Professional Information for Medicines for Human Use

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ANNIN CO 50/12,5 mg (film-coated tablets)

ANNIN CO 100/25 mg (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ANNIN CO 50 /12,5mg:

Each film coated tablet contains 50 mg Losartan potassium and 12,5 mg hydrochlorothiazide.

Contains sugar: 111 mg of lactose.

For full list of excipients, see section 6.1.

ANNIN CO 100/25 mg:

Each film coated tablet contains 100 mg Losartan potassium and 25 mg hydrochlorothiazide.

Contains sugar: 222 mg of lactose.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ANNIN CO 50/12,5 mg:

Yellow coloured, oval shaped, beveled edge, biconvex film-coated tablets debossed with ‘E’ on one side and ‘48’ on the other side.

ANNIN CO 100/25 mg:

Yellow coloured, oval shaped, beveled edge, biconvex film-coated tablets debossed with ‘E’ on one side and ‘49’ on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ANNIN CO is indicated for the treatment of hypertension in patients established on identical doses of the individual medicines.

4.2. Posology and method of administration

The maximum dose is one tablet of **ANNIN CO** (100 mg losartan potassium and 25 mg hydrochlorothiazide) once daily. The maximum antihypertensive effect is attained within three weeks after initiation of therapy.

ANNIN CO should not be initiated in patients who are intravascularly volume depleted (e.g. those treated with high dose of diuretics).

ANNIN CO is not recommended for patients with severe renal impairment or for patients with hepatic impairment (see also section 4.4)

ANNIN CO should not be used as initial therapy in elderly patients.

ANNIN CO may be administered with other antihypertensive medicines, such as calcium channel blockers and beta-blockers.

ANNIN CO may be administered with or without food.

Special Populations

Renally and Hepatically Impaired Patients

ANNIN CO is not recommended for patients with severe renal impairment or for patients with hepatic impairment (see also section 4.3 and 4.4)

Elderly

A higher dose (100 mg losartan potassium and 25 mg hydrochlorothiazide should not be used as initial therapy in elderly patients.

Method of administration

ANNIN CO is administered orally, with or without food.

4.3. Contraindications

ANNIN CO is contraindicated in:

- Hypersensitivity to losartan or hydrochlorothiazide or any of the components of **ANNIN CO** (see section 6.1).
- A history of angioedema related to previous therapy with Angiotensin Converting Enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs):

  These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see also section 4.5).
- Porphyria.
- Thiazide diuretics in (fixed dose) combination with **ANNIN CO** should not be given to patients with Addison's disease.
- This therapy is also contraindicated in patients with severe renal impairment or is also contraindicated in patients with anuria, and hypersensitivity to other sulphonamide-derived medicines.
- Lithium therapy: Concomitant administration with **ANNIN CO** may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see also section 4.6).
- Hepatic impairment.
- The concomitant use of **ANNIN CO** with aliskiren- containing products is contraindicated (see also section 4.4 and 4.5).
- The concomitant use of fluoroquinolones with ACE inhibitors/Renin-Angiotensin blockers is

contraindicated in patients with moderate to severe renal impairment.

- Patients with a history or previous and\or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.

Paediatric Use: Safety and efficacy in children has not been established.

4.4. Special warnings and precautions for use

Pregnancy

Should a woman become pregnant while receiving **ANNIN CO**, the treatment should be stopped immediately and if appropriate, alternative therapy should be started. (see section 4.6).

Hypersensitivity:

Angioedema - patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored.

Hepatic and renal impairment

ANNIN CO is not recommended for patients with hepatic impairment or severe renal impairment (see section 4.2 and 4.3).

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported. These changes in renal function may not be reversible upon discontinuation of therapy.

ANNIN CO may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney (see also section 4.3).

Hypotension and electrolyte/fluid imbalance

In patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur, especially after the first dose. These conditions should be corrected prior to administration of **ANNIN CO** or a lower starting dose should be used (see also section 4.2).

Periodic determination of serum electrolytes should be performed at appropriate intervals.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic medicines, including insulin, may be required (see also section 4.5).

Hydrochlorothiazide as in **ANNIN CO** may decrease urinary calcium excretion and may cause an elevation of serum calcium. Marked hypercalcaemia may be evidence of occult hyperparathyroidism. **ANNIN CO** should be discontinued before carrying out tests for parathyroid function.
Increases in cholesterol and triglyceride levels may be associated with hydrochlorothiazide therapy.
ANNIN CO may precipitate hyperuricaemia and/or gout in certain patients.

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 **ANNIN CO** 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.

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.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Concomitant use with Lithium

Concomitant administration of lithium with **ANNIN CO** may lead to toxic blood concentrations of lithium (see also section 4.3).

Other

In patients receiving hydrochlorothiazide as in **ANNIN CO** hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Dual blockade of renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE inhibitors, ARBs or aliskiren may increase the risk of hypotension hyperkalaemia and decrease renal function (including acute renal failure). Dual blockade of RAAS through the combined use of **ANNIN CO** and aliskiren is therefore not recommended. **ANNIN CO** should not be used concomitantly with aliskiren (see also section 4.3). Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may

precipitate acute kidney injury inpatients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment, with fluoroquinolones or ACE inhibitors/renin-angiotensin receptor blockers.

Excipient

ANNIN CO contains lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **ANNIN CO**.

Paediatric Use

Safety and efficacy in children has not been established.

4.5. Interaction with other medicines and other forms of interaction

INTERACTIONS

Losartan potassium

In clinical pharmacokinetic trials, no interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbitone (see Hydrochlorothiazide, Alcohol, barbiturates or narcotics below) ketoconazole and erythromycin. Rifampin and fluconazole have been reported to reduce levels of the active metabolite. The clinical consequences of these interactions have not been evaluated.

Concomitant use of fluoroquinolones and ACE inhibitors/renin angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3).

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

Lithium excretion may be reduced. Therefore, concomitant administration of lithium and **ANNIN CO** is contraindicated (see section 4.3).

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of **ANNIN CO**. Therefore, the antihypertensive effect of **ANNIN CO** may be attenuated by NSAIDs including selective COX 2 inhibitors.

In some patents with compromised renal function (e.g. elderly patients or patients who are volume-depleted including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of **ANNIN CO** may result in a further deterioration of renal function, including possible acute renal failure.

Therefore the combination should be administered with caution in patients with compromised renal function.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with angiotensin receptor blockers such as **ANNIN CO** ACE inhibitors and/or aliskiren is associated with increased risks of hypotension, syncope, hyperkalaemia and changes in renal function (including acute renal failure) compared to monotherapy. Do not co-administer aliskiren with **ANNIN CO** in patients with diabetes. Avoid use of aliskiren with **ANNIN CO** in patients with renal impairment (GFR < 60 ml/min) (see also section 4.3 and 4.4).

Hydrochlorothiazide

When administered concurrently the following medication may interact with thiazide diuretics:

Alcohol, barbiturates or narcotics:

Potentiation of orthostatic hypotension may occur.

Antidiabetic medicines (oral medicines and insulin):

Dosage adjustment of the antidiabetic medicine may be required.

Other antihypertensive medicines:

Additive effect or potentiation.

Cholestyramine and colestipol resins:

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption

from the gastrointestinal tract by up to 85 and 43 % respectively. **ANNIN CO** should therefore be administered one hour before the intake of the resin.

Corticosteroids, ACTH or glycyrrhizin (found in liquorice):

Intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g. norepinephrine):

Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, non-depolarising (e.g. tubocurarine):

Possible increased responsiveness to the muscle relaxant.

Lithium:

Diuretic medicines reduce the renal clearance of lithium and add a high risk of lithium toxicity. Therefore, the concomitant use of lithium and **ANNIN CO** is contraindicated (see section 4.3).

Non-steroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 Inhibitors:

The administration of a non-steroidal anti-inflammatory medicine including a selective cyclooxygenase - 2 inhibitor can reduce the diuretic, natriuretic and antihypertensive effects of **ANNIN CO**

Paediatric Use

Safety and efficacy in children has not been established.

4.6. Fertility, pregnancy and lactation

When pregnancy is detected or suspected ANNIN CO should be discontinued as soon as possible. ANNIN CO should not be used in pregnancy as teratogenicity has been shown in experimental animals.

Pregnancy

Safety in pregnancy and lactation has not been established (see also section 4.3). The use of **ANNIN CO** is contra-indicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take **ANNIN CO** during pregnancy. 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 **ANNIN CO** should be stopped immediately and if appropriate, alternative therapy should be started. Women of childbearing age should ensure effective contraception.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult. Diuretics do not prevent development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxaemia.

Lactation

Safety in breastfeeding has not been established (see section 4.3). Thiazides appear in human milk.

4.7. Effects on ability to drive and use machines

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

a. Tabulated list of adverse reactions

The adverse reactions below are classified where appropriate by system organ class.

SYSTEM ORGAN CLASS	ADVERSE REACTION	FREQUENCY
Nervous system disorders	Dizziness	Frequent
General disorders and administration site conditions	Asthenia/fatigue.	Frequent

Losartan potassium

SYSTEM ORGAN CLASS	ADVERSE REACTION	FREQUENCY
Psychiatric disorders	Insomnia	Frequent
Nervous system disorders	Headache, dizziness	Frequent
Cardiac disorders	Palpitation, tachycardia	Frequent
Vascular disorders	Orthostatic hypotension	Less frequent
Respiratory, thoracic and mediastinal disorders	Cough, pharyngitis, nasal congestion, sinus disorder, upper respiratory infection	Frequent:
Gastrointestinal disorder	Diarrhoea, nausea, abdominal pain, dyspepsia	Frequent
Skin and subcutaneous tissue disorders	Rash	Less Frequent
Musculoskeletal, connective tissue and bone disorders	Back pain, muscle cramps	Frequent
General disorders and administration site conditions	Asthenia/fatigue, oedema/swelling, chest pain	Frequent
Investigations	Hyperkalaemia, elevations of ALT	Frequent

Hydrochlorothiazide

SYSTEM ORGAN CLASS	ADVERSE REACTION	FREQUENCY
Blood and the lymphatic system disorders	Thrombocytopenia, leukopenia, agranulocytosis, haemolytic anaemia	Less frequent:

Metabolic and nutrition disorders	Anorexia, hyperuricaemia, hyperglycaemia	Less frequent
Nervous system disorders	Paraesthesia, headache	Less frequent
Vascular disorders	Hypotension (including orthostatic hypotension)	Less frequent
Respiratory, thoracic and mediastinal disorders	Respiratory distress including pneumonitis and pulmonary oedema	Less frequent
Gastrointestinal disorder	Nausea, vomiting, diarrhoea, constipation, pancreatitis	Less frequent
Hepatobiliary disorders	Jaundice (intrahepatic cholestatic jaundice)	Less frequent
Skin and subcutaneous tissue disorders	Rash, urticaria, photosensitivity. necrotising angitis (vasculitis and cutaneous vasculitis)	Less Frequent
Renal and urinary disorders	Glycosuria	Less frequent

Post-marketing data

The following adverse reactions have been reported in post-marketing experience; they are derived from spontaneous reports for which precise incidences cannot be determined therefore, the frequency is unknown:

SYSTEM ORGAN CLASS	**ADVERSE REACTION**
Blood and the lymphatic system disorders	Aplastic anaemia, thrombocytopenia
Immune system disorders	Anaphylactic reactions, angioederna 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 angioederna with other medicine including ACE inhibitors
Metabolic and nutrition disorders	Electrolyte imbalance including hyponatraemia and hypokalaemia
Psychiatric disorders	Restlessness
Nervous system disorders	Dysgeusia (reported with losartan)
Eye disorders	Xanthopsia, transient blurred vision
Ear and labyrinth disorders	Vertigo
Vascular disorders	Hypotension, vasculitis, including Henoch-Schoenlein purpura
Respiratory, thoracic and mediastinal disorders	Cough
Gastrointestinal disorder	Gastric irritation, sialoadenitis, diarrhoea, vomiting
Hepatobiliary disorders	Hepatitis
Skin and subcutaneous tissue disorders	Purpura (including Henoch-Schoenlein purpura), pruritus, toxic epidermal necrolysis, cutaneous lupus erythematosus, urticaria, erythroderma has been reported with losartan, photosensitivity
Musculoskeletal, connective tissue and bone disorders	Cramping, muscle spasm, myalgia, arthralgia (reported with losartan)
Renal and urinary disorders	Renal dysfunction, interstitial nephritis, renal failure
General disorders and administration site conditions	Fever, weakness, malaise
Investigations	Liver function abnormalities.

Losartan:

The following adverse reactions have been reported for losartan in clinical studies and in post-marketing experience:

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis	Less Frequent
	thrombocytopaenia	Frequency unknown
Cardiac disorders	hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitation, arrhythmias (atrial fibrillations, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation)	Frequent
Ear and labyrinth disorders	vertigo, tinnitus	Less frequent
Eye disorders	blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity	Less frequent
Gastrointestinal disorders	abdominal pain, nausea, diarrhoea, dyspepsia	Frequent
	constipation, dental pain, dry mouth, flatulence, gastritis, vomiting, obstipation	Less frequent
	pancreatitis	Frequency unknown

General disorders and administration site conditions	asthenia, fatigue, chest pain	Frequent
	facial oedema, oedema, fever	Less frequent
	flu-like symptoms, malaise	Frequency unknown
Immune system disorders	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; in some of these patients angioedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors;	Less frequent
Metabolism and nutrition disorders	anorexia, gout	Less frequent
Musculoskeletal and connective tissue disorders	muscle cramp, back pain, leg pain, myalgia	Frequent
	arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness	Less frequent
	rhabdomyolysis	Frequency unknown
Nervous system disorders	headache, dizziness	Frequent

	nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope	Less frequent
	dysgeusia	Frequency unknown
Psychiatric disorders	insomnia	Frequent
	restlessness, anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment	Less frequent
Renal and urinary disorders	renal impairment, renal failure	Frequent
	nocturia, urinary frequency, urinary tract infection	Less frequent
Reproductive system and breast disorders	decreased libido, erectile dysfunction/impotence	Frequency unknow
Respiratory, thoracic and mediastinal disorders	cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder	Frequent
	pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion	Less frequent
Skin and subcutaneous tissue disorders	alopecia, dermatitis, dry skin, erythroderma, flushing, photosensitivity, pruritus, rash, urticaria, sweating, toxic epidermal necrolysis	Less frequent
Vascular disorders	vasculitis	Less frequent

	orthostatic hypotension	Frequency unknown
Investigations	hyperkalaemia, elevations of ALT, mild reduction of haematocrit and haemoglobin, hypoglycaemia	Frequent
	mild increase in urea and creatinine serum levels, increase in hepatic enzymes and bilirubin,	Less frequent
	hyponatraemia	Frequency unknown

Hydrochlorothiazide

System organ class	**Adverse reaction**	**Frequency**
Blood and the lymphatic system disorders	agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura,thrombocytopaenia	Less frequent
Immune system disorders	anaphylactic reaction	Less frequent
Metabolism and nutrition disorders	anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia	Less frequent
Psychiatric disorders	insomnia	Less frequent
Nervous system disorders	cephalalgia	Frequent
Eye disorders	transient blurred vision, xanthopsia	Less frequent
Vascular disorders	necrotizing angiitis (vasculitis, cutaneous vasculitis)	Less frequent

Respiratory, thoracic and mediastinal disorders	respiratory distress including pneumonitis and pulmonary oedema	Less frequent
Gastrointestinal disorders	sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation	Less frequent
Hepato-biliary disorders	jaundice (intrahepatic cholestatic jaundice), pancreatitis	Less frequent
Skin and subcutaneous tissue disorders	rash, urticaria, photosensitivity, necrotising angitis (vasculitis and cutaneous vasculitis)	Less frequent
Musculoskeletal and connective tissue disorders	muscle cramps	Less frequent
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)	Frequency unknown
Renal and urinary disorders	glycosuria, interstitial nephritis, renal dysfunction, renal failure	Less frequent
General disorders and administration site conditions	fever, weakness, malaise	Less frequent

b. Description of selected adverse reactions

Immune system disorders

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 medicine including ACE inhibitors.

Skin and subcutaneous tissue disorders

Purpura (including Henoch-Schoenlein purpura), pruritus, toxic epidermal necrolysis, cutaneous lupus erythematosus, urticaria, erythroderma has been reported with losartan, photosensitivity.

c. Paediatric Use

Safety and efficacy in children has not been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8.

4.9. Overdose

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.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypokalaemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digoxin has also been administered, hypokalaemia may accentuate cardiac dysrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and class: A 7.1.3 Other hypotensives

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics

ATC code: CO9DA01

Mechanism of action

Pharmacodynamic properties

ANNIN CO (losartan potassium-hydrochlorothiazide) combines an angiotensin II receptor (type AT1) antagonist and a diuretic, hydrochlorothiazide.

Losartan

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, 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 is a synthetic, orally active compound which binds selectively to the AT, receptor. Both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block the actions of angiotensin II, regardless of the source of synthesis.

Losartan binds selectively to the AT, receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation.

Losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin.

Hydrochlorothiazide

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive medicine. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium, magnesium and bicarbonate.

Losartan potassium - Hydrochlorothiazide

Losartan and hydrochlorothiazide are additive in their antihypertensive efficacy.

After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

5.2. Pharmacokinetic properties

Losartan

Absorption

Following 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. There was no clinically significant effect on the plasma concentration profile of losartan when losartan was administered with a standardised meal.

Distribution

Both losartan and its active metabolite are 99 % and more 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

About 14 % of an intravenously- or orally-administered dose of losartan is converted to its active metabolite.

Elimination

Plasma clearance of losartan and its active metabolite is about 600 ml/mm and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/mm and 26 ml/min, respectively. When losartan potassium is administered orally, about 4 % of the dose is excreted unchanged m 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.

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.

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.

Neither losartan nor the metabolite can be removed by haemodialysis.

Hydrochlorothiazide

The plasma half-life ranges between 5,6 and 14,8 hours. Hydrochlorothiazide is eliminated unchanged by the kidney. At least 61 % of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Losartan potassium - Hydrochlorothiazide

In a pharmacokinetic interaction study, hydrochlorothiazide 12,5 mg did not alter the pharmacokinetics of losartan 50 mg and vice versa.

5.3. Preclinical safety data

Not applicable

Environmental Risk Assessment

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Cellulose, Microcrystalline Ph.Eur (Avicel PH 101)

Cellulose, Microcrystalline Ph.Eur (Avicel PH 200)

Starch, Pre-gelatinised Ph.Eur (Starch 1500)

Silica Colloidal anhydrous Ph.Eur (Aerosil® 200 Pharma)

Magnesium Stearate Ph.Eur

Ingredients of Coating material:

Opadry Yellow 20A52067

6.2. Incompatibilities

Not applicable

6.3. Shelf life

36 months

6.4. Special precautions for storage

The tablets should be stored in marketed, moisture-proof containers.

Store at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

ANNIN CO 50 mg/12.5 mg and **ANNIN CO 100 mg/25 mg**

Blister Pack

PVC / Aclar

Blister pack comprises of 250 micron white opaque PVC film laminated with 50 micron aclar as the forming material and 25 micron aluminum foil with 7gsm heat seal lacquer as the lidding material.

PVC / PE / PVdc

Blister pack comprises of 250 micron white opaque PVC film laminated with 25 micron PE, coated with 90 gsm PVdc as the forming material and 25 micron aluminum foil with 7gsm heat seal lacquer as the lidding material

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

HDPE

White opaque round 40 mL HDPE container with 33 mm neck finish closed with 33 mm -400 RS white opaque polypropylene stock ribbed closure with wad having induction sealing liner.

Pack Size: 30's Each HDPE container contains 30 tablets.

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

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (PTY) LTD

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER (S)

ANNIN CO 50 mg/12.5 mg: 45/7.1.3/1054

ANNIN CO 100 mg/25 mg: 45/7.1.3/1055

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 February 2023