COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Losartankalium 25 mg, 50 mg and 100 mg PCH, film-coated tablets (losartan potassium)

NL/H/4831/001-003/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Losartankalium 25 mg PCH, film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/0925/02-04/DC). After a transfer in 2019, 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.

Public Assessment Report

Decentralised Procedure

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

UK/H/925/02-04/DC

UK licence no: PL 00289/0963-5

Applicant: TEVA UK Limited

LAY SUMMARY

The MHRA granted TEVA UK Limited Marketing Authorisations (licences) for the medicinal products Losartan Potassium 25mg, 50mg & 100mg Film-coated Tablets (PL 00289/0963-5) on 22nd April 2008. These medicines are 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.

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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	TEVA UK Limited
RMS	UK
CMS	NL, NO, IT, HU, FR, FI, DK, and AT, PT, SE, SI (only 50 and 100 mg strengths)
Procedure Number	UK/H/925/02-04/DC
Timetable	Day 210– 29th August 2007

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Losartan potassium 25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each losartan potassium tablet contains 25 mg losartan potassium.
Excipients:
Each 25 mg tablet contains 4.50 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
25 mg: White, oval, slightly arched film-coated tablets, debossed "2", scoreline and "5" on one side, scoreline on the other.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.
Treatment of patients with hypertension with left ventricular hypertrophy to reduce the risk of stroke (see section 5.1).
Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment

4.2 Posology and method of administration

Losartan tablets should be swallowed with a glass of water.
Losartan may be administered with or without food.
Hypertension
The usual initial and maintenance dose is 50 mg once daily. 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 2 x 50 mg losartan daily (in the morning and in the evening) or 100 mg losartan once daily (in the morning).
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.
Hypertensive type 2 diabetic patients with proteinuria ≥ 0.5 g/day
The usual initial 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.
Use in patients with intravascular volume depletion
For the very small proportion of patients who have intravascular volume depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see section 4.4).
Use in patients with renal impairment and haemodialysis patients
No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.
Use in patients with hepatic impairment
A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is not recommended in patients with severe hepatic impairment (see sections 4.3 and 4.4).
Use in the elderly
Although consideration should be given to initiating therapy with 25 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.
Use in children and adolescents (<18 years)
There is no experience in children and adolescents. Therefore, losartan should not be administered to children and adolescents.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see sections 4.4 and 6.1)
Pregnancy and lactation (see section 4.6)
Severe hepatic impairment

4.4 Special warnings and precautions for use

Angioedema
Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8).
Intravascular volume depletion
Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected prior to administration of losartan, or a lower starting dose should be used (see section 4.2).
Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group (see section 4.8 'Hypertension and type 2 diabetes with renal disease - Investigations' and 'Post-marketing experience - Investigations').
Therefore, the plasma concentrations of potassium and creatinine should be closely monitored, especially patients with heart failure and plasma creatinine concentrations between 1.2 mg/dl and 2.5 mg/dl should be closely monitored.
Liver function impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan should not be administered in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).
Renal function impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction).
As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy.
Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.
Renal transplantation
There is no experience in patients with recent kidney transplantation.
Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of losartan is not recommended.
Coronary heart disease and cerebrovascular disease:
As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.
Heart failure
In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment. There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life-threatening cardiac arrhythmias.
Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.
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).
Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorbtion

Losartan Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Other warnings and precautions
As observed for angiotensin-converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

4.5 Interaction with other medicinal products and other forms of interaction
Other antihypertensive agents may increase the hypotensive effects of losartan.
Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan with rifampicin (inducer of metabolic enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).
As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.
Non-steroidal anti-inflammatory drugs: When angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
In patients with pre-existing renal dysfunction the co-administration of non-steroidal anti-inflammatory drugs (such as indomethacin), including selective COX-2 inhibitors, may lead to a worsening of renal function. These changes in renal function may be reversible upon discontination of therapy.
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with antiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

4.6 Pregnancy and lactation
Pregnancy
There are very limited data from the use of losartan in pregnant women. These data are insufficient to allow conclusions about potential risks for the fetus when used during the first trimester.
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 potassium 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 system can cause fetal and neonatal injury (hypotension, renal dysfunction, oliguria and/or anuria, oligohydramnios, skull hypoplasia, intrauterine growth retardation) and death. Cases of lung hypoplasia, facial abnormalities and limb contractures have also been described.
Animal studies with losartan have demonstrated late fetal and neonatal injury in the kidney. The mechanism is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.
Based on the above information, losartan potassium is contraindicated in pregnancy. If pregnancy is detected during treatment losartan potassium should be discontinued (see section 4.3).
Lactation
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the breast-fed infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug.

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

4.8 Undesirable effects
The frequency of adverse events listed below is defined using the following convention:

very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).
In controlled clinical trials for essential hypertension, hypertensive patients with left ventricular hypertrophy, chronic heart failure as well as for hypertension and type 2 diabetes mellitus with renal disease, the most common adverse event was dizziness.
Hypertension
In controlled clinical trials for essential hypertension with losartan the following adverse events were reported:
Nervous system disorders
Common: dizziness, vertigo
Uncommon: somnolence, headache, sleep disorders
Cardiac disorders
Uncommon: palpitations, angina pectoris
Vascular disorders
Uncommon: symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash
Gastrointestinal disorders
Uncommon: abdominal pain, obstipation
General disorders and administration site conditions
Uncommon: asthenia, fatigue, oedema
Hypertensive patients with left ventricular hypertrophy
In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy the following adverse events were reported:
Nervous system disorders
Common: dizziness
Ear and labyrinth disorders
Common: vertigo
General disorders and administration site conditions
Common: asthenia/fatigue
Chronic heart failure
In a controlled clinical trial in patients with cardiac insufficiency the following adverse events were reported:
Nervous system disorders
Uncommon: dizziness, headache
Rare: paraesthesia
Cardiac disorders
Rare: syncope, artrial fibrillation, cerebrovascular accident
Vascular disorders
Uncommon: hypotension, including orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea
Gastrointestinal disorders
Uncommon: diarrhoea, nausea, vomiting
Skin and subcutanous tissue disorders
Uncommon: urticaria, pruritus, rash
General disorders and administration site conditions
Uncommon: asthenia/fatigue
Hypertension and type 2 diabetes with renal disease
In a controlled clinical trial in type 2 diabetic patients with proteinuria (RENAAL study, see section 5.1) the most common drug-related adverse events which were reported for losartan are as follows:
Nervous system disorders
Common: dizziness
Vascular disorders
Common: hypotension
General disorders and administration site conditions
Common: asthenia/fatigue
Investigations
Common: hypoglycaemia, hyperkalaemia
The following adverse events occurred more often in patients receiving losartan than placebo:
Blood and lymphatic system disorders

Not known: anaemia
Cardiac disorders
Not known: syncope, palpitations
Vascular disorders
Not known: orthostatic hypotension
Gastrointestinal disorders
Not known: diarrhoea
Musculoskeletal and connective tissue disorders
Not known: back pain
Renal and urinary disorders
Not known: urinary tract infections
General disorders and administration site conditions
Not known: flu-like symptoms
Post-marketing experience
The following adverse events have been reported in post-marketing experience:
Blood and lymphatic system disorders
Not known: anaemia
Very rare: thrombocytopenia
Immune system disorders
Rare: hypersensitivity: anaphylactic reactions, angiooedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angiooedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors; vasculitis, including Henoch-Schonlein purpura.
Nervous system disorders
Not known: migraine
Respiratory, thoracic and mediastinal disorders
Not known: cough
Gastrointestinal disorders
Not known: diarrhoea, vomiting, dysgeusia
Hepatobiliary disorders
Rare: hepatitis
Not known: liver function abnormalities
Skin and subcutaneous tissue disorders
Not known: urticaria, pruritus, rash, erythroderma
Musculoskeletal and connective tissue disorders
Not known: myalgia, arthralgia
Renal disorders
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy (see section 4.4).
Investigations
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with losartan developed hyperkalaemia >5.5 mEq/l and 3.4% of patients treated with placebo (see section 4.4, 'Electrolyte imbalances').
In a controlled clinical trial on patients with cardiac insufficiency, increase in blood urea, serum creatinine and serum potassium has been reported.

4.9 Overdose

Symptoms of intoxication
No experience with overdose in man is available so far. The most likely symptoms, depending on the extent of overdose, are hypotension, tachycardia, possibly bradycardia.
Treatment of intoxication
Measures are depending on the time of intake and kind and severity of symptoms. Stabilisation of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.
Neither losartan nor the active metabolite can be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonist, plain
ATC code: C09C A01

Losartan is a synthetic oral angiotensin II receptor (type AT_1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation.

Losartan selectively blocks the AT_1 receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of its source or route of synthesis.

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

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

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

Hypertension studies

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

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

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

LIFE study

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or 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.

There was a generally good level of tolerance in this study, and losartan's tolerability profile was superior, when seen in relation to atenolol, based on a significantly lower number of patients forced to abandon the study due to side effects.

Race

In the LIFE study the black patients treated with losartan had a higher risk of suffering the primary composite endpoint, i.e. a cardiovascular event (e.g. myocardial infarction, cardiovascular death) and especially stroke, than the black patients treated with atenolol. Therefore the results observed with

losartan in comparison with atenolol in the LIFE study with regard to cardiovascular morbidity/mortality do not apply for black patients with hypertension and left ventricular hypertrophy.

RENAAL Study

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a controlled clinical study conducted worldwide in 1,513 type 2 diabetic patients with proteinuria, with (96.7%) or without hypertension. 751 patients were treated with losartan.

The objective of the study was to demonstrate the nephroprotective effect of losartan potassium over and above the benefit of a lowering of blood pressure. Patients with proteinuria and a serum creatinine of 1.3-3.0 mg/dl 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 the study medication to 100 mg daily as appropriate; 72% of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensives (diuretic agents, calcium antagonists, alpha and beta receptor blockers and centrally active antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed for up to 4.6 years (3.4 years on average.)

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

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

The all-cause mortality rate was not significantly different between the two treatment groups.

In this study, losartan was generally well tolerated, as shown by a therapy discontinuation rate on account of adverse events that was comparable to the placebo group.

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. Peak plasma concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. The systemic bioavailability of losartan potassium is approx. 33%.

Distribution

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

Biotransformation

Approximately 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, circulating plasma radioactivity is attributed primarily to losartan and its active metabolite. In approximately 1% of subjects, a low conversion of losartan to the active metabolite was found.

Elimination

Plasma clearance of losartan and its active metabolite is approximately 600 ml/min and 50 ml/min, respectively. Following oral administration, plasma concentrations of losartan potassium and its active metabolite decline polyexponentially with a terminal half-life of approximately 2 hours and 6-9 hours, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, approximately 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite.

Both biliary and urinary excretion contribute to the elimination of losartan potassium and its metabolites. Following an oral dose of 14C-labelled losartan potassium in man, approximately 35% of radioactivity is recovered in the urine and 58% in the faeces. Following intravenous administration of 14C-labelled losartan potassium, approximately 43% of the radioactivity is recovered in the urine and 50% in the faeces.

Linearity

The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg.

During once-daily dosing, neither losartan nor its active metabolite accumulates significantly in plasma.

Characteristics in patients

In elderly hypertensive patients the plasma concentrations of losartan and its active metabolite do not differ essentially from those found in young hypertensive patients.
In female hypertensive patients the plasma levels of losartan were up to twice as high as in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women.
In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma levels of losartan and its active metabolite after oral administration were, respectively, 5 and 1.7 times higher than in young male volunteers (see sections 4.2 and 4.4).
Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/minute. Compared to patients with normal renal function, the AUC for losartan is approximately 2 times 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
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to cause weight loss, mortality and/or renal toxicity in rat fetuses and newborn rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core
Lactose monohydrate
Cellulose, microcrystalline
Maize starch, pregelatinized
Magnesium stearate
Coating
Polyvinyl alcohol
Titanium dioxide (E 171)
Macrogol
Talc

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

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

6.5 Nature and contents of container
25 mg:
White PVC/PVdC/Al blisters or
White PVC/PE/PVdC/Al blisters or
OPA/Alu/PVC/Al blisters
Pack sizes: 1, 14, 20, 28, 30, 56, 60, 90 and 98 film-coated tablets. Hospital packs of 50 (50 x 1) film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
TEVA UK Limited,
Brampton Road,

Hampden Park
Eastbourne
East Sussex
BN22 9AG
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0963

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/04/2008

10 DATE OF REVISION OF THE TEXT
22/04/2008

1 NAME OF THE MEDICINAL PRODUCT

Losartan potassium 50 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each losartan potassium tablet contains 50 mg losartan potassium.
Excipients:
Each 50 mg tablet contains 9 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
50 mg: White, oval, slightly arched film-coated tablets, debossed "50" on one side, scoreline on the other.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.
Treatment of patients with hypertension with left ventricular hypertrophy to reduce the risk of stroke (see section 5.1).
Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment

4.2 Posology and method of administration

Losartan tablets should be swallowed with a glass of water.
Losartan may be administered with or without food.
Hypertension
The usual initial and maintenance dose is 50 mg once daily. 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 2 x 50 mg losartan daily (in the morning and in the evening) or 100 mg losartan once daily (in the morning).
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.
Hypertensive type 2 diabetic patients with proteinuria ≥ 0.5 g/day
The usual initial 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.
Use in patients with intravascular volume depletion
For the very small proportion of patients who have intravascular volume depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see section 4.4).
Use in patients with renal impairment and haemodialysis patients
No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.
Use in patients with hepatic impairment
A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is not recommended in patients with severe hepatic impairment (see sections 4.3 and 4.4).
Use in the elderly
Although consideration should be given to initiating therapy with 25 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.
Use in children and adolescents (<18 years)
There is no experience in children and adolescents. Therefore, losartan should not be administered to children and adolescents.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see sections 4.4 and 6.1)
Pregnancy and lactation (see section 4.6)
Severe hepatic impairment

4.4 Special warnings and precautions for use

Angioedema

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

Intravascular volume depletion

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

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group (see section 4.8 'Hypertension and type 2 diabetes with renal disease - Investigations' and 'Post-marketing experience - Investigations').

Therefore, the plasma concentrations of potassium and creatinine should be closely monitored; especially patients with heart failure and plasma creatinine concentrations between 1.2 mg/dl and 2.5 mg/dl should be closely monitored.

Liver function impairment

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

Renal function impairment

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

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

Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Renal transplantation

There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism

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

Coronary heart disease and cerebrovascular disease:

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

Heart failure

In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment. There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life-threatening cardiac arrhythmias.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

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

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).

Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorbtion

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

Other warnings and precautions

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

4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents may increase the hypotensive effects of losartan.
Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan with rifampicin (inducer of metabolic enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).
As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.
Non-steroidal anti-inflammatory drugs: When angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
In patients with pre-existing renal dysfunction the co-administration of non-steroidal anti-inflammatory drugs (such as indomethacin), including selective COX-2 inhibitors, may lead to a worsening of renal function. These changes in renal function may be reversible upon discontinuation of therapy.
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with antiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

4.6 Pregnancy and lactation

Pregnancy
There are very limited data from the use of losartan in pregnant women. These data are insufficient to allow conclusions about potential risks for the fetus when used during the first trimester.
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 potassium 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 system can cause fetal and neonatal injury (hypotension, renal dysfunction, oliguria and/or anuria, oligohydramnios, skull hypoplasia, intrauterine growth retardation) and death. Cases of lung hypoplasia, facial abnormalities and limb contractures have also been described.
Animal studies with losartan have demonstrated late fetal and neonatal injury in the kidney. The mechanism is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.
Based on the above information, losartan potassium is contraindicated in pregnancy. If pregnancy is detected during treatment losartan potassium should be discontinued (see section 4.3).
Lactation
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the breast-fed infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequency of adverse events listed below is defined using the following convention:
very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).
In controlled clinical trials for essential hypertension, hypertensive patients with left ventricular hypertrophy, chronic heart failure as well as for hypertension and type 2 diabetes mellitus with renal disease, the most common adverse event was dizziness.
Hypertension

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

Nervous system disorders
Common: dizziness, vertigo
Uncommon: somnolence, headache, sleep disorders
Cardiac disorders
Uncommon: palpitations, angina pectoris
Vascular disorders
Uncommon: symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash
Gastrointestinal disorders
Uncommon: abdominal pain, obstipation
General disorders and administration site conditions
Uncommon: asthenia, fatigue, oedema

Hypertensive patients with left ventricular hypertrophy

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy the following adverse events were reported:

Nervous system disorders
Common: dizziness
Ear and labyrinth disorders
Common: vertigo
General disorders and administration site conditions
Common: asthenia/fatigue

Chronic heart failure

In a controlled clinical trial in patients with cardiac insufficiency the following adverse events were reported:

Nervous system disorders
Uncommon: dizziness, headache
Rare: paraesthesia
Cardiac disorders
Rare: syncope, artrial fibrillation, cerebrovascular accident
Vascular disorders
Uncommon: hypotension, including orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea
Gastrointestinal disorders
Uncommon: diarrhoea, nausea, vomiting
Skin and subcutanous tissue disorders
Uncommon: urticaria, pruritus, rash
General disorders and administration site conditions
Uncommon: asthenia/fatigue

Hypertension and type 2 diabetes with renal disease

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

Nervous system disorders
Common: dizziness
Vascular disorders
Common: hypotension
General disorders and administration site conditions
Common: asthenia/fatigue
Investigations
Common: hypoglycaemia, hyperkalaemia

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

Blood and lymphatic system disorders
Not known: anaemia
Cardiac disorders
Not known: syncope, palpitations
Vascular disorders
Not known: orthostatic hypotension
Gastrointestinal disorders

Not known: diarrhoea
Musculoskeletal and connective tissue disorders
Not known: back pain
Renal and urinary disorders
Not known: urinary tract infections
General disorders and administration site conditions
Not known: flu-like symptoms
Post-marketing experience
The following adverse events have been reported in post-marketing experience:
Blood and lymphatic system disorders
Not known: anaemia
Very rare: thrombocytopenia
Immune system disorders
Rare: hypersensitivity: anaphylactic reactions, angiooedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angiooedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors; vasculitis, including Henoch-Schonlein purpura.
Nervous system disorders
Not known: migraine
Respiratory, thoracic and mediastinal disorders
Not known: cough
Gastrointestinal disorders
Not known: diarrhoea, vomiting, dysgeusia
Hepatobiliary disorders
Rare: hepatitis
Not known: liver function abnormalities
Skin and subcutaneous tissue disorders
Not known: urticaria, pruritus, rash, erythroderma
Musculoskeletal and connective tissue disorders
Not known: myalgia, arthralgia
Renal disorders
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy (see section 4.4).
Investigations
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with losartan developed hyperkalaemia >5.5 mEq/l and 3.4% of patients treated with placebo (see section 4.4, 'Electrolyte imbalances').
In a controlled clinical trial on patients with cardiac insufficiency, increase in blood urea, serum creatinine and serum potassium has been reported.

4.9 Overdose

Symptoms of intoxication
No experience with overdose in man is available so far. The most likely symptoms, depending on the extent of overdose, are hypotension, tachycardia, possibly bradycardia.
Treatment of intoxication
Measures are depending on the time of intake and kind and severity of symptoms. Stabilisation of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.
Neither losartan nor the active metabolite can be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonist, plain
ATC code: C09C A01
Losartan is a synthetic oral angiotensin II receptor (type AT_1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system and an important

determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation.

Losartan selectively blocks the AT_1 receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of its source or route of synthesis.

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

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

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

Hypertension studies

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

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

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

LIFE study

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or 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.

There was a generally good level of tolerance in this study, and losartan's tolerability profile was superior, when seen in relation to atenolol, based on a significantly lower number of patients forced to abandon the study due to side effects.

Race

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

RENAAL Study

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a controlled clinical study conducted worldwide in 1,513 type 2 diabetic patients with proteinuria, with (96.7%) or without hypertension. 751 patients were treated with losartan.

The objective of the study was to demonstrate the nephroprotective effect of losartan potassium over and above the benefit of a lowering of blood pressure. Patients with proteinuria and a serum creatinine of 1.3-3.0 mg/dl 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 the study medication to 100 mg daily as appropriate; 72% of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensives (diuretic agents, calcium antagonists, alpha and beta receptor blockers and centrally active antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed for up to 4.6 years (3.4 years on average.)
The primary endpoint of the study was a composite endpoint of doubling of serum creatinine, end-stage renal failure (need for dialysis or transplantation) or death.
The results showed that treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint. For the following individual and combined components of the primary endpoint, the results also showed a significant risk reduction in the group treated with losartan: 25.3% risk reduction for doubling of serum creatinine (p=0.006); 28.6% risk reduction for end-stage renal failure (p=0.002); 19.9% risk reduction for end-stage renal failure or death (p=0.009); 21.0% risk reduction for doubling of serum creatinine or end-stage renal failure (p=0.01).
The all-cause mortality rate was not significantly different between the two treatment groups.
In this study, losartan was generally well tolerated, as shown by a therapy discontinuation rate on account of adverse events that was comparable to the placebo group.

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. Peak plasma concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. The systemic bioavailability of losartan potassium is approx. 33%.
Distribution
Both losartan and its active metabolite are ≥ 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.
Biotransformation
Approximately 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, circulating plasma radioactivity is attributed primarily to losartan and its active metabolite. In approximately 1% of subjects, a low conversion of losartan to the active metabolite was found.
Elimination
Plasma clearance of losartan and its active metabolite is approximately 600 ml/min and 50 ml/min, respectively. Following oral administration, plasma concentrations of losartan potassium and its active metabolite decline polyexponentially with a terminal half-life of approximately 2 hours and 6-9 hours, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, approximately 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite.
Both biliary and urinary excretion contribute to the elimination of losartan potassium and its metabolites. Following an oral dose of 14C-labelled losartan potassium in man, approximately 35% of radioactivity is recovered in the urine and 58% in the faeces. Following intravenous administration of 14C-labelled losartan potassium, approximately 43% of the radioactivity is recovered in the urine and 50% in the faeces.
Linearity
The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg.
During once-daily dosing, neither losartan nor its active metabolite accumulates significantly in plasma.
Characteristics in patients
In elderly hypertensive patients the plasma concentrations of losartan and its active metabolite do not differ essentially from those found in young hypertensive patients.
In female hypertensive patients the plasma levels of losartan were up to twice as high as in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women.

In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma levels of losartan and its active metabolite after oral administration were, respectively, 5 and 1.7 times higher than in young male volunteers (see sections 4.2 and 4.4).
Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/minute. Compared to patients with normal renal function, the AUC for losartan is approximately 2 times 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
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to cause weight loss, mortality and/or renal toxicity in rat fetuses and newborn rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core
Lactose monohydrate
Cellulose, microcrystalline
Maize starch, pregelatinized
Magnesium stearate
Coating
Polyvinyl alcohol
Titanium dioxide (E 171)
Macrogol
Talc

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

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

6.5 Nature and contents of container
50 mg:
White PVC/PVdC/Al blisters or
White PVC/PE/PVdC/Al blisters or
OPA/Alu/PVC/Al blisters
Pack sizes: 1, 14, 20, 28, 30, 56, 60, 90, 98 and 100 film-coated tablets. Hospital packs of 50 (50 x 1) & 280 (10 x 28) film-coated tablets..
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
TEVA UK Limited,
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0964

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/04/2008

10 DATE OF REVISION OF THE TEXT
22/04/2008

1 NAME OF THE MEDICINAL PRODUCT

Losartan potassium 100 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each losartan potassium tablet contains 100 mg losartan potassium.
Excipients:
Each 100 mg tablet contains 18 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
100 mg: White, oval, slightly arched film-coated tablets, debossed "100" on one side, scoreline "on the other.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.
Treatment of patients with hypertension with left ventricular hypertrophy to reduce the risk of stroke (see section 5.1).
Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment

4.2 Posology and method of administration

Losartan tablets should be swallowed with a glass of water.
Losartan may be administered with or without food.
Hypertension
The usual initial and maintenance dose is 50 mg once daily. 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 2 x 50 mg losartan daily (in the morning and in the evening) or 100 mg losartan once daily (in the morning).
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.
Hypertensive type 2 diabetic patients with proteinuria ≥ 0.5 g/day
The usual initial 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.
Use in patients with intravascular volume depletion
For the very small proportion of patients who have intravascular volume depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see section 4.4).
Use in patients with renal impairment and haemodialysis patients
No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.
Use in patients with hepatic impairment
A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is not recommended in patients with severe hepatic impairment (see sections 4.3 and 4.4).
Use in the elderly
Although consideration should be given to initiating therapy with 25 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.
Use in children and adolescents (<18 years)
There is no experience in children and adolescents. Therefore, losartan should not be administered to children and adolescents.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see sections 4.4 and 6.1)
Pregnancy and lactation (see section 4.6)
Severe hepatic impairment

4.4 Special warnings and precautions for use

Angioedema

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

Intravascular volume depletion

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

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group (see section 4.8 'Hypertension and type 2 diabetes with renal disease - Investigations' and 'Post-marketing experience - Investigations').

Therefore, the plasma concentrations of potassium and creatinine should be closely monitored; especially patients with heart failure and plasma creatinine concentrations between 1.2 mg/dl and 2.5 mg/dl should be closely monitored.

Liver function impairment

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

Renal function impairment

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

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

Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Renal transplantation

There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism

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

Coronary heart disease and cerebrovascular disease:

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

Heart failure

In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment. There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life-threatening cardiac arrhythmias.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

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

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).

Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorbtion

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

Other warnings and precautions

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

4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents may increase the hypotensive effects of losartan.
Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan with rifampicin (inducer of metabolic enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).
As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.
Non-steroidal anti-inflammatory drugs: When angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
In patients with pre-existing renal dysfunction the co-administration of non-steroidal anti-inflammatory drugs (such as indomethacin), including selective COX-2 inhibitors, may lead to a worsening of renal function. These changes in renal function may be reversible upon discontinuation of therapy.
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with antiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

4.6 Pregnancy and lactation

Pregnancy
There are very limited data from the use of losartan in pregnant women. These data are insufficient to allow conclusions about potential risks for the fetus when used during the first trimester.
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 potassium 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 system can cause fetal and neonatal injury (hypotension, renal dysfunction, oliguria and/or anuria, oligohydramnios, skull hypoplasia, intrauterine growth retardation) and death. Cases of lung hypoplasia, facial abnormalities and limb contractures have also been described.
Animal studies with losartan have demonstrated late fetal and neonatal injury in the kidney. The mechanism is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.
Based on the above information, losartan potassium is contraindicated in pregnancy. If pregnancy is detected during treatment losartan potassium should be discontinued (see section 4.3).
Lactation
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the breast-fed infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequency of adverse events listed below is defined using the following convention:
very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).
In controlled clinical trials for essential hypertension, hypertensive patients with left ventricular hypertrophy, chronic heart failure as well as for hypertension and type 2 diabetes mellitus with renal disease, the most common adverse event was dizziness.
Hypertension

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

Nervous system disorders
Common: dizziness, vertigo
Uncommon: somnolence, headache, sleep disorders
Cardiac disorders
Uncommon: palpitations, angina pectoris
Vascular disorders
Uncommon: symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash
Gastrointestinal disorders
Uncommon: abdominal pain, obstipation
General disorders and administration site conditions
Uncommon: asthenia, fatigue, oedema

Hypertensive patients with left ventricular hypertrophy

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy the following adverse events were reported:

Nervous system disorders
Common: dizziness
Ear and labyrinth disorders
Common: vertigo
General disorders and administration site conditions
Common: asthenia/fatigue

Chronic heart failure

In a controlled clinical trial in patients with cardiac insufficiency the following adverse events were reported:

Nervous system disorders
Uncommon: dizziness, headache
Rare: paraesthesia
Cardiac disorders
Rare: syncope, artrial fibrillation, cerebrovascular accident
Vascular disorders
Uncommon: hypotension, including orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea
Gastrointestinal disorders
Uncommon: diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders
Uncommon: urticaria, pruritus, rash
General disorders and administration site conditions
Uncommon: asthenia/fatigue

Hypertension and type 2 diabetes with renal disease

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

Nervous system disorders
Common: dizziness
Vascular disorders
Common: hypotension
General disorders and administration site conditions
Common: asthenia/fatigue
Investigations
Common: hypoglycaemia, hyperkalaemia

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

Blood and lymphatic system disorders
Not known: anaemia
Cardiac disorders
Not known: syncope, palpitations
Vascular disorders
Not known: orthostatic hypotension
Gastrointestinal disorders

Not known: diarrhoea
Musculoskeletal and connective tissue disorders
Not known: back pain
Renal and urinary disorders
Not known: urinary tract infections
General disorders and administration site conditions
Not known: flu-like symptoms
Post-marketing experience
The following adverse events have been reported in post-marketing experience:
Blood and lymphatic system disorders
Not known: anaemia
Very rare: thrombocytopenia
Immune system disorders
Rare: hypersensitivity: anaphylactic reactions, angiooedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angiooedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors; vasculitis, including Henoch-Schonlein purpura.
Nervous system disorders
Not known: migraine
Respiratory, thoracic and mediastinal disorders
Not known: cough
Gastrointestinal disorders
Not known: diarrhoea, vomiting, dysgeusia
Hepatobiliary disorders
Rare: hepatitis
Not known: liver function abnormalities
Skin and subcutaneous tissue disorders
Not known: urticaria, pruritus, rash, erythroderma
Musculoskeletal and connective tissue disorders
Not known: myalgia, arthralgia
Renal disorders
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy (see section 4.4).
Investigations
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with losartan developed hyperkalaemia >5.5 mEq/l and 3.4% of patients treated with placebo (see section 4.4, 'Electrolyte imbalances').
In a controlled clinical trial on patients with cardiac insufficiency, increase in blood urea, serum creatinine and serum potassium has been reported.

4.9 Overdose

Symptoms of intoxication
No experience with overdose in man is available so far. The most likely symptoms, depending on the extent of overdose, are hypotension, tachycardia, possibly bradycardia.
Treatment of intoxication
Measures are depending on the time of intake and kind and severity of symptoms. Stabilisation of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.
Neither losartan nor the active metabolite can be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonist, plain
ATC code: C09C A01
Losartan is a synthetic oral angiotensin II receptor (type AT_1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system and an important

determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation.

Losartan selectively blocks the AT_1 receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of its source or route of synthesis.

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

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

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

Hypertension studies

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

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

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

LIFE study

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or 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.

There was a generally good level of tolerance in this study, and losartan's tolerability profile was superior, when seen in relation to atenolol, based on a significantly lower number of patients forced to abandon the study due to side effects.

Race

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

RENAAL Study

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a controlled clinical study conducted worldwide in 1,513 type 2 diabetic patients with proteinuria, with (96.7%) or without hypertension. 751 patients were treated with losartan.

The objective of the study was to demonstrate the nephroprotective effect of losartan potassium over and above the benefit of a lowering of blood pressure. Patients with proteinuria and a serum creatinine of 1.3-3.0 mg/dl 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 the study medication to 100 mg daily as appropriate; 72% of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensives (diuretic agents, calcium antagonists, alpha and beta receptor blockers and centrally active antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed for up to 4.6 years (3.4 years on average.)
The primary endpoint of the study was a composite endpoint of doubling of serum creatinine, end-stage renal failure (need for dialysis or transplantation) or death.
The results showed that treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint. For the following individual and combined components of the primary endpoint, the results also showed a significant risk reduction in the group treated with losartan: 25.3% risk reduction for doubling of serum creatinine (p=0.006); 28.6% risk reduction for end-stage renal failure (p=0.002); 19.9% risk reduction for end-stage renal failure or death (p=0.009); 21.0% risk reduction for doubling of serum creatinine or end-stage renal failure (p=0.01).
The all-cause mortality rate was not significantly different between the two treatment groups.
In this study, losartan was generally well tolerated, as shown by a therapy discontinuation rate on account of adverse events that was comparable to the placebo group.

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. Peak plasma concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. The systemic bioavailability of losartan potassium is approx. 33%.
Distribution
Both losartan and its active metabolite are ≥ 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.
Biotransformation
Approximately 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, circulating plasma radioactivity is attributed primarily to losartan and its active metabolite. In approximately 1% of subjects, a low conversion of losartan to the active metabolite was found.
Elimination
Plasma clearance of losartan and its active metabolite is approximately 600 ml/min and 50 ml/min, respectively. Following oral administration, plasma concentrations of losartan potassium and its active metabolite decline polyexponentially with a terminal half-life of approximately 2 hours and 6-9 hours, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, approximately 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite.
Both biliary and urinary excretion contribute to the elimination of losartan potassium and its metabolites. Following an oral dose of 14C-labelled losartan potassium in man, approximately 35% of radioactivity is recovered in the urine and 58% in the faeces. Following intravenous administration of 14C-labelled losartan potassium, approximately 43% of the radioactivity is recovered in the urine and 50% in the faeces.
Linearity
The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200mg.
During once-daily dosing, neither losartan nor its active metabolite accumulates significantly in plasma.
Characteristics in patients
In elderly hypertensive patients the plasma concentrations of losartan and its active metabolite do not differ essentially from those found in young hypertensive patients.
In female hypertensive patients the plasma levels of losartan were up to twice as high as in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women.

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

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to cause weight loss, mortality and/or renal toxicity in rat fetuses and newborn rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Lactose monohydrate
Cellulose, microcrystalline
Maize starch, pregelatinized
Magnesium stearate
Coating
Polyvinyl alcohol
Titanium dioxide (E 171)
Macrogol
Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

100 mg:
White PVC/PVdC/Al blisters or
White PVC/PE/PVdC/Al blisters or
OPA/Alu/PVC/Al blisters
Pack sizes: 1, 14, 20, 28, 30, 56, 60, 90, 98 and 100 film-coated tablets. Hospital packs of 50 (50 x 1) & 280 (10 x 28) film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited,
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0965

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/04/2008

10 DATE OF REVISION OF THE TEXT
22/04/2008

MODULE 3

LOSARTAN POTASSIUM 25 mg, 50 mg and 100 mg FILM-COATED TABLETS

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

IN THIS LEAFLET:

1 WHAT LOSARTAN POTASSIUM IS AND WHAT IT IS USED FOR

- Losartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body, which binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Losartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax which in turn lowers the blood pressure. Losartan slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes.
- Losartan potassium is used:
  - To treat patients with high blood pressure (hypertension)
  - To decrease the risk of stroke in patients with high blood pressure and a thickening of the left chamber of the heart (left ventricular hypertrophy)
  - To protect the kidney in hypertensive type 2 diabetic patients whose urine contains an abnormal amount of protein.

2 BEFORE YOU TAKE LOSARTAN POTASSIUM FILM-COATED TABLETS

Do NOT take Losartan potassium Film-coated Tablets
- If you are allergic (hypersensitive) to losartan or any of the other ingredients of this medicine
- If you have severe liver disease
- If you are pregnant or breast-feeding (see also section 2 'Pregnancy and breast-feeding').

Take special care with Losartan potassium Film-coated Tablets
It is important to tell your doctor before taking Losartan potassium Film-coated Tablets:
- if you have had a history of angioedema (swelling of the face, lips, throat, and/or tongue) (see also section 4 'Possible side effects')
- if you suffer from excessive vomiting or diarrhoea
- if you receive diuretics (medicines that increase the amount of water that you pass out through your kidneys) or are under dietary salt restriction (see section 3 'Dosage in special patient groups')
- if you are known to have narrowing or blockage of the blood vessels leading to your kidneys or if you have received a kidney transplant recently
- if your liver function is impaired (see sections 2 "Do not take Losartan" and 3 'Dosage in special patient groups')
- if you have problems with your heart valves or heart muscle
- if you suffer from heart disease or stroke
- if you suffer from primary hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldosterone).

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or herbal medicines and natural products.

Take particular care if you are taking the following medicines while under treatment with losartan potassium:
- other blood pressure-lowering medicines as they may additionally reduce your blood pressure
- medicines which retain potassium or may increase potassium levels (e.g. potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines such as certain diuretics [amiloride, triamterene, spironolactone] or heparin)
- non-steroidal anti-inflammatory drugs such as indometacin, including cox-2-inhibitors (medicines that reduce inflammation, and can be used to help relieve pain) as they may reduce the blood pressure-lowering effect of losartan. If your kidney function is impaired the concomitant use of these medicines may lead to a worsening of the kidney function.
- lithium-containing medicines should not be taken in combination with losartan without close supervision by your doctor. Special precautionary measures (e.g. blood tests) may be appropriate.

Taking Losartan potassium Film-coated Tablets with food and drink
The tablets can be taken with or without food.

Pregnancy and breast-feeding
You must not take losartan potassium if you are pregnant. If you become pregnant while on losartan treatment, tell your doctor immediately, as losartan can harm the unborn child especially in the second and third trimester of pregnancy. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

You must not take losartan if you are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed.
Losartan is unlikely to directly affect your ability to drive or use machines. However, as with many other medicines used to treat high blood pressure, losartan may cause dizziness or drowsiness in some people. If you experience dizziness or drowsiness, you should consult your doctor before attempting such activities.

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

3 HOW TO TAKE LOSARTAN POTASSIUM FILM-COATED TABLETS

Always take Losartan potassium Film-coated Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Patients with high blood pressure
Treatment usually starts with 50 mg losartan (one 50 mg tablet) once a day. The maximal blood pressure lowering effect should be reached 3-6 weeks after beginning treatment. In some patients the dose may later be increased to 50 mg losartan twice a day (one 50 mg tablet in the morning and one 50 mg tablet in the evening) or 100 mg losartan (two 50 mg tablets or one 100 mg tablet) once daily (in the morning).

If you have the impression that the effect of losartan is too strong or too weak, please talk to your doctor or pharmacist.

High blood pressure and a thickening of the left chamber of the heart (left ventricular hypertrophy)
The usual starting dose is 50 mg (one 50 mg tablet) once per day. Depending on how well losartan works, a low dose of hydrochlorothiazide may be added and/or the dose of losartan potassium increased to 100 mg (one 100 mg tablet) once per day.

Patients with high blood pressure and type 2 diabetes
Treatment usually starts with 50 mg losartan (one 50 mg tablet) once a day. The dose may later be increased to 100 mg losartan (two 50 mg tablets or one 100 mg tablet) once daily depending on your blood pressure response.

Dosage in special patient groups
The doctor may advise a lower dose, especially when starting treatment in certain patients such as those treated with diuretics in high doses, in patients with liver disease, or in patients over the age of 75 years. The use of losartan is not recommended in patients with severe liver disease (see section "Do not take Losartan").

Children and adolescents
Losartan should not be given to children and adolescents.

Administration
The tablets should be swallowed with a glass of water. You should try to take your daily dose at about the same time each day. It is important that you continue to take losartan until your doctor tells you otherwise.

If you take more Losartan potassium Film-coated Tablets than you should
If you accidentally take too many tablets, or a child swallows some, contact your doctor immediately. Symptoms of overdose are low blood pressure, increased heartbeat, possibly decreased heartbeat.

If you forget to take Losartan potassium Film-coated Tablets
If you accidentally miss a daily dose, just take the next dose as normal. Do not take a double dose to make up for a forgotten tablet.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 POSSIBLE SIDE EFFECTS

Like all medicines, losartan potassium can cause side effects, although not everybody gets them.

The following side effects have been reported in:

Common (affecting fewer than one person in 10 but more than one person in 100)
- Dizziness
- Feeling of abnormal motion (vertigo)
- Low blood pressure
- Debility, fatigue
- Too little sugar in the blood (hypoglycaemia), too much potassium in the blood (hyperkalaemia).

Uncommon (affecting fewer than one person in 100 but more than one person in 1,000):
- Sleepiness, headache, sleep disorders
- Feeling of increased heart rate (palpitations), severe chest pain (angina pectoris)
- Low blood pressure (especially after excessive loss of water from the body e.g. in patients on treatment with high dose diuretics), dose-related orthostatic effects such as lowering of blood pressure appearing when rising from a lying or sitting position
- Shortness of breath
- Abdominal pain, obstipation, diarrhoea, nausea, vomiting, taste alterations
- Hives (urticaria), itching (pruritus), rash, exfoliative dermatitis
- Localised swelling (oedema).

Rare (affecting fewer than one person in 1,000 but more than one person in 10,000):
- Reduced number of red blood cells (anaemia)
- Severe allergic reactions (anaphylactic reactions), swelling of the face, lips, throat, and/or tongue (angioedema) including hives, difficulties to swallow and to breathe (in some patients in connection with the administration of other medicines, including ACE inhibitors), inflammation of blood vessels (vasculitis including Henoch-Schonlein purpura). **If you develop any of these symptoms you should stop taking losartan and contact your doctor immediately.**
- Numbness or tingling sensation (paraesthesia)
- Fainting, very rapid and irregular heartbeat, stroke
- Inflammation of the liver (hepatitis)
- Elevated blood enzyme levels, usually resolved upon discontinuation of treatment.

Very rare (affecting fewer than one person in 10,000):
- Easy bruising or bleeding.

Not known (cannot be estimated from the available data):
- Migraine
- Fainting (syncope)
- Cough
- Liver function abnormalities
- Muscle and joint pain
- Changes in kidney function including kidney failure
- Flu-like symptoms
- Increase in blood urea, serum creatinine and serum potassium in patients with heart failure.

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

5 HOW TO STORE LOSARTAN POTASSIUM

Keep out of the reach and sight of children. Do not use Losartan Potassium after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
This medicinal product does not require any special storage conditions.

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

6 FURTHER INFORMATION

What Losartan Potassium contains:
- Each film-coated tablet contains 25 mg, 50 mg or 100 mg of the active substance, losartan potassium.
- The other ingredients are as follows:
  Tablet core: lactose monohydrate, microcrystalline cellulose (E460a), pregelatinised starch, magnesium stearate (E572)
  Film-coat: polyvinyl alcohol (partially hydrolysed), titanium dioxide (E171), macrogol, talc.

What Losartan Potassium looks like and contents of the pack:

Losartan potassium 25 mg Film-coated Tablets are white, oval, slightly arched film-coated tablets, debossed "2" scoreline and "5" on one side, scoreline on the other. Available in pack sizes of: 1, 14, 20, 28, 30, 56, 60, 90 and 98. Hospital packs of 50 (50 x 1).

Losartan potassium 50 mg Film-coated Tablets are white, oval, slightly arched film-coated tablets, debossed "50" on one side, scoreline on the other. Available in pack sizes of: 1, 14, 20, 28, 30, 56, 60, 90, 98 and 100. Hospital packs of 50 (50 x 1) & 280 (10 x 28 tablets).

Losartan potassium 100 mg Film-coated Tablets are white, oval, slightly arched film-coated tablets, debossed "100" on one side, scoreline on the other. Available in pack sizes of: 1, 14, 20, 28, 30, 56, 60, 90, 98 and 100. Hospital packs of 50 (50 x 1) & 280 (10 x 28 tablets).

The tablets are packed in white opaque PVC/PVdC/Al blisters or in white opaque PVC/PE/PVdC/Al blisters or in OPA/Alu/PVC/Al blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
TEVA UK Limited, Eastbourne, BN22 9AG

This leaflet was last approved in September 2007

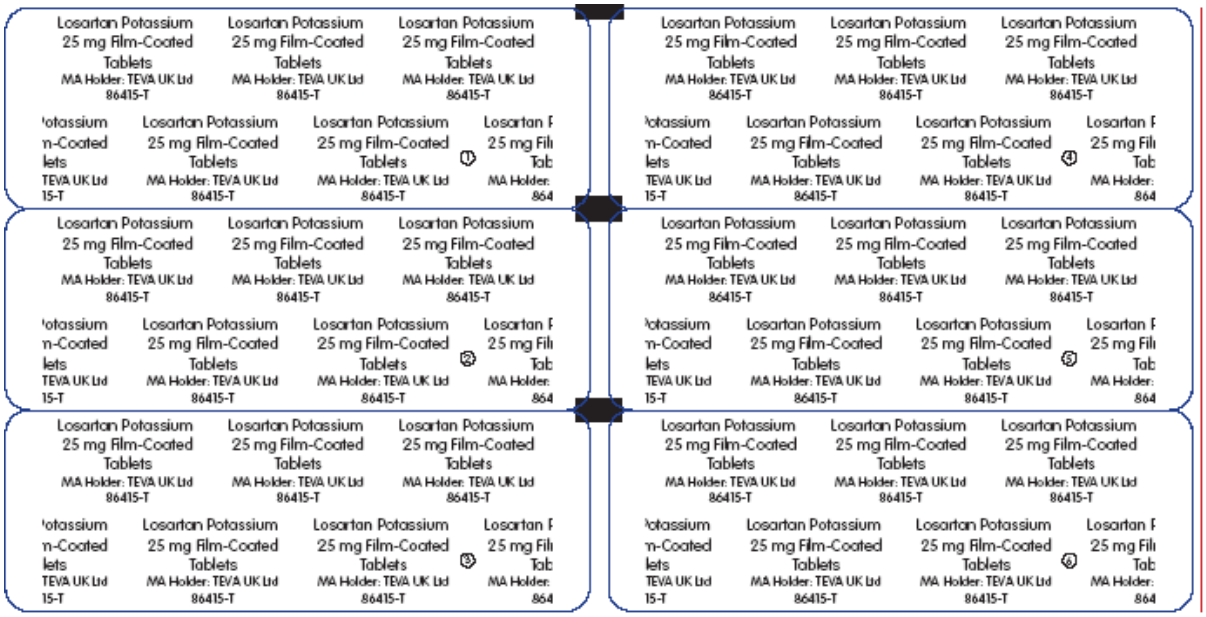
PL 00289/0963
PL 00289/0964
PL 00289/0965

TEVA UK Limited

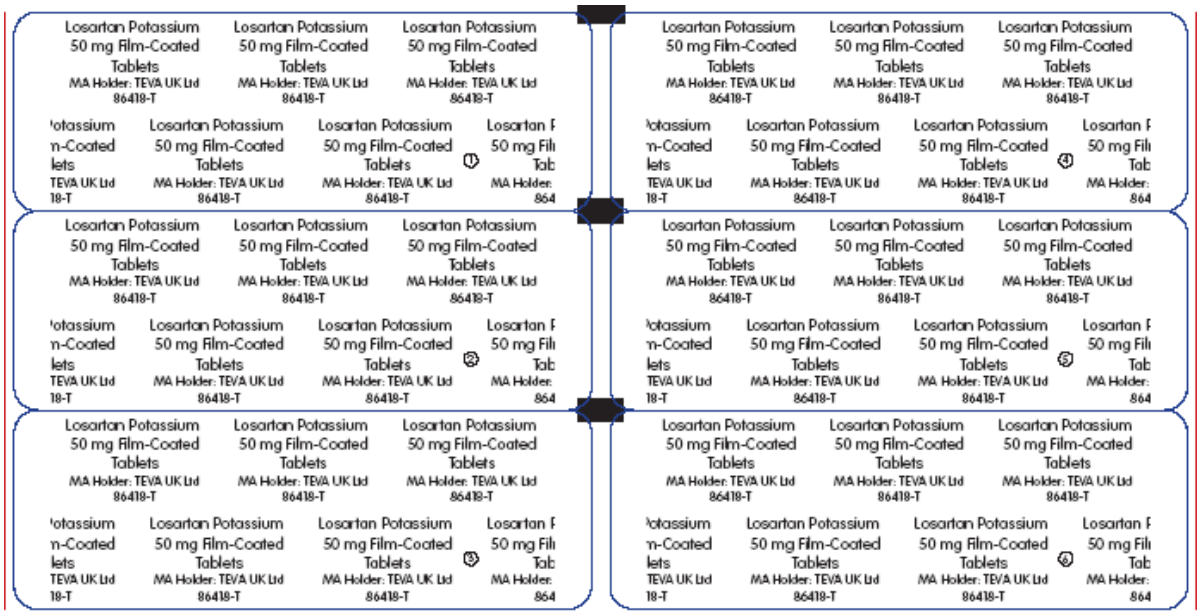
86421-T

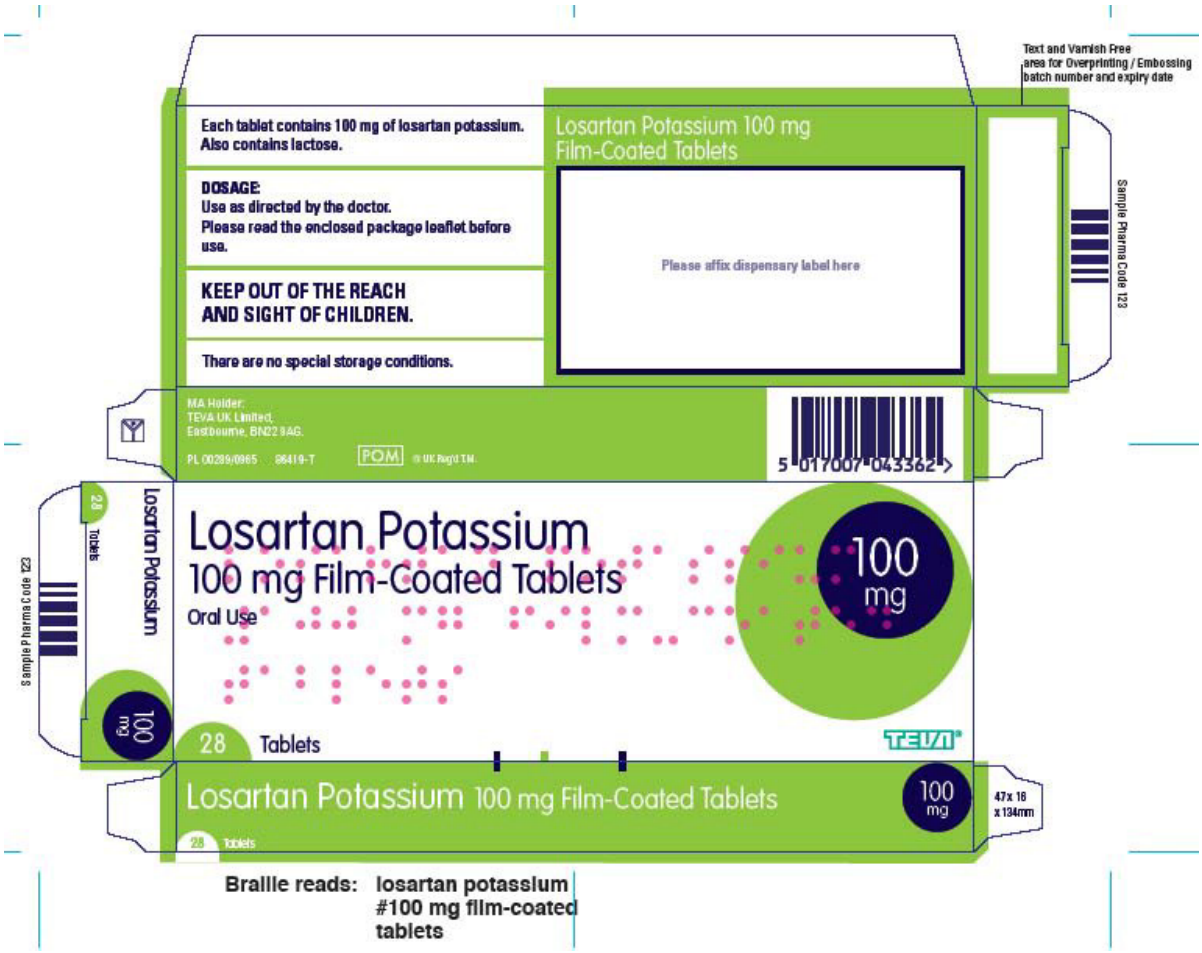
Module 4

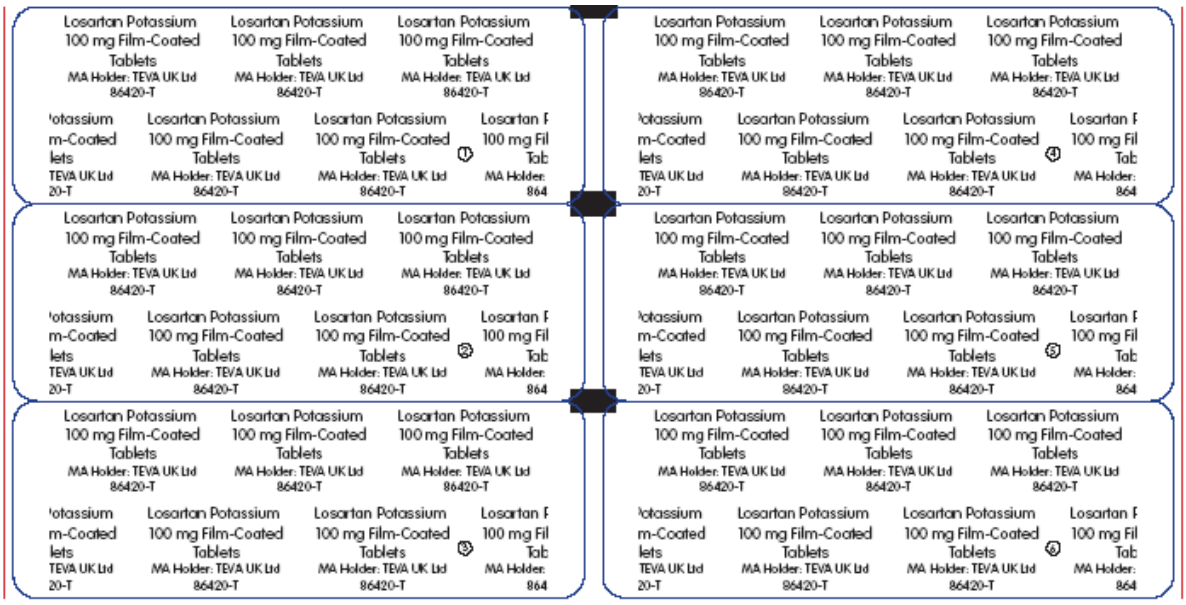

Text and Varnish Free area for Overprinting / Embossing batch number and expiry date
Each tablet contains 25 mg of losartan potassium.
Also contains lactose.
DOSAGE:
Use as directed by the doctor.
Please read the enclosed package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
There are no special storage conditions.
Losartan Potassium 25 mg Film-Coated Tablets
Please affix dispensary label here
Sample Pharma Code 123
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 00289/0863 86414-T
POM
5 017007 043263
Losartan Potassium
25 mg Film-Coated Tablets
Oral Use
25 mg
28 Tablets
TEVA
Losartan Potassium 25 mg Film-Coated Tablets
47x 18 x 134mm
Braille reads: losartan potassium #25 mg film-coated tablets


Losartan Potassium 25 mg Film-Coated Tablets
MA Holder: TEVA UK Ltd
86415-T


Text and Varnish Free area for Overprinting / Embossing batch number and expiry date
Each tablet contains 50 mg of losartan potassium. Also contains lactose.
Losartan Potassium 50 mg Film-Coated Tablets
DOSAGE:
Use as directed by the doctor.
Please read the enclosed package leaflet before use.
Please affix dispensary label here
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
There are no special storage conditions.
Sample Pharma Code 123
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 00289/0964 86417-T
POM
5 017007 043294
Losartan Potassium
50 mg Film-Coated Tablets
Oral Use
50 mg
28 Tablets
TEVA
Losartan Potassium 50 mg Film-Coated Tablets
47x 16 x 134mm
Braille reads: losartan potassium #50 mg film-coated tablets


Losartan Potassium 50 mg Film-Coated Tablets
MA Holder: TEVA UK Ltd
86418-T


Text and Varnish Free area for Overprinting / Embossing batch number and expiry date
Each tablet contains 100 mg of losartan potassium. Also contains lactose.
Losartan Potassium 100 mg Film-Coated Tablets
DOSAGE:
Use as directed by the doctor.
Please read the enclosed package leaflet before use.
Please affix dispensary label here
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
There are no special storage conditions.
Sample Pharma Code 123
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 00289/0965 86419-T
POM
5 017007 043362
Losartan Potassium
100 mg Film-Coated Tablets
Oral Use
100 mg
28 Tablets
TEVA
Losartan Potassium 100 mg Film-Coated Tablets
47 x 18 x 134mm
Braille reads: losartan potassium #100 mg film-coated tablets


Losartan Potassium 100 mg Film-Coated Tablets
MA Holder: TEVA UK Ltd 86420-T

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.

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.
These are immediate release formulations to be marketed in the UK and the Netherlands, Norway, Hungary, France, Italy, Finland, Denmark, Portugal, Sweden, Slovenia and Austria by TEVA UK Limited. The applications are considered to be generic medicinal products of Cozaar Tablets and the applicant has provided the required bioavailability/bioequivalence studies.

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/925/02-04/DC
Reference Member State	United Kingdom
Member States Concerned	NL, NO, IT, HU, FR, FI, DK, and AT PT, SE, SI (only 50 and 100 mg strengths)
Marketing Authorisation Number(s)	PL 00289/0963-5
Name and address of the authorisation holder	TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug Substance

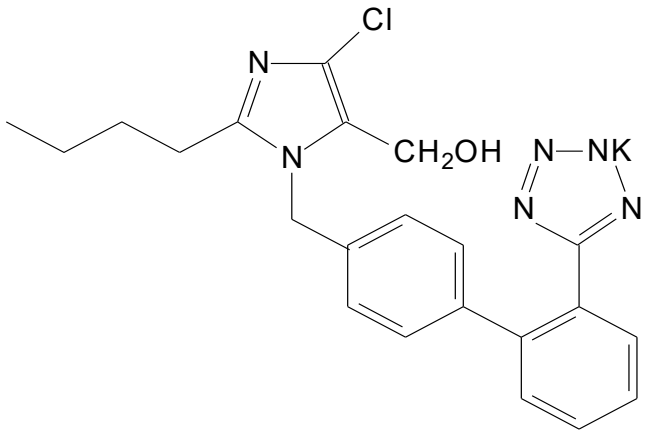
Nomenclature and structure

INN: Losartan potassium
In-house name: Losartan potassium

Chemical name:
(i) 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl-phenyl)benzyl]-imidazole-5-methanol monopotassium salt
(ii) 2-n-butyl-4-chloro-5-hydroxymethyl-1-[((2'-1H-tetrazol-5-yl)biphenyl-4-yl0methyl] imidazol potassium salt

CAS number: 124750-99-8

Structure



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

General properties

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

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 18 months is justified.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, starch pregelatinised, microcrystalline cellulose, magnesium stearate, titanium dioxide E171, macrogol, talc, and polyvinyl alcohol. 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 PVC/PVDC/PE/OPA/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 3 years with no special storage conditions is proposed. 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 Potassium 25 mg, 50 mg & 100 mg Film-coated tablets (PL 00289/0963-5) 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).

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:

Treatment of essential hypertension.

Treatment of patients with hypertension with left ventricular hypertrophy to reduce the risk of stroke (see section 5.1).

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

4. DOSE & DOSE SCHEDULE

See the SPC for full details. The recommended dosages and dose schedules are consistent with the reference product.

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.

Bioequivalence studies

A single pivotal biostudy was conducted with the 50mg strength at the clinical facility. The analytical part of the studies were conducted at the same centre.

Study title; Randomised, 2-way cross-over, bioequivalence study of Losartan 50mg tablet and Cozaar administered 1x50mg tablet in healthy subjects under fasting conditions.

Study design

The study was a single centre, Randomised, two-way, two-period, single dose crossover design in healthy fasted volunteers. While 80 healthy adults aged 18-55 years were enrolled, only 72 were available for analysis as 6 dropped out and there were 2 withdrawals.

The Pre-defined bioequivalence acceptance criteria were 0.8 to 1.25 for both AUC and C_{max}. This is satisfactory.

The sampling frequency (21 samples; one pre dose and 20 samples up to 36 hours post dose), the duration of sampling, the LOQ of the assay (1.00ng/ml) and the washout period (of 7 days) appear satisfactory.

The active metabolite of Losartan was assayed in all subjects and data are presented. This is appropriate.

Results

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

Losartan (parent)

	Test	**Reference**	***Pt Est (90%CI)***
C_{max} (ng/mL)	235.23 ± 116.97	215.14 ± 115.83	**110.4 (98.7 -123.5)**
AUC_t (ng.h/mL)	449.84 ± 174.66	441.19 ± 163.76	**101.4 (98.7 – 104.2)**
AUC_∞ (ng.h/mL)	459.32 ± 181.15	453.99 ±173.94	**100.6 (97.9 to 103.5)**
T_{max}	1.18 ± 0.91	1.43 ±1.09	
Residual Area (%)	1.97 ±1.09	2.70 ±4.11	

E-3174 (metabolite)

	Test	**Reference**	***Pt Est (90%CI)***
C_{max} (ng/mL)	277.68 ±110.4	263.7 ± 102.27	**105.03 (100.3 – 109.9)**
AUC_t (ng.h/mL)	2070.89± 789.76	2019.04 ±743.69	**102.3 (100.35 – 104.35)**
AUC_∞ (ng.h/mL)	2110.48 ±800.6	2061.66 ± 755.58	**102.06 (100.17-103.99)**
T_{max}	3.84 ±1.21	4.18 ±1.54	
Residual Area (%)	2.07 ±1.85	2.34 ± 2.60	

In the pivotal study the 90% confidence intervals for both parent and metabolite lie within the pre-defined limits of 0.8 – 1.25 and these also fulfil the acceptance criteria for bioequivalence. Importantly, the 90% CI were narrow and close for both the parent and the metabolite, especially for the AUC. The residual areas were also small and clearly <20% suggesting that the point of extrapolation was appropriate (by corollary, the sampling period was of sufficient duration).

There were no significant sequence or period effect in any of the studies and the validity of the assay was acceptable.

Assessor's comment
The Pivotal bioequivalence studies had sufficient number of subjects. The confidence intervals for all parameters for both parent and metabolite are within the acceptance limits.

Assessor's conclusion on bioequivalence
Bioequivalence can be concluded based on the pivotal study data according to conditions in Note for guidance on the investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4. The applicant has provided details of the pilot II study.

6. EFFICACY

The applicant has provided the requisite Biostudy in support of these applications. A single biostudy comparing 50mg 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.

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 TEVA UK Ltd is a generic product with losartan potassium as the active ingredient. The documentation with regard to quality, non-clinical and the clinical parts has been satisfactory and appropriate justifications have been provided in accordance with relevant guidelines. Bioequivalence with the originator has been established for the 50 mg strength and biowaiver criteria fulfilled for other strengths. The results form the 50 mg strength may be extrapolated to 100mg as the kinetics of Losartan have been demonstrated to be linear.

Overall the benefit: risk ratio is considered positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome