Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

LOSARTAN POTASSIUM 25MG, 50MG AND 100MG FILM-COATED TABLETS

UK/H/1096/001-3/DC
UK Licence No: PL 20075/0021-3

ACCORD HEALTHCARE LIMITED

LAY SUMMARY

On 23rd January 2009, the UK granted Accord Healthcare Limited Marketing Authorisations (licences) for the prescription only medicinal products Losartan Potassium 25mg, 50mg and 100mg Film-Coated Tablets (PL 20075/0021-3, UK/H/1096/001-3/DC).

Losartan belongs to a group of medicines called angiotensin receptor antagonists. Angiotensin is a naturally occurring chemical in the body that narrows blood vessels and makes it harder for blood to pass through, causing blood pressure to increase. Losartan blocks the effects of angiotensin, causing blood vessels to relax.

Losartan Potassium is used:

- To treat patients with high blood pressure (hypertension)
- To protect the kidney in some diabetics with high blood pressure.
- To reduce the risk of stroke in patients with high blood pressure and a thickening of the heart muscle.

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

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Module 1

Product Name	Losartan Potassium 25mg, 50mg and 100mg Film-Coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Losartan Potassium
Form	Film-Coated Tablets
Strength	25mg, 50mg, 100mg
MA Holder	Accord Healthcare Limited Sage House, 319 Pinner road, Harrow, Middlesex, HA1 4HF
Reference Member State (RMS)	UK
CMS	Belgium, Estonia, Germany, Hungary, Ireland, Italy, Latvia, Malta, The Netherlands, Portugal and Spain
Procedure Number	UK/H/1096/001-3/DC
End of Procedure	Day 60 after referral- 23rd December 2008

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 film-coated tablet contains 25mg of losartan potassium, equivalent to 22.9mg of Losartan.
Excipient:
26mg of lactose/film-coated tablet.
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablet
White to off white, round, biconvex, film-coated tablets with breakline on one side and "25" debossing on other side.
The break line 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 renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria 0.5 g/day as part of an antihypertensive treatment.
- Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

4.2 Posology and method of administration
Losartan tablets should be swallowed with a glass of water.
The Losartan Potassium tablet can be taken with or without food.
Hypertension
The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning).
Losartan Potassium Tablets may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

Pediatric hypertension
There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 years old for the treatment of hypertension (see section 5.1). Limited pharmacokinetic data are available in hypertensive children above one month of age (see section 5.2).

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

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

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.
It is not recommended in children with glomerular filtration rate < 30 ml/ min / 1.73 m2, as no data are available (see section 4.4).
Losartan is also not recommended in children with hepatic impairment (see section 4.4).

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

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

Use in patients with intravascular volume depletion:
For patient with 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 patient with renal impairment and haemodialysis patients:
No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

Use in patient 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 section 4.3 and 4.4).

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

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

4.4 Special warnings and precautions for use
Hypersensitivity:
Angiooedema. Patients with a history of angiooedema (swelling of the face, lips, throat, and/ or tongue) should be closely monitored (See section 4.8).

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

Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with Losartan Potassium Tablets ' as compared to the placebo group (see section 4.8). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a Creatinine Clearance between 30-50 ml/ min should be closely monitored.
The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with losartan is not recommended (see section 4.5)

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

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

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

Use in pediatric patients with renal function impairment
Losartan is not recommended in children with glomerular filtration rate < 30ml/ min/ 1.73 m^2as no data are available (see section 4.2).
Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.
Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

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 tablets 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. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution (see section 5.1).

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents may increase the hypotensive action of Losartan. Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.

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

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.

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

4.6 Pregnancy and lactation

Pregnancy

The use of Losartan is not recommended during the first trimester of pregnancy (see section 4.4).The use of Losartan is contraindicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there are no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitor (AIIRAs), similar risks may exist for this class of drugs. Unless continued ARB therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with Losartan should be stopped immediately, and, if appropriate, alternative therapy should be started.

Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Should exposure to Losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken losartan should be closely observed for hypotension (see section 4.3 and 4.4).

Lactation

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

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 disorder:
Uncommon: palpitations, angina pectoris
Vascular disorders:
Uncommon: symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash.
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
Muscoskeletal and connective tissue disorders:
not known: back pain
Renal and urinary disorders:
not known: urinary tract infections
General disorders and administration site conditions:
not known: flu-like symptoms

Post-marketing experience
The following adverse events have been reported in post-marketing experience:
Blood and lymphatic system disorders:
not known: Anaemia, thrombocytopenia
Immune system disorders:
rare: hypersensitivity: anaphylactic reactions, angiooedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angiooedema had been reported in the past in connection with 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: diarrhea
Hepatobiliary disorders:
rare: hepatitis
not known: liver function abnormalities
Skin and subcutaneous tissue disorders:
not known: urticaria, pruritus, rash
Muscoskeletal 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 tablets. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan tablets developed hyperkalaemia >5.5 mEq/l and 3.4% of patients treated with placebo (see section 4.4).

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

The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients. Data in the pediatric population are limited.

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 drug intake and kind and severity of symptoms. Stabilisation of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. 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 antagonists, plain

ATC code: C09 CA 01

Losartan is a synthetic oral, angiotensin-II receptor (type AT_1) Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

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

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

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity (PRA). 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 the baseline values.

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

Hypertension Studies

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

Discontinuation of losartan in hypertensive patients did not result in an abrupt rise 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 Potassium Tablets 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of Losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.

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

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

RENAAL Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a controlled clinical study conducted worldwide in 1,513 type 2 diabetic patients with proteinuria-with or without hypertension. 751 Patients were treated with Losartan The objective of the study was to demonstrate a nephroprotective effect of Losartan potassium over and above the benefit of a blood lowering pressure.
Patients with proteinuria and a serum creatinine of 1.3 – 3.0 mg/dl were randomised to receive Losartan 50 mg once a day, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE-inhibitors and angiotension II antagonists.

Investigators were instructed to titrate the study medication to 100 mg daily as appropriate; 72% of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed up for up to 4.6 years (3.4 years on average).
The primary endpoint of the study was a composite endpoint of doubling of the serum creatinine end-stage renal failure(need for dialysis or transplantation) or death.

The results showed that treatment with Losartan Potassium Tablets ' (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 composite end point, the results also showed significant risk reduction in the group treated with Losartan: 25.3% risk reduction in doubling of serum creatinine (p=0.006); 28.6% risk reduction in end-stage renal failure (p=0.002); 19.9% risk reduction in end-stage renal failure or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal failure (p=0.01).
All-cause mortality alone was not significantly different between the two treatment groups.
In this study losartan was generally well tolerated, as shown by a therapy discontinuation rate on account of adverse events that was comparable to the placebo group.

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

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

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

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

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

Pediatric Hypertension
The antihypertensive effect of Losartan potassium Tablet was established in a clinical study involving 177 hypertensive pediatric patients 6 to 16 years of age with a body weight > 20 kg and a glomerular filtration rate > 30 ml/ min/ 1.73 m2. Patients who weighted >20kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighted > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious in the low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg), but was attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/ kg, did not appear to offer consistent antihypertensive efficacy.
These results were confirmed during period II of the study where patients were randomized to continue losartan or placebo, after three weeks of treatment. The difference in blood pressure increase as compared to placebo was largest in the middle dose group (6.70 mm Hg middle dose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

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

5.2 Pharmacokinetic properties

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

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

Biotransformation
About 14% of an intravenously or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied. In addition to the active metabolite, inactive metabolites are formed

Elimination
Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

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

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labelled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58% / 50% in the faeces.

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

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

In patients with mild to moderate alcoholic cirrhosis, plasma level of losartan and its active metabolite after oral administration were, respectively, 5 and 1.7 times higher than in young male volunteers.

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

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

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

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

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose
Pregelatinised maize starch
Povidone K-90 (E1201)
Colloidal anhydrous silica (E551)
Talc (E553b)
Magnesium stearate (E572)

Film-coat:
Hyprolose (E463)
Hypromellose (E464)
Polyethylene glycol 400
Titanium dioxide (E171)
Talc (E553b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Clear 250µ polyvinyl chloride (PVC) film coated with 90-gsm polyvinylidene chloride (PVdC) and plain 25µ aluminium blister foil.
Pack size
Tablets are packed in blisters of 28 tablets.

6.6 Special precautions for disposal

No special requirement.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House,
319, Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0021

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/01/2009

10 DATE OF REVISION OF THE TEXT

23/01/2009

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium 50 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg of losartan potassium, equivalent to 45.8mg of Losartan.
Excipient:
52mg of lactose/film-coated tablet.
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
White to off white, round, biconvex, film-coated tablets with breakline on one side and "50" debossing on other side.
The break line 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 renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria 0.5 g/day as part of an antihypertensive treatment.
- Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1).

4.2 Posology and method of administration

Losartan tablets should be swallowed with a glass of water.
The Losartan Potassium tablet can be taken with or without food.

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

Pediatric hypertension
There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 years old for the treatment of hypertension (see section 5.1). Limited pharmacokinetic data are available in hypertensive children above one month of age (see section 5.2).

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

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

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

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

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

Use in patients with intravascular volume depletion:
For patient with 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 patient with renal impairment and haemodialysis patients:
No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

Use in patient 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 section 4.3 and 4.4).

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity:
Angiooedema. Patients with a history of angiooedema (swelling of the face, lips, throat, and/ or tongue) should be closely monitored (See section 4.8).

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

Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with Losartan Potassium Tablets ' as compared to the placebo group (see section 4.8). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a Creatinine Clearance between 30-50 ml/ min should be closely monitored.
The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with losartan is not recommended (see section 4.5)

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

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

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

Use in pediatric patients with renal function impairment
Losartan is not recommended in children with glomerular filtration rate < 30ml/ min/ 1.73 m^2as no data are available (see section 4.2).
Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.
Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

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 tablets 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. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution (see section 5.1).

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction
Other antihypertensive agents may increase the hypotensive action of Losartan. Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.

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

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.

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

4.6 Pregnancy and lactation

Pregnancy

The use of Losartan is not recommended during the first trimester of pregnancy (see section 4.4).The use of Losartan is contraindicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there are no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitor (AIIRAs), similar risks may exist for this class of drugs. Unless continued ARB therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with Losartan should be stopped immediately, and, if appropriate, alternative therapy should be started.

Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Should exposure to Losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken losartan should be closely observed for hypotension (see section 4.3 and 4.4).

Lactation

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

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 disorder:
Uncommon: palpitations, angina pectoris
Vascular disorders:
Uncommon: symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash.
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
Muscoskeletal and connective tissue disorders:
not known: back pain
Renal and urinary disorders:
not known: urinary tract infections
General disorders and administration site conditions:
not known: flu-like symptoms

Post-marketing experience
The following adverse events have been reported in post-marketing experience:
Blood and lymphatic system disorders:
not known: Anaemia, thrombocytopenia
Immune system disorders:
rare: hypersensitivity: anaphylactic reactions, angiooedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angiooedema had been reported in the past in connection with 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: diarrhea
Hepatobiliary disorders:
rare: hepatitis
not known: liver function abnormalities
Skin and subcutaneous tissue disorders:
not known: urticaria, pruritus, rash
Muscoskeletal 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 tablets. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan tablets developed hyperkalaemia >5.5 mEq/l and 3.4% of patients treated with placebo (see section 4.4).

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

The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients. Data in the pediatric population are limited.

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 drug intake and kind and severity of symptoms. Stabilisation of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. 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 antagonists, plain

ATC code: C09 CA 01

Losartan is a synthetic oral, angiotensin-II receptor (type AT_1). Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

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

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

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity (PRA). 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 the baseline values.

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

Hypertension Studies

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

Discontinuation of losartan in hypertensive patients did not result in an abrupt rise 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 Potassium Tablets 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of Losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.

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

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

RENAAL Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a controlled clinical study conducted worldwide in 1,513 type 2 diabetic patients with proteinuria-with or without hypertension. 751 Patients were treated with Losartan The objective of the study was to demonstrate a nephroprotective effect of Losartan potassium over and above the benefit of a blood lowering pressure.
Patients with proteinuria and a serum creatinine of 1.3 – 3.0 mg/dl were randomised to receive Losartan 50 mg once a day, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE-inhibitors and angiotension II antagonists.

Investigators were instructed to titrate the study medication to 100 mg daily as appropriate; 72% of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed up for up to 4.6 years (3.4 years on average).
The primary endpoint of the study was a composite endpoint of doubling of the serum creatinine end-stage renal failure(need for dialysis or transplantation) or death.

The results showed that treatment with Losartan Potassium Tablets ' (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 composite end point, the results also showed significant risk reduction in the group treated with Losartan 25.3% risk reduction in doubling of serum creatinine (p=0.006); 28.6% risk reduction in end-stage renal failure (p=0.002); 19.9% risk reduction in end-stage renal failure or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal failure (p=0.01).
All-cause mortality alone was not significantly different between the two treatment groups.
In this study losartan was generally well tolerated, as shown by a therapy discontinuation rate on account of adverse events that was comparable to the placebo group.

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

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

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

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

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

Pediatric Hypertension
The antihypertensive effect of Losartan potassium Tablet was established in a clinical study involving 177 hypertensive pediatric patients 6 to 16 years of age with a body weight > 20 kg and a glomerular filtration rate > 30 ml/ min/ 1.73 m2. Patients who weighted >20kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighted > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious in the low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg), but was attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/ kg, did not appear to offer consistent antihypertensive efficacy.
These results were confirmed during period II of the study where patients were randomized to continue losartan or placebo, after three weeks of treatment. The difference in blood pressure increase as compared to placebo was largest in the middle dose group (6.70 mm Hg middle dose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

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

5.2 Pharmacokinetic properties

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

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

Biotransformation
About 14% of an intravenously or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied. In addition to the active metabolite, inactive metabolites are formed

Elimination
Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

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

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labelled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58% / 50% in the faeces.

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

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

In patients with mild to moderate alcoholic cirrhosis, plasma level of losartan and its active metabolite after oral administration were, respectively, 5 and 1.7 times higher than in young male volunteers.

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

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

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

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose
Pregelatinised maize starch
Povidone K-90 (E1201)
Colloidal anhydrous silica (E551)
Talc (E553b)
Magnesium stearate (E572)

Film-coat:
Hyprolose (E463)
Hypromellose (E464)
Polyethylene glycol 400
Titanium dioxide (E171)
Talc (E553b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Clear 250µ polyvinyl chloride (PVC) film coated with 90-gsm polyvinylidene chloride (PVdC) and plain 25µ aluminium blister foil.
Pack size
Tablets are packed in blisters of 28 tablets.

6.6 Special precautions for disposal

No special requirement.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House,
319, Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0022

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/01/2009

10 DATE OF REVISION OF THE TEXT

23/01/2009

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

1 NAME OF THE MEDICINAL PRODUCT

Losartan Potassium 100 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100mg of losartan potassium, equivalent to 91.6mg of Losartan.
Excipient:
104mg of lactose/film-coated tablet.
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
White to off white, round, biconvex, film-coated tablets plain on one side and "100" debossing on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Losartan tablets should be swallowed with a glass of water.
The Losartan Potassium tablet can be taken with or without food.

Hypertension

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

Pediatric hypertension

There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 years old for the treatment of hypertension (see section 5.1). Limited pharmacokinetic data are available in hypertensive children above one month of age (see section 5.2).

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients >20 to <50 kg. In exceptional cases the dose can be increased to a maximum of 50 mg once daily. Dosage should be adjusted according to blood pressure response.
In patients >50 kg, the usual dose is 50 mg once daily. In exceptional cases the dose can be adjusted to a maximum of 100 mg once daily. Doses above 1.4 mg/ kg (or in excess of 100 mg) daily have not been studied in pediatric patients.

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.
It is not recommended in children with glomerular filtration rate < 30 ml/ min / 1.73 m2, as no data are available (see section 4.4).
Losartan is also not recommended in children with hepatic impairment (see section 4.4).

Hypertensive type II diabetic patients with proteinuria 0.5 g/day

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

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG

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

Use in patients with intravascular volume depletion:
For patient with 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 patient with renal impairment and haemodialysis patients:
No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

Use in patient 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 section 4.3 and 4.4).

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity:
Angiooedema. Patients with a history of angiooedema (swelling of the face, lips, throat, and/ or tongue) should be closely monitored (See section 4.8).

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

Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with Losartan Potassium Tablets ' as compared to the placebo group (see section 4.8). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a Creatinine Clearance between 30-50 ml/ min should be closely monitored.
The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with losartan is not recommended (see section 4.5)

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

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

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

Use in pediatric patients with renal function impairment
Losartan is not recommended in children with glomerular filtration rate < 30ml/ min/ 1.73 m^2as no data are available (see section 4.2).
Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.
Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

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 tablets 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. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution (see section 5.1).

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction
Other antihypertensive agents may increase the hypotensive action of Losartan. Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.

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

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.

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

4.6 Pregnancy and lactation

Pregnancy

The use of Losartan is not recommended during the first trimester of pregnancy (see section 4.4).The use of Losartan is contraindicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there are no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitor (AIIRAs), similar risks may exist for this class of drugs. Unless continued ARB therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with Losartan should be stopped immediately, and, if appropriate, alternative therapy should be started.

Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Should exposure to Losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken losartan should be closely observed for hypotension (see section 4.3 and 4.4).

Lactation

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

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 disorder:
Uncommon: palpitations, angina pectoris
Vascular disorders:
Uncommon: symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash.
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
Muscoskeletal and connective tissue disorders:
not known: back pain
Renal and urinary disorders:
not known: urinary tract infections
General disorders and administration site conditions:
not known: flu-like symptoms

Post-marketing experience
The following adverse events have been reported in post-marketing experience:
Blood and lymphatic system disorders:
not known: Anaemia, thrombocytopenia
Immune system disorders:
rare: hypersensitivity: anaphylactic reactions, angiooedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angiooedema had been reported in the past in connection with 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: diarrhea
Hepatobiliary disorders:
rare: hepatitis
not known: liver function abnormalities
Skin and subcutaneous tissue disorders:
not known: urticaria, pruritus, rash
Muscoskeletal 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 tablets. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan tablets developed hyperkalaemia >5.5 mEq/l and 3.4% of patients treated with placebo (see section 4.4,).

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

The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients. Data in the pediatric population are limited.

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 drug intake and kind and severity of symptoms. Stabilisation of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. 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 antagonists, plain

ATC code: C09 CA 01

Losartan is a synthetic oral, angiotensin-II receptor (type AT_1) Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

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

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

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity (PRA). 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 the baseline values.

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

Hypertension Studies

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

Discontinuation of losartan in hypertensive patients did not result in an abrupt rise 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 Potassium Tablets 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached,

hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of Losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.

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

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

RENAAL Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a controlled clinical study conducted worldwide in 1,513 type 2 diabetic patients with proteinuria-with or without hypertension. 751 Patients were treated with Losartan The objective of the study was to demonstrate a nephroprotective effect of Losartan potassium over and above the benefit of a blood lowering pressure.

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

Investigators were instructed to titrate the study medication to 100 mg daily as appropriate; 72% of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed up for up to 4.6 years (3.4 years on average).
The primary endpoint of the study was a composite endpoint of doubling of the serum creatinine end-stage renal failure(need for dialysis or transplantation) or death.

The results showed that treatment with Losartan Potassium Tablets ' (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 composite end point, the results also showed significant risk reduction in the group treated with Losartan ': 25.3% risk reduction in doubling of serum creatinine (p=0.006); 28.6% risk reduction in end-stage renal failure (p=0.002); 19.9% risk reduction in end-stage renal failure or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal failure (p=0.01).
All-cause mortality alone was not significantly different between the two treatment groups.
In this study losartan was generally well tolerated, as shown by a therapy discontinuation rate on account of adverse events that was comparable to the placebo group.

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

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

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

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

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

Pediatric Hypertension
The antihypertensive effect of Losartan potassium Tablet was established in a clinical study involving 177 hypertensive pediatric patients 6 to 16 years of age with a body weight > 20 kg and a glomerular filtration rate > 30 ml/ min/ 1.73 m2. Patients who weighted >20kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighted > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious in the low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg), but was attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/ kg, did not appear to offer consistent antihypertensive efficacy.
These results were confirmed during period II of the study where patients were randomized to continue losartan or placebo, after three weeks of treatment. The difference in blood pressure increase as compared to placebo was largest in the middle dose group (6.70 mm Hg middle dose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

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

5.2 Pharmacokinetic properties

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

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

Biotransformation
About 14% of an intravenously or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied. In addition to the active metabolite, inactive metabolites are formed

Elimination
Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

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

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labelled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58% / 50% in the faeces.

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

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

In patients with mild to moderate alcoholic cirrhosis, plasma level of losartan and its active metabolite after oral administration were, respectively, 5and 1.7 times higher than in young male volunteers.

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

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

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

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

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose
Pregelatinised maize starch
Povidone K-90 (E1201)
Colloidal anhydrous silica (E551)
Talc (E553b)
Magnesium stearate (E572)

Film-coat:
Hyprolose (E463)
Hypromellose (E464)
Polyethylene glycol 400
Titanium dioxide (E171)
Talc (E553b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Clear 250µ polyvinyl chloride (PVC) film coated with 90-gsm polyvinylidene chloride (PVdC) and plain 25µ aluminium blister foil.
Pack size
Tablets are packed in blisters of 28 tablets.

6.6 Special precautions for disposal

No special requirement.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House,
319, Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/01/2009

10 DATE OF REVISION OF THE TEXT

23/01/2009

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Module 3

accord

PACKAGE LEAFLET:
INFORMATION FOR THE USER

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

Losartan Potassium

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

In this leaflet:

1. What Losartan Potassium Tablets 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 prevent the effect of angiotensin-II, causing the blood vessels to relax which in turn lowers your blood pressure. Losartan slows the decrease of kidney function in patients with high blood pressure and type II diabetes.

Losartan Potassium is used
- to treat patient with high blood pressure (hypertension)
- to protect the kidney in hypertensive type II diabetic patients with laboratory evidence of impaired renal function and proteinuria 0.5 g per day (a condition in which urine contains an abnormal amount of protein).
- in patients with high blood pressure and a thickening of the left ventricle, Losartan potassium has been shown to decrease the risk of stroke ("LIFE indication").

2. Before you take Losartan Potassium Tablets

Do not take Losartan Potassium Tablets:
- if you are allergic (hypersensitive) to Losartan or any of its other ingredients
- if your liver function is severely impaired
- if you are, think you may be or are planning to become pregnant
- if you are breast-feeding

Take special care with Losartan Potassium Tablets:
It is important to tell your doctor before taking Losartan Potassium Tablets:
- if you have had a history of angiooedema (swelling of the face, lips, throat, and/or tongue)
- if you suffer from excessive vomiting or diarrhoea leading to an extreme loss of fluid and/or salt in your body
- if you receive diuretics (medicines that increase the amount of water that you pass out through your kidneys) or are under dietary salt restriction leading to an extreme loss of fluid and salt in your body
- 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
- if you suffer from heart failure with or without renal impairment or concomitant severe life threatening cardiac arrhythmias Special caution is necessary when you are treated with a ß-blocker concomitantly
- if you have problems with your heart valves or heart muscle
- if you suffer from coronary heart disease (caused by a reduced blood flow in the blood vessels of the heart) or from cerebrovascular disease (caused by a reduced blood circulation in the brain)
- if you suffer from primary hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldosterone by the adrenal gland, caused by an abnormality within the gland)

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. Blood pressure may also be lowered by one of the following drugs/ class of drugs: tricyclic antidepressants, antipsychotics, baclofen, amifostine,
- 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 indomethacin, including cox-2-inhibitors (medicines that reduce inflammation, and can be used to help relieve pain) as they may reduce the blood 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 Tablets with food and drink:
Losartan Potassium Tablets may be taken with or without food.

Pregnancy and breast-feeding:
You should not take losartan in the first 12 weeks of pregnancy, and you must not take them at all after the 13th week as their use during pregnancy may possibly be harmful to the baby. If you become pregnant while on losartan, tell your doctor immediately. 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.

Use in children and adolescents
Losartan Potassium Tablets has been studied in children. For more information, talk to your doctor.

Driving and using machines:
No studies on the effects on the ability to drive and use machines have been performed.
Losartan Potassium Tablet is unlikely to 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 Tablets
This medicine contains lactose.
If you have been told by your doctor that you have an intolerance to some sugars (e.g. Lactose), contact your doctor before taking this medicine.

3. How to take Losartan Potassium Tablets

Always take Losartan Potassium Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Your doctor will decide on the appropriate dose of Losartan Potassium Tablets, depending on your condition and whether you are taking other medicines. It is important to continue taking Losartan Potassium Tablets for as long as your doctor prescribes it in order to maintain smooth control of your blood pressure.

Patient with High Blood Pressure (Hypertension)
- Treatment usually starts with 50 mg losartan (one tablet of Losartan Potassium 50 mg) 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 100 mg losartan (two tablets of Losartan Potassium 50 mg) once daily

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

Patients with high blood pressure and type II diabetes

- Treatment usually starts with 50 mg losartan (one tablet of Losartan Potassium 50 mg) once a day.
- The dose may later be increased to 100 mg losartan (two tablets of Losartan Potassium 50 mg) once daily depending on your blood pressure response.

Losartan tablets may be administered with other blood pressure lowering medicines (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used medicines that decrease the level of glucose in the blood (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

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 impairment, or in patients over the age of 75 years. The use of losartan is not recommended in patients with severe hepatic impairment

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 Potassium Tablets until your doctor tells you otherwise.

If you take more Losartan Potassium 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 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 stop taking Losartan Potassium Tablets

Do not discontinue the treatment without consulting your doctor even if you feel better. It is important that you take Losartan Potassium Tablets for as long as your doctor prescribes it.

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.
If you experience the following, stop taking losartan tablets and tell your doctor immediately or go to the casualty department of your nearest hospital:
A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing).
This is a serious but rare side effect, which affects more than 1 out of 10,000 patients but fewer than 1 out of 1,000 patients. You may need urgent medical attention or hospitalisation.

Possible side effects are listed under headings of frequency, using the following categories:

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

Common:

- dizziness,
- low blood pressure,
- debility,
- fatigue,
- too less sugar in the blood (hypoglycaemia),
- too much potassium in the blood (hyperkalaemia).

Uncommon:

- somnolence,
- headache,
- sleep disorders,
- feeling of increased heart rate (palpitations),
- severe chest pain (angina pectoris),
- low blood pressure (especially after excessive loss of water from the body within blood vessels e.g. in patients with severe heart failure or under 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 (dyspnoea),
- abdominal pain,
- obstipation,
- diarrhoea,
- nausea,
- vomiting,
- hives (urticaria),
- itching (pruritus),
- rash,
- localised swelling (oedema).

Rare:

- inflammation of blood vessels (vasculitis including Henoch-Schönlein purpura),
- numbness or tingling sensation (paraesthesia),
- fainting (syncope),
- very rapid and irregular heartbeat (atrial fibrillation) brain attack (stroke),
- inflammation of the liver (hepatitis),
- elevated blood alanine aminotransferase (ALT) levels, usually resolved upon discontinuation of treatment.

not known:

- reduced number of red blood cells (anaemia),
- reduced number of thrombocytes,
- migraine,
- cough,
- liver function abnormalities,
- muscle and joint pain,
- changes in kidney function (may be reversible upon discontinuation of treatment) including kidney failure,
- flu-like symptoms,
- increase in blood urea,
- serum creatinine and serum potassium in patient
- back pain and urinary track infection.

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

5. How to store Losartan Potassium Tablets

- Keep out of the reach and sight of children
- Do not use the Losartan Potassium Tablets after the expiry date, which is stated on the carton (EXP). The expiry date refers to the last day of that month.
- Do not store above 25°C. Store in the original package in order to protect from moisture.
- 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 Tablets contains:
The active substance is Losartan Potassium.
For 25mg: Each film-coated tablet contains 25 mg of losartan potassium, equivalent to 22.9mg of losartan.
For 50mg: Each film-coated tablet contains 50 mg of losartan potassium, equivalent to 45.8mg of losartan.
For 100mg: Each film-coated tablet contains 100 mg of losartan potassium, equivalent to 91.6mg of losartan.

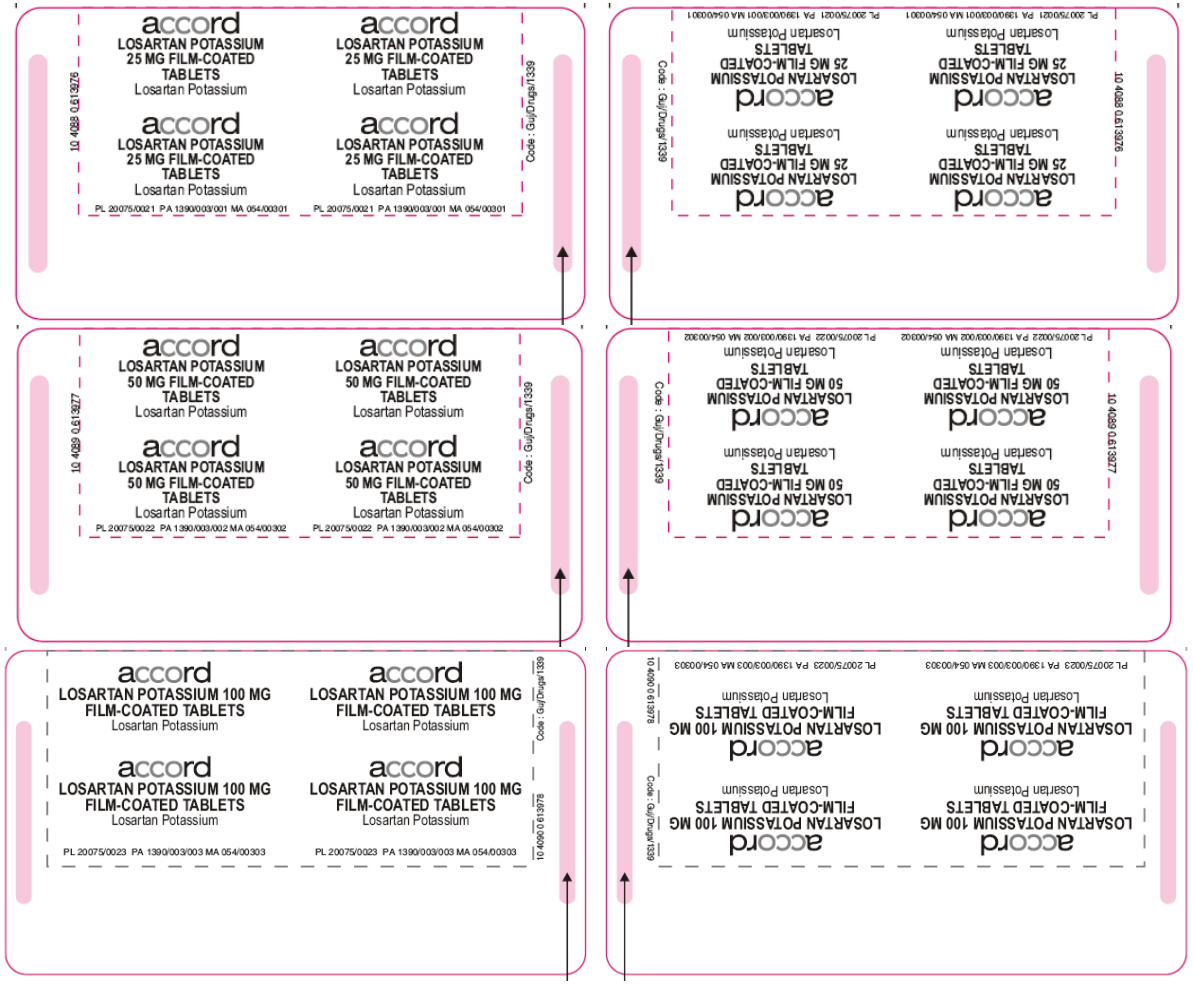
The other ingredients are:
Core tablet: Lactose, pregelatinised maize starch, povidone K-90 (E1201), colloidal anhydrous silica (E551), talc (E553b), magnesium stearate (E572).
Coating materials: Hyprolose (E463), hypromellose (E464), polyethylene glycol 400, titanium dioxide (E171), talc (E553b).

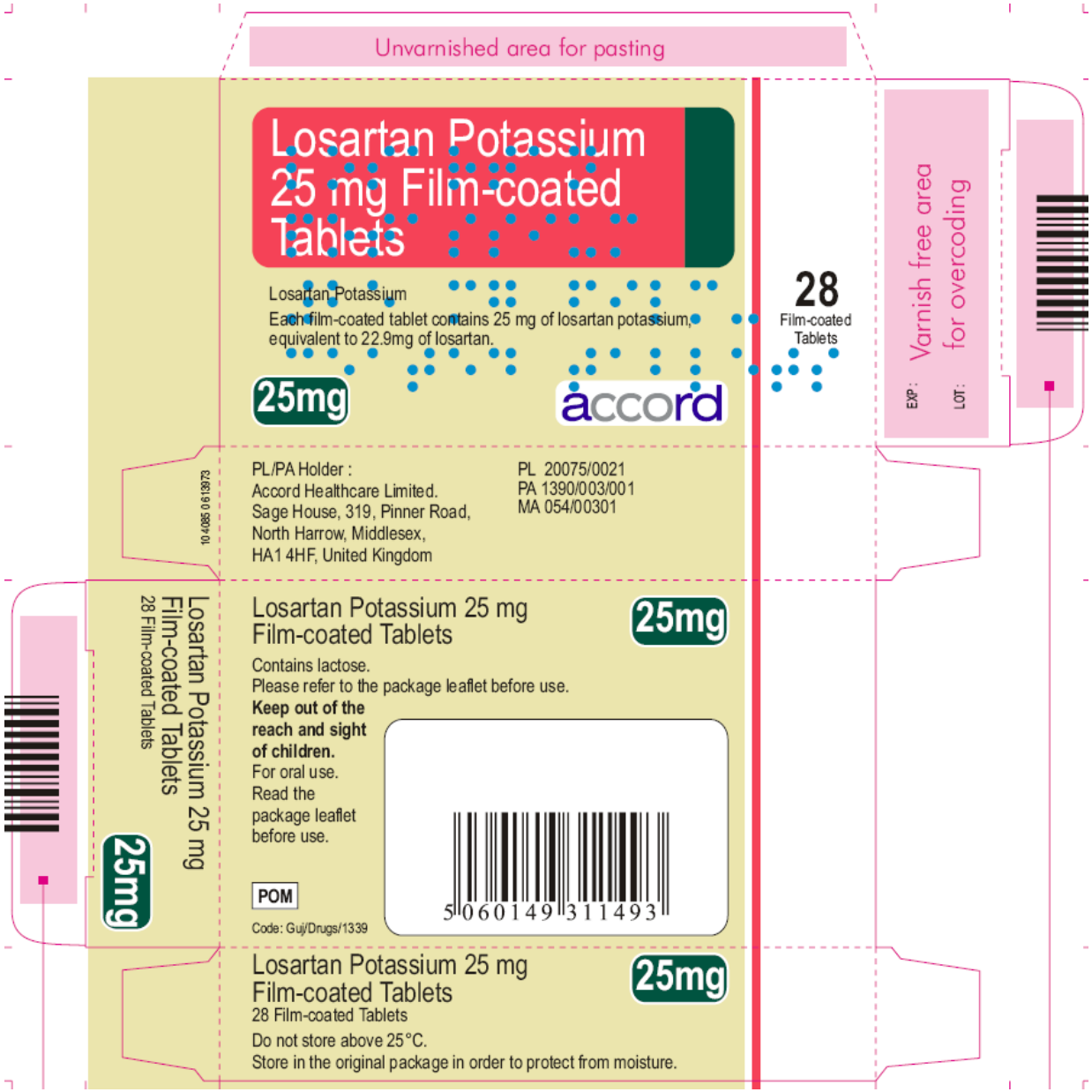
What Losartan Potassium Tablets looks like and content of the pack:
Losartan Potassium Tablets 25mg: White to off white, round, biconvex, film coated tablets with breakline on one side and "25" debossing on other side.
The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses
Losartan Potassium Tablets 50mg: White to off white, round, biconvex, film coated tablets with breakline on one side and "50" debossing on other side.
The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses
Losartan Potassium Tablets 100mg: White to off white, round, biconvex, film coated tablets plain on one side and "100" debossing on other side.
Losartan Potassium Tablets are available in blisters in pack of 28 tablets.

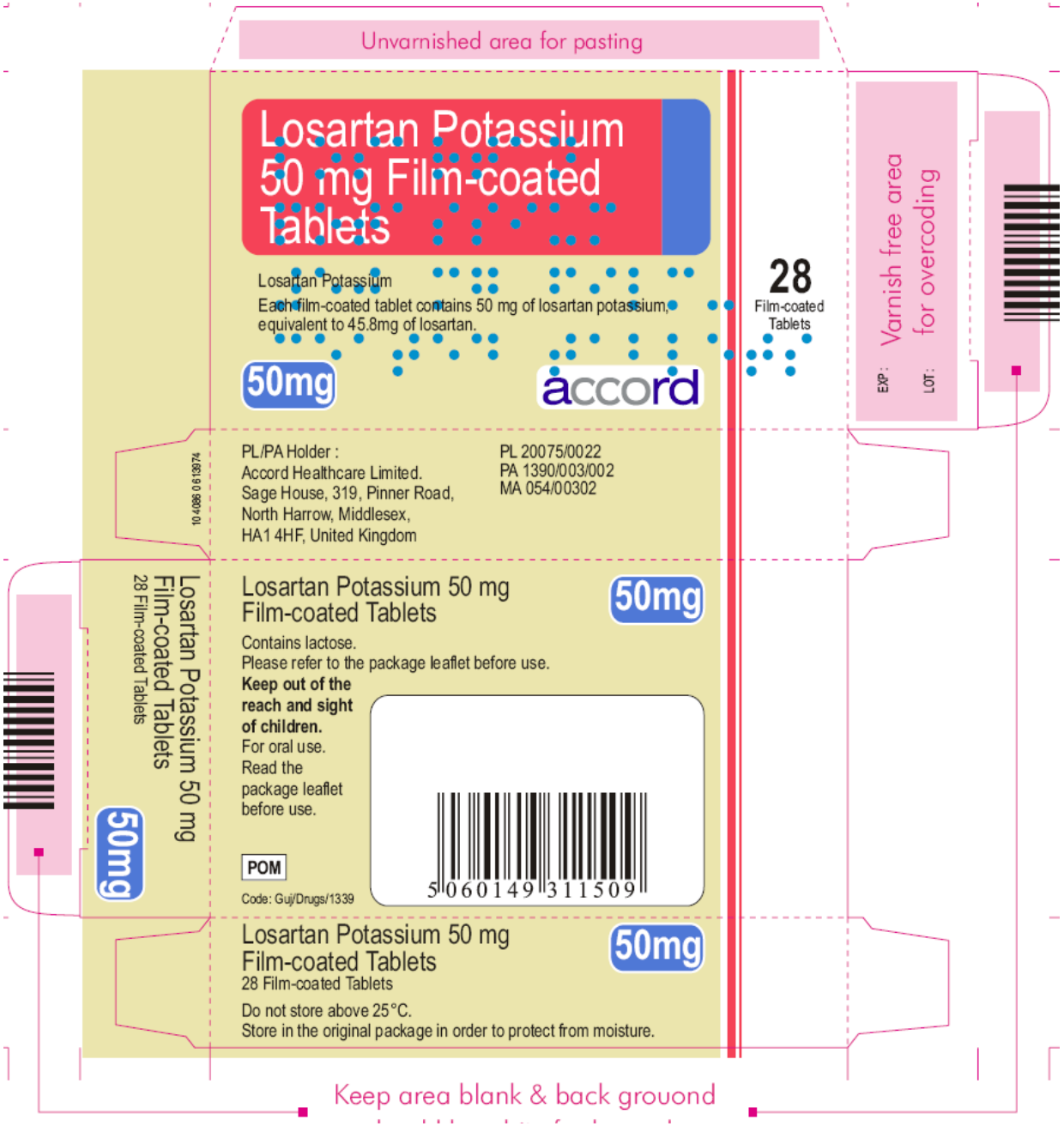
Marketing Authorisation Holder and Manufacturer:
Accord Healthcare Limited
Sage House,
319, Pinner Road,
North Harrow,
Middlesex, HA1 4HF, United Kingdom

The leaflet was last approved in 01/2009.

Module 4
Labelling




Unvarnished area for pasting
Losartan Potassium 25 mg Film-coated Tablets
Losartan Potassium
Each film-coated tablet contains 25 mg of losartan potassium, equivalent to 22.9mg of losartan.
25mg
accord
28
Film-coated Tablets
Varnish free area for overcoding
EXP:
LOT:
10 4085 019873
PL/PA Holder :
Accord Healthcare Limited.
Sage House, 319, Pinner Road,
North Harrow, Middlesex,
HA1 4HF, United Kingdom
PL 20075/0021
PA 1390/003/001
MA 054/00301
Losartan Potassium 25 mg Film-coated Tablets
28 Film-coated Tablets
25mg
Losartan Potassium 25 mg Film-coated Tablets
25mg
Contains lactose.
Please refer to the package leaflet before use.
Keep out of the reach and sight of children.
For oral use.
Read the package leaflet before use.
POM
Code: Guj/Drugs/1339
5 060149 311493
Losartan Potassium 25 mg Film-coated Tablets
25mg
28 Film-coated Tablets
Do not store above 25°C.
Store in the original package in order to protect from moisture.


Unvarnished area for pasting
Losartan Potassium 50 mg Film-coated Tablets
Losartan Potassium
Each film-coated tablet contains 50 mg of losartan potassium, equivalent to 45.8mg of losartan.
50mg
accord
28
Film-coated Tablets
Varnish free area for overcoding
EXP :
LOT :
PL/PA Holder :
Accord Healthcare Limited.
Sage House, 319, Pinner Road,
North Harrow, Middlesex,
HA1 4HF, United Kingdom
PL 20075/0022
PA 1390/003/002
MA 054/00302
10-4086-0181-24
Losartan Potassium 50 mg Film-coated Tablets
28 Film-coated Tablets
50mg
Losartan Potassium 50 mg Film-coated Tablets
50mg
Contains lactose.
Please refer to the package leaflet before use.
Keep out of the reach and sight of children.
For oral use.
Read the package leaflet before use.
POM
Code: Guj/Drugs/1339
5 060149 311509
Losartan Potassium 50 mg Film-coated Tablets
50mg
28 Film-coated Tablets
Do not store above 25°C.
Store in the original package in order to protect from moisture.
Keep area blank & back grouond


Unvarnished area for pasting
Losartan Potassium 100 mg Film-coated Tablets
Losartan Potassium
Each film-coated tablet contains 100 mg of losartan potassium equivalent to 91.6mg of losartan.
100mg
accord
28
Film-coated Tablets
Keep area blank for overcoding
PL/PA Holder :
Accord Healthcare Limited.
Sage House, 319, Pinner Road,
North Harrow, Middlesex,
HA1 4HF, United Kingdom
PL 20075/0023
PA 1390/003/003
MA 054/00303
10 0497 0 65975
Losartan Potassium 100 mg Film-coated Tablets
28 Film-coated Tablets
100mg
Losartan Potassium 100 mg Film-coated Tablets
100mg
Contains lactose.
Please refer to the package leaflet before use.
Keep out of the reach and sight of children. Do not store above 25°C.
Store in the original package in order to protect from moisture.
For oral use.
Read the package leaflet before use.
POM
Code: Guj/Drugs/1339
5 060149 311516
Losartan Potassium 100 mg Film-coated Tablets
100mg
28 Film-coated Tablets

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Belgium, Estonia, Germany, Hungary, Ireland, Italy, Latvia, Malta, The Netherlands, Portugal, Spain and the UK considered that the applications for Losartan Potassium 25mg, 50mg and 100mg Film-Coated Tablets could be approved. These products are prescription only medicines (POM) for the following indications:

- Treatment of essential hypertension.
- 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.
- Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG

These applications for Losartan Potassium 25mg, 50mg and 100mg Film-Coated Tablets are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Cozaar 25mg, 50mg and 100mg Film-Coated Tablets, first authorised in the United Kingdom to Merck Sharp and Dohme Limited since December 1994.

Losartan is an oral, specific, and selective 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, regardless of the source or route of synthesis.

No new preclinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies have been performed and none are required for this application as the pharmacology of losartan potassium is well-established. Clinical studies on Losartan Potassium 25mg, 50mg and 100mg Film-Coated Tablets were carried out in accordance with Good Clinical Practice (GCP).

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

At the end of the decentralised procedure, these products were referred to CMD(h) by one member state because of the following issue:

- The upper bound of the 90% confidence interval for C_{max} of losartan is outside the conventional acceptance criteria of 80%-125%.

The justification for widening of the C_{max} confidence intervals for active losartan and whether wider confidence intervals of 75-133% would represent a serious risk to public health for these products was discussed at CMD(h). In this particular case, it was considered that wider Cmax intervals would not represent a concern in relation to the safety or efficacy of the product and the data in this instance was considered acceptable.

Day 60 of the CMD(h) referral was 23rd December 2008. National licences in the UK were granted on 8th January 2009 after completion of the national phase.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Losartan Potassium 25mg, 50mg and 100mg Film-Coated Tablets
Name(s) of the active substance(s) (INN)	Losartan Potassium
Pharmacotherapeutic classification (ATC code)	Angiotensin II antagonists, plain (C09CA 01)
Pharmaceutical form and strength(s)	25mg, 50mg and 100mg Film-Coated Tablets
Reference numbers for the Decentralised Procedure	UK/H/1096/001-3/DC
Reference Member State	United Kingdom
Member States concerned	Belgium, Estonia, Germany, Hungary, Ireland, Italy, Latvia, Malta, The Netherlands, Portugal, Spain
Marketing Authorisation Number(s)	PL 20075/0021-3
Name and address of the authorisation holder	Accord Healthcare Limited Sage House, 319 Pinner road, Harrow, Middlesex, HA1 4HF

III SCIENTIFIC OVERVIEW AND DISCUSSION

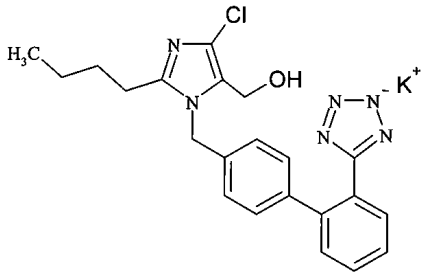
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Losartan potassium

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

Structural formula:



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

Appearance: White to off-white crystalline powder.
It is freely soluble in water, soluble in isopropyl alcohol and slightly soluble in acetonitrile.
Solubility is greatest at pH 7.0

Molecular weight: 461.0

Chirality: The drug substance contains no chiral centres.

Losartan potassium complies with the United States Pharmacopoeia.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

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

Satisfactory specifications and certificates of analysis have been provided all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients colloidal anhydrous silica, pregelatinised starch, lactose, povidone K90, isopropyl alcohol, talc and magnesium stearate. The tablet coating contains hydroxypropyl cellulose, polyethylene glycol, titanium dioxide, talc, purified water and hypromellose.

All excipients comply with their European Pharmacopoeia monograph.

None of the excipients contain materials of animal or human origin, with the exception of lactose monohydrate. The supplier of lactose monohydrate has confirmed that the lactose used is sourced from healthy animals under the same conditions as milk for human consumption.

Magnesium stearate is sourced from vegetable origin and therefore a European Pharmacopoeia Certificate of suitability for TSE in not required.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to produce products that could be considered generic medicinal products of Cozaar 25mg, 50mg and 100mg Film-Coated Tablets (Merck Sharp and Dohme, December 1994).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid.

Comparative *in vitro* dissolution profiles and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. The applicant has committed to perform process validation with future production batches of the drug products.

Finished Product Specification

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

Container-Closure System

These products are packaged in clear polyvinyl chloride (PVC) film coated with polyvinylidene chloride (PVdC) and plain aluminium foil.
Specifications and certificates of analysis for the packaging used have been provided.

All primary packaging complies with the EU legislation regarding contact with food. The product is packaged in a size of 28 tablets.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of two years with storage conditions "Do not store above 25 °C. Store in the original package in order to protect from moisture."

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPCs, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for a typical PIL for these products. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

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

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of losartan potassium are well-known. As losartan potassium is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required. The pre-clinical expert report is based on literature sources and has been written by an appropriately qualified person.

The applicant gave the following justifications for not submitting an environmental risk assessment:
This product is already available as generic product and marketing authorisation of the proposed product will not lead to any increased environmental risk. This risk assessment is based on the following assumptions:

1. *The proposed marketing authorisation will not increase the use of this product; this would rather replace some of the product already available in the market.*
2. *There is no additional precautionary or safety measures required to be taken for this generic form if already available product in the market for more than 10 years.*
3. *There is no specific requirement to be included on SPC and PIL in line with the Cozaar Tablets of Merck Sharp & Dohme Limited.*

These justifications were considered satisfactory and the absence of the Environmental Risk Assessment was accepted.

III.3 CLINICAL ASPECTS

1. Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

The summary of product characteristics (SPC), the patient information leaflet (PIL) and labels are all clinically satisfactory, and consistent with those for the reference products, albeit with the indication for heart failure not included. However, as the generic products will be used clinically along in the same manner as the brand leader, sections 4.3 and 5.3 of the SPC include the relevant information about heart failure as well as all other indications.

2. Clinical study reports

To support the applications, the marketing authorisation holder has submitted one single dose bioequivalence study.

A two-way, open label, single dose cross-over, experimental evaluation of relative bioavilabilities of two formulations of Losartan 100mg tablets in healthy adult subjects under fasting conditions.

All 60 subjects were in a fasted state before dosing. Blood sampling was performed, one pre-dose and up to 48 hours post dose (sampling sequence of every 15 minutes in the initial 4 hours), with a washout period of 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

Geometric Least Mean Squares and 90% Confidence Interval

Treatment	AUC_{0-t} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/ml)
Losartan Potassium:			
Test	1421.97	1447.73	943.74
Reference	1348.17	1373.59	839.30
Ratio (90% CI)	105.5 (101.38-109.7)	105.4 (101.36-109.36)	111.4 (97.74-126.90)

Pharmacokinetic parameters of Losartan carboxy acid

Treatment	AUC_{0-t} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/ml)
Losartan carboxy acid:			
Test	7801.49±2104.36	7865.82±2107.04	1362.14±495.26
Reference	7540.05±2138.92	7605.65±2143.77	1275.45±434.02
Ratio (90% CI)	103.3 (100.85-105.88)	103.4 (100.88-105.96)	106.2 (101.95-110.56)

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of the means for metabolite losartan carboxy acid lie within the 80-125% boundaries. The results for the 90% confidence intervals test/reference ratio of the geometric means AUC_{0-t} and $AUC_{0-\infty}$ for losartan potassium lie within 80-125% boundaries. However, the upper limit of the 90% confidence interval test/reference ratio of C_{max} lies outside the agreed boundary. This was raised as an issue and discussed by CMD(h).

The applicant gave the following justification for the higher upper limit of the 90% confidence interval for C_{max} from the bioequivalence study:
The upper limit of the 90% confidence interval for the C_{max} of losartan is marginally higher (at 126.90%) than the upper conventional limit (80-125%) recommended under CPMP guidance (CPMP/EWP/QWP/1401/98)[1]. The reason for this was the high intrasubject variability (44.4%). Supportive data were not provided to substantiate this claim.
The applicant has also argued that the marginally higher upper limit of the 90% confidence interval for C_{max} is unlikely to have any impact on the safety of the patients for the following reasons:

- *The major clinical concern for a marginally higher C_{max} would be if this was considered likely to result in a greater incidence of first dose (or first switch of formulation) hypotension. However, this is highly unlikely since the difference between the formulations is only marginally greater than the accepted reference level and because losartan has a reported low incidence of dose-related hypotension (less than 1%)*
- *Single measurements of the peak concentration of losartan or its primary metabolite were found to be poor predictors of drug effect.*
- *Losartan is very well-tolerated, with no specific adverse effect or complaints different from placebo. There is no effect of losartan on heart rate in healthy subjects and no interference with orthostatic mechanisms. Extensive formal investigations of sympathetic and parasympathetic autonomic reflexes have revealed no evidence of an effect of losartan; in addition plasma and urinary catecholamines have been shown to be unaffected in normal or hypertensive individuals.*
- *The active metabolite of losartan is 10 to 40 times more potent by weight than the parent compound and appears to be a reversible, non-competitive inhibitor of the angiotensin II type 1 receptor. According to the available published literature, the active metabolite is primarily responsible for the therapeutic effects. Losartan and its active metabolite do not influence normal blood pressure or its regulatory system.*
- *Losartan and its active metabolite exhibit linear pharmacokinetics, with oral doses up to 200mg, which do not change over time. It is not a Narrow Therapeutic Index drug.*

Finally, no serious or significant adverse events were observed during the conduct of the study.

The applicant's justification for acceptability of a wider Cmax parent confidence interval was accepted in this case.
As the 25mg, 50mg and 100mg strength products meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 100mg strength can be extrapolated to these strength tablets also.
Thus, bioequivalence has been shown between the test and reference products in this study.

3. Post marketing experience

Losartan potassium has a well-recognised efficacy and an acceptable level of safety in the indications approved for Cozaar 25mg, 50mg and 100mg Film-Coated Tablets, which is widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

[1] Note For Guidance On The Investigation Of Bioavailability And Bioequivalence.

4. Benefit-Risk assessment

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

5. Conclusions

The grant of marketing authorisations for Losartan Potassium 25mg, 50mg and 100mg Film-Coated Tablets is recommended from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

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

PRECLINICAL

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

EFFICACY

Bioequivalence has been demonstrated between the applicant's Losartan Potassium 100mg Film-Coated Tablets and the originator product Cozaar 100mg Film-Coated Tablets (Merck Sharp and Dohme). Extrapolation of this outcome to the other strengths is acceptable

No new or unexpected safety concerns arise from this application.

The SPCs, PIL and labelling are satisfactory and consistent with that for the innovator products.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with losartan potassium is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome