen between the test and reference product.

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

The PIL is in compliance with current guidelines. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

Conclusion
The proposed product has been shown to be a generic product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence. Similar dissolution profiles have been demonstrated for the proposed and reference products. It is recommended that Marketing Authorisations should be granted for these applications.

PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic products. The non-clinical overview provides a reasonable review of the known pharmacological and toxicological properties of losartan potassium.

CLINICAL ASPECTS

1. INTRODUCTION

These are applications for Losartan 25 mg, 50 mg & 100 mg Film-coated tablets (PL 17871/0009-11) using the decentralised procedure. These were submitted on the basis of Directive 2001/83/EC Article 10(1) generic application. The applicant considers these products as generic medicinal products of Cozaar® Tablets (Merck Sharp & Dohme). Cozaar® Tablets were authorised in the UK in 1994 (PL: 00025/0324 & 36). Cozaar® 100 mg Tablets manufactured for the Spanish market was used in bioequivalence studies.

2. BACKGROUND

Losartan is a class of Angiotensin-II receptor blockers that are used for control of hypertension as monotherapy or in combination with other agents, primarily thiazide diuretics.

3. INDICATIONS

The applicant has submitted the following:

Hypertension
Losartan is indicated for the treatment of hypertension.

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

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

4. DOSE & DOSE SCHEDULE

See the SPC for full details. The recommended dosages and dose schedules are consistent with those for Cosaar 100mg Tablets.

5. CLINICAL PHARMACOLOGY

Pharmacodynamics

The pharmacodynamics of Losartan are well established in various situations and specifically in the indications sought. Losartan is an oral, angiotensin-II receptor (type AT1) antagonist. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II. Losartan is equally effective in males and females and in younger (<65 years) and older (≥65 years) hypertensives. In clinical studies, once-daily administration of losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; in clinical studies of up to one year the antihypertensive effect was maintained. Black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.

6. EFFICACY

The applicant has provided the requisite Biostudy in support of these applications. A single biostudy comparing 100mg strengths of Losartan tablets, test and reference has been included

in the dossier. Acceptance criteria are satisfactory and the results support the claim for bioequivalence between test and reference products.

Biowaiver and extrapolation;
The applicant has fulfilled the essential criteria for Biowaiver for the two lower strengths as per section 5.4 of the CHMP guidance note (CPMP/EWP/QWP/1401/98);

7. SAFETY

No new data are submitted and none are required for this type of application. The safety of losartan has been well established for use in the indications sought and sufficient published literature has been submitted in support of this. The bioequivalence studies did not raise any new safety concerns.

BENEFIT RISK ASSESSMENT

Losartan Film coated tablets from Jenson Pharmaceuticals are generic products with losartan potassium as the active ingredient. The documentation with regard to quality, non-clinical and clinical is satisfactory. Bioequivalence with the originator has been established for the 100mg strength and biowaiver criteria fulfilled for other strengths.

The SPC adequately reflects the characteristics of the product with appropriate warnings. Overall the benefit: risk ratio is considered positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome