

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Lopress® 12.5 mg or 50 mg.

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Losartan potassium salt, 12.5 mg or 50 mg.

About excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Tablets.

### 4. CLINICAL PARTICULARS

#### 4.1 Indications

Hypertension.

Heart failure when treatment with ACE blocking agents is not considered indicated. Changing over to treatment with losartan is not recommended if the heart patient is stable with ACE blocking agents.

#### 4.2 Dosage and administration

Doses are prescribed individually.

##### ***Dosage for adults.***

***Hypertension:*** The usual initial and maintenance dose for most patients is 50 mg once a day. Losartan may be administered once or twice a day, the total daily dose being 25-100 mg per day. If enough blood pressure control is not obtained by administering losartan once a day, it may be advisable to split the dose into two parts or increase it to 100 mg once a day. The maximum reduction of blood pressure is gained in 3-6 weeks after treatment is initiated. An initial dose of 25 mg shall be used once a day for patients who are dehydrated, e.g. who have been treated with high doses of diuretics and for those who have a history of impaired liver function (See Special warnings and special precautions for use).

It is not necessary to reduce the initial dose of elderly patients or patients with impaired liver function, including patients receiving abdominal dialysis or hemodialysis. (See Special warnings and special precautions for use).

Losartan may be administered with other hypertensive drugs. Losartan may be taken with or without food.

***Heart failure:*** The initial dose for patients with heart failure is 12.5 mg once a day. The dose may be increased by 12.5 mg at a week's interval (i.e. to the dose 25 mg every day or 50 mg every day) to the usual maintenance dose of 50 mg once a day, or as the patient can tolerate. Losartan is usually administered along with diuretics and digitalis.

Losartan may be taken with or without food.

***Dosage for children***

Lopress is not intended for children.

**4.3 Contraindications**

Hypersensitivity to losartan or any of its constituents. See also the section on pregnancy and breast-feeding.

**4.4 Special warnings and special precautions for use**

Allergy. Allergic edema. (see Undesirable Effects).

*Hypotension and imbalance in blood electrolytes:* For patients who are dehydrated (e.g. those who have been treated with high doses of diuretics) symptoms of hypotension may appear. Such dehydration should be corrected before the administration of losartan or a lower initial dose of losartan administered (see *Dosage for adults*).

*Impaired liver function:* A lower initial dose should be considered for patients with a history of impaired liver function, as the pharmacokinetics literature has revealed a significant increase in plasma concentration for patients with cirrhosis (see *Dosage for adults*).

*Impaired renal function:* As a result of the blocking effect of the renin-angiotensin system, changes in renal function, including renal failure, have been recorded for sensitive individuals; such changes may subside if treatment is discontinued. Other drugs, that may influence the renin-angiotensin system, can increase urea and creatinine in the serum in patients with stenosis in one or both renal arteries. Similar effects have been recorded for losartan; such changes in renal function may subside if treatment is discontinued.

No potassium supplements or potassium-preserving diuretics should be used at the same time as losartan without consulting a doctor.

**4.5 Interaction with other medicinal products, other forms of interaction**

Not known. Compounds already tested include: hydrochlorothiazide, digoxin, warfarin, cimetidine, phenemal, ketoconazole and erythromycin. Rifampicin and fluconazole have lowered the concentration of the active metabolite in blood. The clinical significance of such interaction has not been assessed.

As applies to other drugs that block angiotensin, or its effects, the simultaneous use of potassium-preserving diuretics (e.g. spironolactone, triamterene and amiloride), potassium supplements and salts containing potassium may cause a rise in potassium concentration in the blood.

As applies to other blood-pressure-reducing drugs, the blood-pressure-reducing effects of losartan may decrease with simultaneous administration of the drug indomethacin.

**4.6 Pregnancy and lactation**

In spite of the lack of experience in the use of the drug for pregnant women, studies on animals have revealed that losartan causes fetal damage, abortion and neonatal deaths; this is presumably caused by the pharmacological effects on the renin-angiotensin system. In human fetuses, blood flow through the kidneys, dependent on the development of the renin-angiotensin system, starts in the second trimester of the pregnancy, thus there is increased danger for the fetus if the drug is administered during the second or third trimester of the pregnancy.

Drugs that directly affect the renin-angiotensin system may cause fetal damage, or even abortion, if they are administered during the second or third trimester of pregnancy. If a woman becomes pregnant, treatment with losartan should be discontinued as soon as possible.

*Lactation:* It is not known whether losartan is excreted in human breast milk. However, a significant amount of losartan, and its active metabolite, has been detected in rats' milk. Due to possible undesirable effects on a breastfed baby, the decision should be taken whether breastfeeding should be discontinued or the administration of the drug with a view to the importance of the drug for the mother.

#### **4.7 Effects on ability to drive and use machines**

Lopress has no known effect on your ability to drive and use machines.

#### **4.8 Undesirable effects**

Undesirable effects are usually mild and temporary.

Common (>1%): Dizziness, hypotension.

Rare (0.1-1%): Postural hypotension.

Very rare (< 0.1%):

*Hypersensitivity:* Anaphylaxis, angioedema including inflammation of the larynx and the vocal cords that closes the respiratory tract and/or swelling of the face, lips, pharynx and/or tongue. Some such patients have previously suffered angioedema caused by other drugs, including ACE blocking agents. Angiitis has infrequently been seen, including purpura, which is similar to both Henoch's purpura and Schönlein's purpura, with abdominal pains, gastrointestinal hemorrhage, arthralgia and nephritis.

*Digestive system:* Diarrhea, hepatitis, impaired liver function.

*Blood:* Anemia.

*Skin:* Urticaria, pruritus.

*Musculo-skeletal system:* Myalgia.

*Nervous system:* Migraine.

*Respiratory system:* Cough.

*Changes in blood values:* Raised potassium levels in blood (>5.5 mmol/l (ca. 1.5%)); slight increase in liver enzymes was rare and usually receded when treatment was discontinued.

#### **4.9 Overdose**

There is limited information on human overdosing. The most likely sign of overdosing is hypotension and tachycardia; bradycardia might occur. Supportive treatment should be started if hypotension becomes symptomatic.

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Categorization by effect; ATC category: C 09 C A 01

Losartan is an angiotensin II receptor blocking agent (type AT<sub>1</sub>) for oral administration. Angiotensin II connects to the AT<sub>1</sub> receptor that is present in many tissues (i.e. smooth muscle of blood vessels, adrenal glands, kidneys and heart) and elicits various important biological effects, including the contraction of blood vessels and the release of aldosterone. Angiotensin II also stimulates the proliferation of smooth muscle cells. On the basis of chemical binding measurements and pharmacological measurements, it is revealed that it connects specifically to the AT<sub>1</sub> receptor. Both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all biologically important effects of angiotensin II. This has been demonstrated in

vitro and in vivo, independent of its metabolic pathway. Losartan connects specifically to the AT<sub>1</sub> receptor and does not connect to nor block any other hormone receptors or ionic passages which are important for function of the cardiovascular system. Furthermore, losartan does not block ACE (kinase II), the enzyme that metabolizes bradykinin.

## 5.2 Pharmacokinetic properties

Losartan is readily absorbed after administration. It is metabolized in the liver and forms an active carboxylic acid metabolite and other inactive metabolites. Losartan's bioavailability is about 33%. Losartan's average maximum concentration is reached in 1 hour and its active metabolite in 3-4 hours. There were no clinically-significant effects on losartan's plasma concentration when the drug was administered along with a standard meal. About 14% of a losartan dose that is injected intravenously, or administered orally, converts into an active metabolite. After the intravenous injection of <sup>14</sup>C-labelled losartan, or after oral administration, the radioactivity in the blood is mostly traced to losartan and its active metabolite. Losartan's minimum transformation into the active metabolite was seen for about 1% of the individuals in the study. In addition to the active metabolite, some inactive metabolites are formed. Both losartan and its active metabolite are ≥ 99% bound to plasma proteins, mostly albumin. Losartan's distribution volume is 34 litres. Losartan's plasma clearance is about 600 ml/min, and that of the active metabolite about 50 ml/min. 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 an active metabolite. The pharmacokinetics of losartan and the active metabolite are linear when up to 200 mg doses of losartan potassium are administered orally.

When it has been administered orally, the plasma concentration of losartan and its active substance falls exponentially as losartan's final half life is about 2 hours, and about 9 hours for the active metabolite. Neither losartan nor the active metabolite show a significant build-up in plasma when 100 mg doses are administered once a day. Both bile and urine excretion take part in the elimination of losartan and the metabolite.

After the oral administration of <sup>14</sup>C-labelled losartan to humans, about 35% of the radioactivity is eliminated in urine and 58% in faeces. After oral administration to patients with mild to moderately serious cirrhosis due to alcohol consumption, losartan's plasma concentration was 5 times higher, and the active metabolite's 1.7 times higher, than in young male volunteers.

## 5.3 Preclinical safety data

Not applicable.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 Excipients

Microcrystalline cellulose, mannitol, croscarmellose, povidone, magnesium stearate, hypromellose, talcum, propylene glycol, and the coloring agent titan dioxide (E171).

### *Form*

Losartan potassium 12.5 mg tablets: White, film-wrapped, round and convex, 6 mm.

Losartan potassium 50 mg tablets: White, film-wrapped, round and convex, 10 mm.

## 6.2 Incompatibilities

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Store in closed containers.

**6.5 Nature and contents of container**

Plastic tablet container with sealed cap.

Losartan potassium 12.5 mg tablets: 28 tablets.

Losartan potassium 50 mg tablets: 28 tablets and 98 tablets.

**6.6 Instructions for use and handling**

Not applicable.

**7. MARKETING AUTHORIZATION HOLDER**

Actavis hf.

Reykjavikurvegi 76-78

220 Hafnarfjordur

[Iceland]

**8. MARKETING AUTHORIZATION NUMBERS**

Losartan potassium 12.5 mg tablets: IS/1/02/115/01

Losartan potassium 50 mg tablets: IS/1/02/115/02

**9. DATE OF THE FIRST AUTHORIZATION/RENEWAL AUTHORIZATION**

Losartan potassium 12.5 mg tablets: Market authorization first granted on 3rd May 2002.

Losartan potassium 50 mg tablets: Market authorization first granted on 3rd May 2002.

**10. DATE OF REVISION OF THE TEXT**

13 July 2004