# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Solvatan 12.5 mg Film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 12.5 mg of losartan potassium
For a full list of excipients, see Section 6.1

## 3 PHARMACEUTICAL FORM

Film coated tablet
White, coated, round biconvex, code: 1L

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Hypertension

Losartan is indicated for the treatment of hypertension.

Reduction in the risk of cardiovascular morbidity in hypertensive patients with left ventricular hypertrophy

### 4.2 Posology and method of administration

Losartan may be administered with or without food.

Losartan may be administered with other antihypertensive agents.

Hypertension

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

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 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 4.4 'Special warnings and precautions for use').

## 4.3 Contraindications

Losartan is contra-indicated in patients who are hypersensitive to any component of this product.

Second and third trimesters of pregnancy (see section 4.4 and 4.6)

## 4.4 Special warnings and precautions for use

Hypersensitivity: Angioedema. See 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 Losartan, or a lower starting dose should be used (see 4.2 'Posology and method of administration').

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with proteinuria, the incidence of hyperkalaemia was higher in the group treated with Losartan as compared to the placebo group; however, few patients discontinued therapy due to hyperkalaemia (see 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 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').

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

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

Pregnancy: AIIRAs should not be initiated during pregnancy. Unless continued AIIRA 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 AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

## 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 Fertility, pregnancy and lactation

Pregnancy

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters 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 is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to AIIRA therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (See section 5.3).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation
Because no information is available regarding the use of Solvatan during breast-feeding, Solvatan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Losartan 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 Losartan was comparable to placebo.

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

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

Losartan 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.

Losartan 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 4.4 'Special warnings and 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.

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 4.4 'Special warnings and 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/m2) and 2,000 mg/kg (11,800 mg/m2) (500 and 1,000 times* the maximum recommended daily human dose), respectively.

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

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

* Based on a patient weight of 50 kg.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group:  C09C A01 Angiotensin II antagonists, plain, Losartan

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

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased

plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

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

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

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

Hypertension Studies:

In clinical studies, once-daily administration of 50 mg Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of Losartan had no clinically significant effect on heart rate.

The antihypertensive effect of Losartan 50 mg 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.

## 5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation

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

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

Elimination

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

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 69 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

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

Characteristics in patients

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

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

## 5.3 Preclinical safety data

Not applicable.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Mannitol
Microcrystalline cellulose
Croscarmellose sodium
Povidone
Magnesium stearate
Hypromellose
Titanium dioxide (E171)
Talc
Propylene glycol

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

4 years.

## 6.4 Special precautions for storage

Do not store above 25ºC.

## 6.5 Nature and contents of container

PVC/PVdC/Al Strip
Pack sizes: 5, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98, 100, 120, 210, 280 or 500 tablets

Not all pack sizes may be marketed.

## 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

Helsinn Birex Therapeutics Limited
Damastown
Mulhuddart
Dublin 15
Ireland

## 8 MARKETING AUTHORISATION NUMBER

PA 915/17/1

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 2nd June 2006

Date of Last Renewal: 2nd June 2011

## 10 DATE OF REVISION OF THE TEXT

February 2012