IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0711/123/004
Case No: 2064317

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Lotanos 75mg Film-coated tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **24/06/2009** until **21/09/2011**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lotanos 75mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75mg of losartan potassium.

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

White, oblong film-coated tablet with two notches on both sides and embossed with a '4' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension
Lotanos is indicated for the treatment for hypertension.

Reduction in the Risk of Cardiovascular Morbidity in Hypertensive Patients with Left Ventricular Hypertrophy.
Lotanos is indicated to reduce the risk of cardiovascular morbidity as measured by the combined incidence of cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy (see section 5.1, Pharmacodynamic properties, LIFE study, Race).

Heart failure
Lotanos is indicated for the treatment of heart failure when treatment with an ACE inhibitor is no longer considered appropriate. Switching patients with heart failure who are stable on an ACE inhibitor to Lotanos is not recommended (see section 5.1 'Pharmacodynamic properties').

Renal Protection in Type 2 Diabetic patients with Proteinuria.
Lotanos is inidicated to delay the progression of renal disease as measured by a reduction in the composite endpoints of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

4.2 Posology and method of administration

Lotanos may be administered with or without food.

Lotanos may be administered with other antihypertensive agents.

Hypertension
The starting and maintenance dose is 50mg 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.

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

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis. A lower dose should be considered for patients with a history of hepatic impairment (see section 4.4, 'Special warnings and special precautions for use').

Reduction in the Risk of Cardiovascular Morbidity in Hypertensive Patients with Left Ventricular Hypertrophy.
The usual starting dose is 50mg of Lotanos once daily. A low dose of hydrochlorothiazide may be added and/or the dose of Lotanos may be increased to 100 mg once daily based on blood pressure.

Heart failure
The initial dose of Lotanos in patients with heart failure is 12.5 mg once daily. The dose should generally be titrated at weekly intervals to the usual maintenance dose of 50mg once daily, as tolerated by the patient. The recommended titration regime is 12.5 mg daily for seven days, followed by 25 mg daily for a further seven days, and then to 50mg once daily. Lotanos is usually given in combination with diuretics and digitalis.

No initial dosage adjustment is required for patients with renal or hepatic impairment or intravascular depletion. (See section 4.4, 'Special warnings and precautions for use').

Renal Protection in Type 2 Diabetic Patients with Proteinuria. The usual starting dose is 50mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response. Lotanos may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

4.3 Contraindications

Lotanos is contra-indicated in pregnancy (see section 4.6, 'Pregnancy and lactation') and in patients who are hypersensitive to any component of this product.

4.4 Special warnings and precautions for use

Hypersensitivity: Angioedema. See section 4.8, 'Undesirable effects'.

Hypotension and electrolyte fluid imbalance: In patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of Lotanos, or a lower starting dose should be used (see section 4.2, 'Posology and method of administration').

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with proteinuria, the incidence of hyperkalaemia was higher in the group treated with Lotanos as compared to the placebo group, however, few patients discontinued therapy due to hyperkalaemia (see section 4.8, 'Undesirable effects' and *Laboratory test findings*).

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

Renal function impairment: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in susceptible individuals; these changes in renal function may be reversible upon discontinuation of therapy.

Other drugs that affect the renin-angiotensin-aldosterone system may increase serum urea and creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with Lotanos; these changes in renal function may be reversible upon discontinuation of therapy.

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium.

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

4.6 Pregnancy and lactation

Use during pregnancy
Although there is no experience with the use of Losartan in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.

In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the foetus increases if Lotanos is administered during the second or third trimesters of pregnancy.

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing foetus. Lotanos should not be used in pregnancy, and if pregnancy is detected Lotanos should be discontinued as soon as possible.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Lotanos has been found to be generally well tolerated; side effects have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with Lotanos was comparable to placebo.

In controlled clinical trials for essential hypertension, dizziness was the only side effect reported as drug-related that occurred with an incidence greater than placebo in 1% or more of patients treated with Lotanos. In addition, dose-related orthostatic effects were seen in less than 1% of patients. Rarely, rash was reported, although the incidence in controlled clinical trials was less than placebo.

Lotanos was generally well tolerated in a controlled clinical trial in hypertensive patients with left ventricular hypertrophy. The most common drug-related side effects were dizziness, asthenia/fatigue and vertigo.

Lotanos has been found to be generally well tolerated in controlled clinical trials in heart failure. Adverse experiences observed were typical of those expected in this population. The most common drug-related side effects were dizziness and hypotension.

Lotanos was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with proteinuria. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalaemia (see section 4.4, 'Special warnings and special precautions for use', *Hypotension and Electrolyte/Fluid Imbalance*).

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

Hypersensitivity: Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction (and/or swelling of the face, lips, pharynx, and/or tongue) has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schoenlein purpura has been reported rarely.

Gastro-intestinal: Hepatitis (reported rarely), diarrhoea, liver function abnormalities.

Haematologic: Anaemia, thrombocytopenia (reported rarely).

Musculoskeletal: Myalgia.

Nervous system/Psychiatric: Migraine.
Respiratory: Cough.

Skin: Urticaria, pruritus.

Laboratory test findings
In controlled clinical trials for essential hypertension, clinically important changes in standard laboratory parameters were rarely associated with administration of Losartan.

Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with proteinuria, 9.9% of patients treated with Losartan and 3.4% of patients treated with placebo developed hyperkalaemia (see section 4.4, 'Special warnings and special precautions for use', *Hypotension and Electrolyte/Fluid Imbalance*). Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

4.9 Overdose

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

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor the active metabolite can be removed by haemodialysis.

* Based on a patient weight of 50kg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Losartan is an oral, specific angiotensin-II receptor (type AT_1) antagonist.

Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT_1 receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.

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

Losartan binds selectively to the AT_1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT_1 receptor, such as the potentiation of bradykinin-mediated effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.

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

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

Losartan has no effect on autonomic reflexes and no sustained effect on plasma noradrenaline (norepinephrine) in hypertensive patients.

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

Hypertension Studies:
In clinical studies, once-daily administration of 50mg Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose.

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

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

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

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

The incidence of cough following administration of Losartan to patients with hypertension is significantly less than seen with ACE inhibitors and results are comparable to results seen with placebo.

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 (mean 67 years) with ECG-documented left ventricular hypertrophy. Patients were randomised to receive once daily Losartan 50mg or atenolol 50mg. 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. If necessary, other antihypertensive treatments (e.g. increase in dose of hydrochlorothiazide therapy to 25 mg or addition of other diuretic therapy, calcium channel blockers, alpha-blockers, or centrally acting agents, but not ACE inhibitors, angiotensin II antagonists, or beta-blockers) were added to the treatment regimen 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. Although blood pressure was significantly lowered to similar levels in the two groups, treatment with Losartan resulted in 13.0% risk reduction (p=0.021, 95% confidence interval 0.77-0.98) as compared with atenolol for patients reaching the primary composite endpoint. Treatment with Losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups. The effect of Losartan on the primary composite endpoint appeared to be over and above its beneficial effects on blood pressure control alone. Patients treated with Losartan had significantly greater reduction in ECG indices of left ventricular hypertrophy as compared to patients treated with atenolol. In the subgroups of patients with a baseline history of diabetes mellitus (n=1195) or isolated systolic hypertension (ISH) (n=1326), the results of treatment with Losartan were consistent with benefit of therapy with Losartan seen in the overall study population: in diabetic patients, a 24% reduction (p=0.06%) was observed and in patients with ISH, a 25% risk reduction (p=0.06) was observed. Consistent with results seen in the overall population, a reduction in stroke was an important contributor to the benefit observed in patients with diabetes or ISH.

In the LIFE study, among patients without diabetes at baseline, there was a lower incidence of new onset diabetes mellitus with Losartan as compared to atenolol (242 patients versus 320 patients respectively, p<0.001). Because there was no placebo group included in the study, it is not known if this represents a beneficial effect of Losartan or an adverse effect of atenolol.

Race: Based on the LIFE study, the benefits of Losartan on cardiovascular morbidity and mortality compared to atenolol do not apply to Black patient with hypertension and left ventricular hypertrophy, although both treatment regimens effectively lowered blood pressure in Black patients. In the LIFE study, Losartan decreased the risk of cardiovascular morbidity and mortality compared to atenolol in non-Black, hypertensive patients with left ventricular hypertrophy (n=8660) as measured by the primary endpoint of the combined incidence of cardiovascular death, stroke and myocardial infarction (p=0.003). In this study, however, Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with Losartan (p=0.03).
In the subgroup of Black patients (n=533; 6% of the LIFE study patients), there were 29 primary endpoints among 263 patients on atenolol (11%, 25.9 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 41.8 per 1000 patient-years) on Losartan.

In this study, Losartan was generally well tolerated and the tolerability profile of Losartan was superior to atenolol as evidenced by a significantly lower incidence of discontinuations due to side effects.

Heart failure
In the 48-week ELITE study in patients (n=722) with heart failure (NYHA Class II-IV), no difference was observed in the primary endpoint of persistent renal dysfunction between those patients treated with Losartan and those treated with captopril. The unexpected observation of superior benefit of Losartan in reducing the risk of death relative to captopril observed in the ELITE study was not confirmed in the definitive ELITE II Survival Study[1] described below:

In a study in patients with heart failure that was prospectively designed to evaluate the mortality (ELITE II), a regimen of Losartan 50mg once daily (starting dose of 12.5 mg titrated to 25 mg and 50mg once daily), was compared to captopril 50mg three times daily (starting dose of 12.5 mg titrated to 25 mg and 50mg three times daily). In this study (n=3,152), patients with heart failure (NYHA Class II-IV) were followed for approximately two years (median follow up 1.5 years) to evaluate whether Losartan was superior to captopril in reducing total mortality.

The primary endpoint showed no statistically significant difference between Losartan and captopril in total mortality (17.7% for Losartan and 15.9% for captopril, P=0.16). The secondary endpoint showed no statistically significant difference in sudden cardiac death and/or resuscitated cardiac arrest (9.0% for Losartan and 7.3% for captopril, p=0.08). The tertiary endpoint of all cause mortality and/or all cause hospitalisation showed no statistically significant difference between Losartan and captopril (47.7% for Losartan and 44.9% for captopril, p=0.18). In general, other morbidity and mortality endpoints including improvement in NYHA Class were not different between the treatment groups.

In both these controlled clinical trials in patients with heart failure, Losartan was generally well tolerated, and the tolerability profile of Losartan was superior to captopril as measured by significantly lower incidence of discontinuations due to side effects and significantly lower incidence of cough.

RENAAL Study:

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a multicentre, randomised, placebo-controlled, double-blind study in 1,513 type 2 diabetic patients with proteinuria (751 treated with Losartan), with or without hypertension.

Patients with proteinuria and serum creatinine of 115 – 265 micromol/l were randomised to receive Losartan 50mg once daily titrated according to blood pressure response, or placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg once daily as appropriate; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Patients were followed for approximately 5 years (mean of 3.4 years).

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

The results also showed significant risk reduction in the group treated with Losartan: 25.3% risk reduction in doubling of serum creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease (p=0.002); there was no significant effect on the rate of death. For combined components there was a 19.9% risk reduction in end-stage renal disease or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal disease (p=0.010)

For the secondary endpoints the results showed an average reduction of 34.3% in the level of proteinuria in the group treated with Losartan (p<0.001) over the mean of 3.4 years. Treatment with Losartan reduced the rate of decline in renal function during the chronic phase of the study by 13.9%, p=0.003 (median rate of decline of 18.5%, p=0.01) as measured by the reciprocal of the serum creatinine concentration-time curve. There was no significant difference between the group treated with Losartan (247 events) and the placebo group (268 events) in the composite endpoint of cardiovascular morbidity and mortality, although the study was not powered to detect such an effect.

In this study, Losartan was generally well tolerated as evidenced by a similar incidence of discontinuations due to side effects compared to placebo.

[1] Pitt B, Poole-Wilson P, Segal R et al. Effects of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE II, The Lancet, 2000, 355; 1582-1587.

5.2 Pharmacokinetic properties

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

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

Biotransformation
About 14% of an intravenously or orally administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

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

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

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

Characteristics in patients
Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.

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

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Microcrystalline Cellulose
Povidone
Sodium starch glycolate (type A)
Colloidal anhydrous silica
Magnesium stearate

Film-coating
Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Macrogol 4000

6.2 Incompatibilities

None.

6.3 Shelf Life

Blisters: 2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White, opaque PVC/PVDC/Aluminium blister packs of 28 and 30 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd,
Bantry,
Co. Cork,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/123/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 22 September 2006

10 DATE OF REVISION OF THE TEXT

June 2009