APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

PROPRIETARY NAME (and dosage form):

ANNIN 25 mg (tablet)

ANNIN 50 mg (tablet)

ANNIN 100 mg (tablet)

COMPOSITION:

ANNIN 25 mg: Each film-coated tablet contains 25 mg losartan potassium. Contains lactose.

ANNIN 50 mg: Each film-coated tablet contains 50 mg losartan potassium. Contains lactose.

ANNIN 100 mg: Each film-coated tablet contains 100 mg losartan potassium. Contains lactose.

The other ingredients are microcrystalline cellulose, lactose monohydrate, pregelatinised starch, low substituted hydroxypropyl cellulose, magnesium stearate and opadry white powder. The coating agent, opadry, contains hydroxypropyl cellulose, hypromellose and titanium dioxide (C.I. No: 77891).

PHARMACOLOGICAL CLASSIFICATION:

A.7.1.3 Other hypotensives.

PHARMACOLOGICAL ACTION:

Mechanism of action:

Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system, and a major determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g., vascular smooth muscle, kidneys, adrenal gland, 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 is a synthetic, orally active compound which binds selectively to the AT_1 receptor.

Both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block the actions of angiotensin II, regardless of the source or route of synthesis.

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 or the generation of oedema are not associated with losartan.

Pharmacokinetics:

Absorption:

After oral administration, losartan 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 greater than or equal to 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.

Metabolism:

Approximately 14 % of an oral or intravenous dose of losartan is converted to its active metabolite.

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 doses up to 200 mg.

Following oral administration in normal volunteers plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6 – 9 hours, respectively.

Both urinary and biliary excretion contributes to the elimination of losartan and its metabolites. Following

an oral dose of ^{14}C-labeled losartan in man, about 35 % of radioactivity is recovered in the urine and 58 % in the faeces. Following an intravenous dose of ^{14}C-labeled losartan in man, about 43 % of radioactivity is recovered in the urine and 50 % 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.

INDICATIONS:

ANNIN is indicated for the treatment of hypertension.

CONTRA-INDICATIONS:

- Sensitivity to any component of **ANNIN**.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs). These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy.
- Moderate to severe renal function impairment (creatinine clearance less than 30 ml/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in a patient with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Porphyria.

- Thiazide diuretics in (fixed dose) combination with **ANNIN** should not be given to patients with Addison's disease. This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines.
- Lithium therapy: Concomitant administration with **ANNIN** may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see "**PREGNANCY AND LACTATION"**).
- **Paediatric use:** Safety and effectiveness in children have not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

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 **ANNIN**, or a lower starting dose should be used (see "**DOSAGE AND DIRECTIONS FOR USE"**).
When impaired renal function is present, changes in renal function as a consequence of inhibiting the renin-angiotensin system including renal failure have been reported in susceptible individuals.
Agents that affect the renin-angiotensin system may increase serum creatinine and blood urea in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with **ANNIN TABLETS**.

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, halving of the dose should be considered for patients with a history of hepatic impairment (see **"DOSAGE AND DIRECTIONS FOR USE"**).

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (less frequently) with acute renal failure and/or death. Similar outcomes have been reported with **ANNIN**.

ANNIN contain lactose and should not be administered to patients with rare hereditary problems, or a history of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Use in the elderly:

In clinical studies there was no age-related difference in efficacy or safety profile of losartan.

Effects on ability to drive and use machines:

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

INTERACTIONS:

The antihypertensive effects of losartan may be potentiated by medicines or other agents that lower blood pressure. An additive hyperkalaemic effect is possible with potassium supplements, potassium-sparing diuretics, or other drugs that can cause hyperkalaemia; losartan and potassium-sparing diuretics should not generally be given together. Losartan and some other angiotensin II receptor antagonists are metabolised by cytochrome P450 isoenzymes and interactions may occur with drugs that affect these enzymes.

Non-steroidal anti-inflammatory medicines (NSAIDS) may antagonise the antihypertensive effect of **ANNIN**.

PREGNANCY AND LACTATION:

Pregnancy:

Safety in pregnancy and lactation has not been established (see "**CONTRA-INDICATIONS"**).

When pregnancy is planned or confirmed **ANNIN** should be discontinued.

Medicines affecting the renin-angiotensin system, such as **ANNIN**, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Women of childbearing age should ensure effective contraception.

ANNIN are contra-indicated in lactation.

DOSAGE AND DIRECTIONS FOR USE:

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained three to six weeks after initiation of therapy. The dose may be increased to 100 mg once daily.

For patients with intravascular volume-depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

For elderly patients and patients with renal impairment, including patients on dialysis, no initial dosage adjustment is necessary. A lower dose should be considered for patients with a history of hepatic impairment (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).).

ANNIN may be administered with other antihypertensive agents.

ANNIN may be administered with or without food.

SIDE EFFECTS:

In controlled clinical trials for essential hypertension, dizziness, orthostatic hypotension, headache and rash were side effects reported.

The following side effects may also occur:

Body as a whole:

Less frequent: Asthenia/fatigue.

The following side effects have been reported and frequencies are unknown: Abdominal pain, chest pain, oedema/swelling.

Cardiovascular:

The following side effects have been reported and frequency is unknown: Palpitation, tachycardia, hypotension.

Digestive:

Less frequent: Diarrhoea.

The following side effects have been reported and frequency is unknown: Dyspepsia, nausea.

Musculoskeletal:

Less frequent: Back pain, muscle cramps.

Nervous/Psychiatric:

More frequent: Headache.

Less frequent: Dizziness, insomnia, migraine.

Respiratory:

Less frequent: Cough, nasal congestion, pharyngitis, sinus disorder, upper respiratory infection.

Hypersensitivity:

The following side effect has been reported and frequency is unknown: Angioedema (involving swelling of the face, lips, and/or tongue).

Skin:

The following side effect has been reported and frequency is unknown: Urticaria.

Laboratory test findings:

In controlled clinical trials, hyperkalemia (serum potassium greater than 5.5 mEq/L) occurred in 1,5 % of patients, but in these trials, discontinuation of losartan therapy due to hyperkalemia was not necessary. Elevations of alanine amino transferase (ALT) have occurred but usually resolved upon discontinuation of therapy.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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. Supportive treatment should be instituted if symptomatic hypotension should occur. Neither losartan nor the active metabolite can be removed by haemodialysis.

IDENTIFICATION:

ANNIN 25 mg: White to off – white, oval shaped, biconvex, film – coated tablets, debossed with “E” on one side and “45” on the other side.

ANNIN 50 mg: White to off – white, oval shaped, biconvex, film – coated tablets, debossed with “E” on one side and “46” on the other side.

ANNIN 100 mg: White to off – white, oval shaped, biconvex, film – coated tablets, debossed with “E” on one side and “47” on the other side.

PRESENTATION:

ANNIN 25 mg, ANNIN 50 mg and ANNIN 100 mg:

Blister Packs:

Tablets are packed in blister packs composed of white opaque PVC / PE / PVdC film or white opaque PVC coated with 60 g/m2 PVdC film and printed silver-coloured aluminium foil. Each blister contains 10 tablets.

Pack size: 30s – Each carton contains 3 blisters of 10 tablets each.

STORAGE INSTRUCTIONS:

Store in a dry place, at or below 25 °C. Keep blisters in the original carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

ANNIN 25 mg: 43/7.1.3/0493

ANNIN 50 mg: 43/7.1.3/0494

ANNIN 100 mg: 43/7.1.3/0495

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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