SCHEDULING STATUS

S3

PATIENT INFORMATION LEAFLET

ANNIN CO 50/12.5 mg

Losartan potassium 50 mg and hydrochlorothiazide 12,5 mg.
Contains sugar: 111 mg of lactose

ANNIN CO 100/25 mg

Losartan potassium 100 mg and hydrochlorothiazide 25 mg.
Contains sugar: 222 mg of lactose

Read all of this leaflet carefully before you start taking ANNIN CO.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- **ANNIN CO** has been prescribed for you personally and you should not share your medicine with other people.
- It may harm them, even if their symptoms are the same as yours.

What is in this leaflet?

1. What **ANNIN CO** is and what it is used for
2. What you need to know before you use **ANNIN CO**
3. How to use **ANNIN CO**
4. Possible side effects
5. How to store **ANNIN CO**
6. Contents of the pack and other information

1. What ANNIN CO is and What it is used for

ANNIN CO is a combination of an angiotensin II receptor antagonist (losartan) and a diuretic (hydrochlorothiazide). Angiotensin II is a substance produced in the body which binds to receptors in blood vessels, causing them to tighten. This results in an increase in blood pressure. Losartan prevents the binding of angiotensin II to these receptors, causing the blood vessels to relax which in turn lowers the blood pressure.
Hydrochlorothiazide works by making the kidneys pass more water and salt. This also helps to reduce blood pressure.
ANNIN CO is indicated for the treatment of essential hypertension (high blood pressure).

2. What you need to know before you take ANNIN CO

Do not take ANNIN CO:

- If you are hypersensitive (allergic) to losartan, hydrochlorothiazide or to any of the other ingredients of this medicine (listed in section 6).
- If you have previously been treated with a medication in the same group of medicines as **ANNIN CO** (angiotensin receptor antagonists) or with a medication in the group of medicines known as ace inhibitors and have had allergic reactions with swelling of the face, lips, tongue, and/or throat with difficulty in swallowing or breathing.
- If you have severely impaired liver function.
- If you have low potassium, low sodium or high calcium levels which cannot be corrected by treatment.
- If you have hereditary or idiopathic angioedema (swelling of the face, lips, mouth, tongue or throat with or without difficulty in swallowing or breathing).
- If you have hypertrophic obstructive cardiomyopathy, a heart disorder in which the walls of the ventricles (lower heart chambers) thicken (hypertrophy) and become stiff and the thickened muscle blocks the flow of blood out of the heart.
- If you have severely impaired kidney function or your kidneys are not producing any urine.
- If you have narrowing of the blood vessels to both kidneys or to a single kidney.
- If you have aortic stenosis, a narrowing of the aortic valve opening between the left ventricle (large pumping chamber of the heart) and the aorta (the main artery leading away from the heart).
- If you are taking diuretics (water pills) that cause your body to retain potassium such as spironolactone, triamterene and amiloride.
- If you have porphyria.
- Thiazide water tablets in (fixed dose) combination as with **ANNIN CO** should not be given to patients with Addison's disease (a long-term endocrine disorder in which the adrenal glands do not produce enough steroid hormones). This therapy should also not be used in patients with severe kidney disease or patients not passing urine, and in patients who show allergy to other sulphonamide-derived medicines (ask your doctor if you are not sure what sulphonamide-derived medicines are).
- Lithium therapy: Concomitant administration with **ANNIN CO** may lead to toxic blood concentrations of lithium.
- If you are pregnant or breastfeeding (see Pregnancy and Breastfeeding)
- If you have liver disease
- If you have previously had or currently have cancer of the skin and/or lip.
- The concomitant use with antibiotics that belong in the class "fluoroquinolones "should be avoided.
- The concomitant use of **ANNIN CO** with aliskiren-containing products should be avoided.

Take special care with ANNIN CO:

Talk to your doctor, pharmacist or nurse before taking **ANNIN CO.** You must tell your doctor if you think you are (or might become) pregnant. **ANNIN CO** is not recommended in pregnancy, and must not be taken if you are pregnant, as it may cause serious harm to your baby.

It is important to tell your doctor before taking ANNIN CO:

- If you have previously suffered from swelling of the face, lips, throat or tongue.
- If you take diuretics (water pills).
- If you are on a salt restricted diet.
- If you have or have had severe vomiting and/or diarrhoea.
- If you have heart failure.
- If your liver function is impaired (see section 2 "Do not take **ANNIN CO**").
- If you have narrow arteries to your kidneys (renal artery stenosis) or only have one functioning kidney, or you have recently had a kidney transplant.
- If you have narrowing of the arteries (atherosclerosis), angina pectoris (chest pain due to poor heart function).
- If you have aortic or mitral valve stenosis' (narrowing of the valves of the heart) or 'hypertrophic cardiomyopathy' (a disease causing thickening of heart muscle).
- If you are diabetic.
- If you have had gout.
- If you have or have had an allergic condition, asthma or a condition that causes joint pain, skin rashes and fever (systemic lupus erythematosus).
- If you have high calcium or low potassium levels or you are on a low potassium diet
- If you need to have an anaesthetic (even at the dentist) or before surgery, or if you are going to have tests to check your parathyroid function, you must tell the doctor or medical staff that you are taking losartan potassium and hydrochlorothiazide tablets, as there may be a sudden fall in blood pressure associated with the anaesthetic.
- If you suffer from primary hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldosterone by the adrenal gland, caused by an abnormality within the gland).
- If you are taking any of the following medicines used to treat high blood pressure: an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
- If you are taking lithium (a medicine used to treat a certain kind of depression).
- Aliskiren.
- Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.
- If you are taking other medicines that may increase serum potassium (see section 2 "Other medicines and **ANNIN CO**").
- If you have had skin cancer or if you develop an unexpected skin lesion during the treatment.

Treatment with hydrochlorothiazide, particularly long-term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking **ANNIN CO**.

Use in children
As there is no experience with the use of **ANNIN CO** in children, **ANNIN CO** should not be given to children.

Taking other medicines with ANNIN CO

Always tell your healthcare professional if you are taking any other medicine. (This includes all complementary or traditional medicines.)

Other medicines and ANNIN CO

ANNIN CO may have an effect on other medicines or other medicines may have an effect on **ANNIN CO**.

- It is especially important for your doctor to know if you are taking other medicines to reduce blood pressure, other diuretics (water tablets),
- medication used to treat diabetes including insulin,
  - resins which reduce high cholesterol,
  - muscle relaxants, pressor amines such as adrenaline, steroids, certain pain and arthritis medicines, or
  - lithium (a medicine used to treat a certain kind of depression). Lithium excretion may be reduced. Therefore, lithium should not be taken at the same time with **ANNIN CO**.
- Sedatives, tranquilizers, narcotics, alcohol and analgesics may increase the blood pressure-lowering effect of **ANNIN CO**, so tell your doctor if you take any of these medicines.
- When non-steroidal anti-inflammatory drugs (NSAIDs), which is used to treat patients with reduced kidney function, is taken together with **ANNIN CO**, further deterioration of kidney function may result.

Pregnancy and Breastfeeding

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking ANNIN CO. 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

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking **ANNIN CO** before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of **ANNIN CO**.
ANNIN CO is not recommended during pregnancy.
Women of childbearing age should ensure effective contraception.

Breastfeeding

Tell your doctor if you are breastfeeding or about to start breastfeeding. Safety in breastfeeding has not been established. Thiazides appear in human milk. **ANNIN CO** is not recommended for mothers who are breastfeeding, and your doctor may choose another treatment for you if you wish to breastfeed your baby.

Driving and using machinery:

When you begin treatment with this medication, you should not perform tasks, which may require special attention (for example, driving an automobile or operating dangerous machinery) until you know how you tolerate your medicine.

Important information about some of the ingredients of ANNIN CO

ANNIN CO contains lactose therefore you should tell your doctor if you are sugar intolerant or have a history of lactose intolerance.

3. How to take ANNIN CO

Do not share medicines prescribed for you with any other person.
Always take **ANNIN CO** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. Your doctor will tell you how long your treatment with **ANNIN CO** will last. If you have the impression that the effect of **ANNIN CO** is too strong or too weak, talk to your doctor or pharmacist.

Taking ANNIN CO with food and drink:

ANNIN CO tablets may be taken with or without food.

Adult dose:
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.

Try to take **ANNIN CO** daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule.

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

Your doctor will tell you how long your treatment with **ANNIN CO** will last. Do not stop treatment early because this may lead to reoccurrence of your condition. If you have the impression that the effect of **ANNIN CO** is too strong or too weak, tell your doctor or pharmacist.

If you take more ANNIN CO than you should:

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

In case of an overdose, contact your doctor immediately so that medical attention may be given promptly. Overdose can cause a drop in blood pressure, palpitations, slow pulse, changes in blood composition, and dehydration.

If you forget to take ANNIN CO:

If you forget to take a dose, take it as soon as you remember unless it is nearly time for your next dose. Do not take a double dose to make up for forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

ANNIN CO can have side effects:

Not all side effects reported for **ANNIN CO** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **ANNIN CO**, please consult your doctor, pharmacist or other healthcare professional for advice.

If any of the following happens, stop taking **ANNIN CO** and tell your doctor immediately or go to the casualty department at your nearest hospital:
- A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing).
This is a serious side effect. You may need urgent medical attention or hospitalisation.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to **ANNIN CO**. You may need urgent medical attention or hospitalisation.

Tell your doctor if you notice any of the following:

The following side effects occur frequently:

- Cough, upper airway infection, congestion in the nose, sinusitis, sinus disorder
- Diarrhoea, abdominal pain, nausea, indigestion
- Muscle pain or cramps, leg pain, back pain
- Insomnia, headache, dizziness
- Weakness, tiredness, chest pain
- Increased potassium levels (which can cause an abnormal heart rhythm), decreased haemoglobin levels
- Changes in kidney function including kidney failure
- Too low sugar in the blood (hypoglycaemia)
- Low blood pressure, which may be associated with changes in posture (feeling light-headed or weak when you stand up, angina (chest pain),abnormal heartbeat, cerebrovascular accident (TIA, "mini-stroke"), heart attack, palpitations
- Improper beating of the heart, whether irregular, too fast or too slow.

The following side effects occur less frequently:

- Anaemia, red or brownish spots on the skin (sometimes especially on the feet, legs, arms and buttocks, with joint pain, swelling of the hands and feet and stomach pain), bruising, reduction in white blood cells, clotting problems
- Loss of appetite, increased uric acid levels or frank gout, increased blood sugar levels, abnormal blood electrolyte levels
- Anxiety, nervousness, panic disorder (recurring panic attacks), confusion, depression, abnormal dreams, sleep disorders, sleepiness, memory impairment
- Blurred vision, burning or stinging in the eyes, conjunctivitis, worsening eyesight, seeing things in yellow
- Ringing, buzzing, roaring or clicking in the ears, vertigo
- Inflammation of blood vessels, which is often associated with a skin rash or bruising
- Sore throat, breathlessness, bronchitis, pneumonia, water on the lungs (which causes difficulty breathing), nosebleed, runny nose, congestion
- Constipation, obstipation, wind, stomach upsets, stomach spasms, vomiting, dry mouth, inflammation of a salivary gland, toothache
- Jaundice (yellowing of the eyes and skin), inflammation of the pancreas
- Itching, inflammation of the skin, rash, redness of the skin, sensitivity to light, dry skin, flushing, sweating, hair loss
- Pain in the arms, shoulders, hips, knees or other joints, joint swelling, stiffness, muscle weakness
- Frequent urination including at night, abnormal kidney function including inflammation of the kidneys, urinary tract infection, sugar in the urine
- Swelling of the face, localised swelling (oedema), fever
- Pins and needles or similar sensations, pain in the extremities, trembling, migraine, fainting
- Increased urea and creatinine levels, increased liver enzymes

The following side effects occur less frequently:

- Hepatitis (inflammation of the liver), abnormal liver function tests.

The following side effects occur with an unknown frequency:

- Thrombocytopenia (a low number of platelets in the blood)
- Pancreatitis (inflammation of the pancreas)
- Flu-like symptoms such as fever, chills, muscle aches, cough, congestion, runny nose, headaches and fatigue
- Liver problems
- Rhabdomyolysis (A breakdown of muscle tissue that causes muscle pain with dark (tea-coloured) urine)
- Decreased sex drive or impotence
- Orthostatic hypotension (A form of low blood pressure that happens when standing up from sitting or lying down)
- Hyponatraemia (A condition that occurs when the level of sodium in the blood is too low)
- Skin and lip cancer (Non-melanoma skin cancer)

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects to SAHPRA via the 6.04 Adverse Drug Reactions Reporting Form. Found under SAHPRAs publications: https://www.sahpra.org.za/Publications/Index/8.
By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store ANNIN CO

Keep out of the sight and reach of children.
Store at or below 25°C.
Store in the original package in order to protect from light and moisture.
Do not use **ANNIN CO** after the expiry date, which is stated on the package. The expiry date refers to the last day of that month.
If your tablets become discoloured or show any other signs of deterioration, consult your doctor or pharmacist who will tell you what to do.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What ANNIN CO contains

There are two active ingredients in **ANNIN CO**. These are losartan potassium and hydrochlorothiazide.

ANNIN CO 50/12,5 mg

Each film-coated tablet contains 50 mg losartan potassium and 12,5 mg of hydrochlorothiazide.

ANNIN CO 100/25 mg

Each film-coated tablet contains 100 mg losartan potassium and 25 mg of hydrochlorothiazide.
Other ingredients:
Cellulose, Microcrystallin Ph.Eur (Avicel PH 101)
Cellulose, Microcrystallin 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 20A02067

What ANNIN CO looks like and contents of the pack

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.

ANNIN CO 50/12,5 mg and **ANNIN CO 100/25 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 aluminium foil with 7gsm heat seal lacquer as the lidding material

Pack size: 30's. Each container 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 seal having induction sealing liner.
Pack Size: 30's . Each HDPE container contains 30 tablets each.

Holder of Certificate of Registration

AUROGEN SOUTH AFRICA (PTY) LTD
Woodhill Office Park,
Building 1, First Floor,
53 Phillip Engelbrecht Avenue
Meyersdal, Ext. 12, 1448
Johannesburg
South Africa

Registration Number

ANNIN CO 50/12,5 mg: 45/7.1.3/1054
ANNIN CO 100/25 mg: 45/7.1.3/1055

This leaflet was last revised in

24 February 2023

PROFESSIONAL INFORMATION 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

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.

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

ANNIN CO 50 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 4.3 and 4.4).

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

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

Special Populations

Renal and Hemodialysis 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:

- 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.
- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- Hypokalemia or hypercalcemia.
- 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).
- 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).
- 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 inhibitor/Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment.
- Patients with a history of previous and/or current basal cell carcinoma and/or squamous cell carcinoma 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).

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).

Intravascular 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).

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.

Thiazide and thiazide-like diuretics have been reported to precipitate hyperuricaemia and/or gout in certain patients.

Hyponatraemia and hypochloraemia
Hyponatraemia and hypochloraemia associated with increased risks of hypotension, syncope, hyperkalaemia and renal function impairment. Rifampin and fluconazole have been reported to reduce levels of losartan's active metabolite and hydroxide levels may be associated with hydrochlorothiazide therapy. **ANNIN CO** may precipitate hyperuricaemia and/or gout in certain patients.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly self-examine 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 investigations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Lactose
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 occasionally 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
Musculoskeletal and connective tissue disorders	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 disorders	Diarrhoea, nausea, abdominal pain, dyspepsia	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, aplastic anaemia, haemolytic anaemia	Less frequent
Metabolic and nutrition disorders	Anorexia, hyperglycaemia, hyperuricaemia, hypercalcaemia, hypokalaemia, hyponatraemia	Less frequent
Nervous system disorders	Paraesthesia, headache, hypotension (including orthostatic hypotension)	Less frequent
Vascular disorders	Respiratory distress including pneumonitis and pulmonary oedema	Less frequent
Respiratory, thoracic and mediastinal disorders	Nausea, vomiting, diarrhoea, constipation, pancreatitis	Less frequent
Gastrointestinal disorders	Jaundice (intrahepatic cholestatic jaundice)	Less frequent
Hepatobiliary disorders	Rash, urticaria, photosensitivity, necrotising angiitis (cutaneous vasculitis)	Less frequent
Skin and subcutaneous tissue disorders	Glycosuria	Less frequent
Renal and urinary disorders		Less frequent

Post-marketing data

Third party post-marketing adverse reactions have been reported but their frequency is unknown:

SYSTEM ORGAN CLASS	ADVERSE REACTION
Blood and the lymphatic system disorders	Aplastic anaemia, thrombocytopenia
Immune system disorders	Anaphylactic reactions, angioedema including swelling of the larynx and airway occlusion, vasculitis, serum sickness, hypersensitivity vasculitis, exacerbation of or activation of systemic lupus erythematosus has been reported rarely in patients treated with hydrochlorothiazide, including ACE inhibitors
Metabolic and nutrition disorders	Electrolyte imbalance including hyponatraemia and hypokalaemia
Psychiatric disorders	Depression, sleep disorders, anxiety, restlessness
Nervous system disorders	Dizziness, paraesthesia, vertigo, transient blurred vision
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 disorders	Gastric irritation, sialadenitis, diarrhoea, vomiting
Hepatobiliary disorders	Hepatitis
Skin and subcutaneous tissue disorders	Purpura (including Henoch-Schoenlein purpura), pruritus, toxic epidermal necrolysis, erythema multiforme, urticaria, erythrodermia has been reported with losartan photosensitivity
Musculoskeletal, connective tissue and bone disorders	Cramping, muscle spasm, myalgia, arthralgia (reported with losartan)

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 risks to the foetus associated with the treatment. Where patients are planning pregnancy, 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 the 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 occasionally 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
Musculoskeletal and connective tissue 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 disorders	Diarrhoea, nausea, abdominal pain, dyspepsia	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, aplastic anaemia, haemolytic anaemia	Less frequent
Metabolic and nutrition disorders	Anorexia, hyperglycaemia, hyperuricaemia, hypercalcaemia, hypokalaemia, hyponatraemia	Less frequent
Nervous system disorders	Paraesthesia, headache, hypotension (including orthostatic hypotension)	Less frequent
Vascular disorders	Respiratory distress including pneumonitis and pulmonary oedema	Less frequent
Respiratory, thoracic and mediastinal disorders	Nausea, vomiting, diarrhoea, constipation, pancreatitis	Less frequent
Gastrointestinal disorders	Jaundice (intrahepatic cholestatic jaundice)	Less frequent
Hepatobiliary disorders	Rash, urticaria, photosensitivity, necrotising angiitis (cutaneous vasculitis)	Less frequent
Skin and subcutaneous tissue disorders	Glycosuria	Less frequent
Renal and urinary disorders		Less frequent

Post-marketing data

Third party post-marketing adverse reactions have been reported but their frequency is unknown:

SYSTEM ORGAN CLASS	ADVERSE REACTION
Blood and the lymphatic system disorders	Aplastic anaemia, thrombocytopenia
Immune system disorders	Anaphylactic reactions, angioedema including swelling of the larynx and airway occlusion, vasculitis, serum sickness, hypersensitivity vasculitis, exacerbation of or activation of systemic lupus erythematosus has been reported rarely in patients treated with hydrochlorothiazide, including ACE inhibitors
Metabolic and nutrition disorders	Electrolyte imbalance including hyponatraemia and hypokalaemia
Psychiatric disorders	Depression, sleep disorders, anxiety, restlessness
Nervous system disorders	Dizziness, paraesthesia, vertigo, transient blurred vision
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 disorders	Gastric irritation, sialadenitis, diarrhoea, vomiting
Hepatobiliary disorders	Hepatitis
Skin and subcutaneous tissue disorders	Purpura (including Henoch-Schoenlein purpura), pruritus, toxic epidermal necrolysis, erythema multiforme, urticaria, erythrodermia has been reported with losartan photosensitivity
Musculoskeletal, connective tissue and bone disorders	Cramping, muscle spasm, myalgia, arthralgia (reported with losartan)

Renal Impairment
Thiazides should be used with caution in patients with severe kidney disease.

Pulmonary Hypersensitivity
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.

Choroidal effusion, acute myopia and secondary acute angle-closure glaucoma
Hydrochlorothiazide, a sulfonamide, can cause a choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Untreated increased intraocular pressure can lead to serious long-term consequences, including permanent vision loss. The primary treatment is to withdraw hydrochlorothiazide as rapidly as possible. Immediate medical or surgical treatments may be necessary if the intraocular pressure remains uncontrolled. Risk factors for the development of acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Cancer
Concomitant administration of lithium with **ANNIN CO** may lead to toxic blood concentrations of lithium.

Concomitant use with Lithium

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 large epidemiological studies based on the Danish National Cancer Registry. Photosensitising actions of hydrochlorothiazide could be the possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly self-examine 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 investigations 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.

Diabetic worsening: hydrochlorothiazide, as in **ANNIN CO**, hyperosmolar 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 decreased renal function. Dual blockade of RAAS through the combined use of **ANNIN CO** with other agents acting on the RAAS is therefore not recommended.
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ANNIN CO should not be used concomitantly with aliskiren-containing products in patients with concomitant diabetes mellitus or renal impairment (GFR< 60 mL/min) (see also section 4.3 and 4.5).

Hydrochlorothiazide

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:

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 at least 4 hours before or 4-6 hours after these drugs.

Corticosteroids, Adrenocorticotropic hormone 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. Concomitant use is not recommended (see section 4.3).

Non-steroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 inhibitors:
When thiazides are taken concomitantly with NS

SKEDULERINGSTATUS

S3

PASIËNTINLIGTINGSPAMFLET

ANNIN CO 50/12,5 mg

losartankalium 50 mg en hidrochloortiasied 12,5 mg.

Bevat suiker: 111 mg laktosemonohidraat

ANNIN CO 100/25 mg

losartankalium 100 mg en hidrochloortiasied 25 mg.

Bevat suiker: 222 mg laktosemonohidraat

Lees die hele pamflet sorgvuldig deur voordat u begin om ANNIN CO te gebruik.

- Hou hierdie pamflet. U moet dit dalk weer lees.
- Indien u verdere vrae het, vra asseblief u dokter, apteker verpleegster of ander gesondheidsorgverskaffer.
- **ANNIN CO** is vir u persoonlik voorgeskryf en u moet nie u medisyne met ander mense deel nie.
- Dit kan skadelik vir hulle wees, selfs al het hulle dieselfde simptome as u.

Wat is in hierdie pamflet:

1. Wat **ANNIN CO** is en waarvoor dit gebruik word
2. Wat u moet weet voor u **ANNIN CO** gebruik
3. Hoe om **ANNIN CO** te gebruik
4. Moontlike newe-effekte
5. Hoe om **ANNIN CO** te berg
6. Inhoud van die verpakking en ander inligting

1. Wat ANNIN CO is en waarvoor dit gebruik word

ANNIN CO is 'n kombinasie van 'n angiotensien-II-reseptorantagonis (losartan) en 'n diuretikum (hidrochloortiasied). Angiotensien-II is 'n stof wat in die liggaam geproduseer word wat aan reseptore in bloedvate bind, wat veroorsaak dat hulle saamtrek. Dit lei tot 'n toename in bloeddruk. Losartan verhoed die binding van angiotensien-II aan hierdie reseptore, wat veroorsaak dat die bloedvate ontspan wat weer die bloeddruk verlaag.Hidrochloortiasied werk deur die niere meer water en sout te laat uitskei. Dit help ook om bloeddruk te verlaag.

ANNIN CO is aangedui vir die behandeling van noodsaaklike hipertensie (hoë bloeddruk).

2. Wat u moet weet voor u ANNIN CO gebruik

Moenie ANNIN CO neem nie:

- Indien u hipersensitief (allergies) is vir losartan, hidrochloortiasied of vir enige van die ander bestanddele van hierdie medisyne (gelys in afdeling 6).
- Indien u voorheen behandel is met 'n medisyne in dieselfde groep medisyne as **ANNIN CO** (angiotensien-reseptorantagoniste) of met 'n medisyne in die groep medisyne bekend as ace-remmers en allergiese reaksies gehad het met swelling van die gesig, lippe, tong, en/of keel met moeilike sluk of asemhaling.
- Indien u 'n ernstige verswakte lewerfunksie het.
- Indien u lae kalium-, lae natrium- of hoë kalsiumvlakke het wat nie deur behandeling reggestel kan word nie.
- Indien u oorerflike of idiopatiese angio-edeem het (swelling van die gesig, lippe, mond, tong, of keel met of sonder moeilike sluk of asemhaling).
- Indien u hipertrofiese obstruktiewe kardiomiopatie het, 'n hartafwyking waarin die wande van die ventrikels (onderste hartkamers) verdik (hipertrofie) en begin styf word en die verdikte spier die vloei van bloed uit die hart uit blokkeer.
- Indien u ernstige verswakte nierfunksie het of u niere produseer geen urine nie.
- Indien u vernouing van die bloedvate na albei niere of 'n enkele nier het.
- Indien u aortastenose het, 'n vernouing van die aortaklepopening tussen die linker ventrikel (groot pompkamer van die hart) en die aorta (die hoofslagaar wat weg van die hart lei).
- Indien u diuretika neem (waterpille) wat veroorsaak dat jou liggaam kalium behou soos spirololaktoon, triamtereen en amiloried.
- Indien u porfirie het.
- Tiasied-watertablette in (vaste dosis) kombinasie soos met **ANNIN CO** moet nie aan pasiënte met Addison se siekte ('n lang-termyn endokriene versteuring waarin die byniere nie genoeg steroïedhormone produseer nie) gegee word nie. Hierdie behandeling moet ook nie gebruik word by pasiënte met ernstige niersiekte of pasiënte wat nie urine kan uitskei nie, en by pasiënte wat allergie toon vir ander sulfonamied-afgeleide medisyne (vra u dokter indien u nie seker is wat sulfonamied-afgeleide medisyne is nie).
- Litiumbehandeling: Gelyktydige toediening met **ANNIN CO** kan lei tot toksiese bloedkonsentrasies van litium.
- Indien u swanger is of borsvoed (sien Swangerskap en Borsvoeding).
- Indien jy tans vel- en/of lipkanker het of dit in die verlede gehad het.
- Die gelyktydige gebruik met antibiotika wat behoort in die klas "fluorokinolone", moet vermy word.
- Die gelyktydige gebruik van **ANNIN CO** met aliskiren-bevattende produkte, moet vermy word.

Neem spesiale sorg met ANNIN CO:

Raadpleeg u dokter, apteker of verpleegster voordat u **ANNIN CO** neem. U moet u dokter vertel indien u dink u is swanger of indien u swanger kan word. **ANNIN CO** word nie tydens swangerskap aanbeveel nie, en moet nie geneem word indien u swanger is nie, aangesien dit ernstige skade aan u baba kan veroorsaak.

Dit is belangrik om u dokter te vertel voordat u ANNIN CO neem:

- Indien u voorheen aan swelling van die gesig, lippe, keel of tong gely het.
- Indien u diuretika (waterpille) neem.
- Indien u op 'n soutbeperkte dieet is.
- Indien u ernstige braking en/of diarree het of gehad het.
- Indien u hartversaking het.
- Indien u lewerfunksie verswak is (sien afdeling 2 "Moenie **ANNIN CO** neem nie")
- Indien u vernoude are na u niere het (nierslagarstenose) of slegs een funksionerende nier het, of u het onlangs 'n nieroorplanting gehad.
- Indien u vernouing van die are het (aterosklerose), angina pectoris (borspyn as gevolg van swak hartfunksie).
- Indien u 'aorta of mitraalklepstenose' het (vernouing van die kleppe van die hart) of 'hipertrofiese kariomiopatie' ('n siekte wat verdikking van die hartspier veroorsaak),
- Indien u 'n diabeet is.
- Indien u jig gehad het.
- Indien u 'n allergiese toestand, asma of 'n toestand wat gewrigspyn, veluitslag en koors het of gehad het (sistemiese lupus eritematose).
- Indien hoë kalsium- of lae kaliumvlakke het of u is op 'n lae kaliumdieet.
- Indien u narkose moet kry (selfs by die tandarts), of voor 'n operasie, of indien u toetse moet ondergaan om u paratiroiedfunksie na te gaan, moet u, u dokter of mediese personeel vertel dat u losartankalium en hidrochloortiasied tablette neem, aangesien daar 'n skielike daling in bloeddruk kan wees wat verband hou met narkose.
- Indien u aan primêre hiperaldosteronisme ly ('n sindroom wat geassosieer word met verhoogde afskeiding van die hormoon aldosteroon deur die byniere, veroorsaak deur 'n abnormaliteit in die klier).
- Indien u enige van die volgende medisyne gebruik, wat gebruik word om hoë bloeddruk te behandeling:
- 'n ACE-inhibeerder (byvoorbeeld enalapriel, lisinopriel, ramipriel), veral as u diabetesverwante nierprobleme het.
- Aliskiren.
- U dokter kan u nierfunksie, bloeddruk, en die hoeveelheid elektroliete (bv. Kalium) in u bloed met gereelde tussenposes nagaan.
- Indien u ander medisyne neem wat moontlik serumkalium kan verhoog (sien afdeling 2 'Ander medisyne en **ANNIN CO**').
- Indien u velkanker gehad het of indien u 'n onverwagte velletsel gedurende behandeling ontwikkel.

Behandeling met hidrochloortiasied, veral lang-termyn gebruik met hoë dosisse, kan die risiko van sommige soorte vel- en lipkanker (nie-melanoom velkanker) verhoog. Beskerm u vel van sonblootstelling en UV-strale terwyl u **ANNIN CO** gebruik.

Gebruik by kinders

Aangesien daar geen ervaring is met die gebruik van **ANNIN CO** by kinders nie, moet **ANNIN CO** nie aan kinders gegee word nie.

Die neem van ander medisyne saam met ANNIN CO:

Vertel altyd u gesondheidsorgkundige indien u enige ander medisyne neem. (Dit sluit alle komplementêre of tradisionele medisyne in).

Ander medisyne en ANNIN CO:

ANNIN CO kan 'n effek hê op ander medisyne of ander medisyne kan 'n effek hê op **ANNIN CO**.

- Dit is veral belangrik vir u dokter om te weet indien u enige ander medisyne neem om bloeddruk te verlaag, ander diuretika (watertablette),
- Medisyne wat gebruik word om diabetes te behandel, insluitend insulien,
  - harse wat hoë cholesterol verlaag,
  - spierverslappers, drukamiene soos adrenalien, steroïede, sekere pyn en artritis medisyne, of
  - litium ('n medisyne wat gebruik word om 'n sekere soort depressie te behandel). Litiumuitskeiding kan verminder word. Daarom, moet litium nie gelyktydig met **ANNIN CO** geneem word nie.
- Sedeermiddels, kalmeermiddels, verdowingsmiddels, alkohol en analgetika kan die bloeddrukverlagende effek van **ANNIN CO** verhoog, vertel daarom u dokter indien u enige van hierdie medisyne gebruik.
- Wanneer Nie-Steroïedale anti-inflammatoriese medisyne (NSAIMs), wat gebruik word om pasiënte met verminderde nierfunksie te behandel, saam met **ANNIN CO** geneem word, kan verdere agteruitgang van die nierfunksie tot gevolg hê.

Swangerskap en Borsvoeding

Indien u swanger is of u baba borsvoed, raadpleeg asseblief u dokter, apteker of ander gesondheidsorgkundige vir advies voordat u ANNIN CO neem. Wanneer swangerskap vasgestel of vermoed word, moet ANNIN CO so gou as moontlik gestaak word. ANNIN CO moet nie in swangerskap gebruik word nie, aangesien teratogenisiteit in proefdiere getoon is.

Swangerskap

U moet u dokter vertel indien u dink u is swanger of indien u swanger kan word. U dokter sal u gewoonlik adviseer om op te hou om **ANNIN CO** te neem voordat u swanger word of sodra u weet dat u swanger is en sal u adviseer om 'n ander medisyne in plaas van **ANNIN CO** te neem. **ANNIN CO** word nie tydens swangerskap aanbeveel nie.

Vroue van vrugbare ouderdom moet effektiewe kontrasepsie verseker.

Borsvoeding

Vertel u dokter indien u borsvoed of gaan begin borsvoed. Veiligheid by borsvoeding is nie vasgestel nie. Tiasiede verskyn in menslike melk. **ANNIN CO** word nie aanbeveel vir moeders wat borsvoed nie, en u dokter kan 'n ander behandeling vir u kies as u, u baba wil borsvoed.

Bestuur en gebruik van masjinerie

Wanneer u behandeling met hierdie medisyne begin, moet u nie take verrig wat spesiale aandag kan vereis nie (byvoorbeeld om 'n voertuig te bestuur of om gevaarlike masjinerie te gebruik) totdat u weet hoe u, u medisyne verdra.

Belangrike inligting oor sommige van die bestanddele van ANNIN CO

ANNIN CO bevat laktose, daarom moet u, u dokter vertel indien u suiker-onverdraagsaam is of 'n geskiedenis van laktose-intoleransie het.

3. Hoe om ANNIN CO te gebruik

Moenie medisyne wat vir u voorgeskryf is met enige ander persoon deel nie.

Neem **ANNIN CO** altyd presies soos u dokter u voorgeskryf het. Raadpleeg u dokter of apteker indien u onseker is. U dokter sal u vertel hoe lank u behandeling met **ANNIN CO** sal duur. Indien u die indruk het dat die effek van **ANNIN CO** te sterk of te swak is, raadpleeg u dokter of apteker.

Die neem van ANNIN CO met voedsel en drank:

ANNIN CO tablette kan met of sonder voedsel geneem word.

<u>**Volwasse dosis:**</u>

Die maksimum dosis is een tablet **ANNIN CO** (100 mg losartankalium en 25 mg hidrochloortiasied) een keer per dag. Die maksimum antihipertensiewe effek word binne drie weke na die aanvang van behandeling bereik.

Probeer om **ANNIN CO** daagliks te neem soos voorgeskryf. Indien u egter 'n dosis mis, moenie 'n ekstra dosis neem nie. Hervat u gewone skedule.

Pediatriese Gebruik:

Veiligheid en effektiwiteit by kinders is nie vasgestel nie.

U dokter sal u vertel hoe lank u behandeling met **ANNIN CO** sal duur. Moenie die behandeling vroeg stop nie, want dit kan lei tot die die herhaling van u toestand. Indien u die indruk het dat die effek van **ANNIN CO** te sterk of te swak is, vertel u dokter of apteker.

Indien u meer ANNIN CO neem as wat u moet:

In die geval van oordosering, raadpleeg u dokter of apteker. Indien geeneen beskikbaar is nie, kontak die naaste hospital of gifbeheersentrum.

In geval van oordosering, kontak u dokter onmiddellik sodat u so gou as moontlik mediese behandeling kan ontvang. Oordosis kan 'n daling in bloeddruk, palpitasies, stadige pols, veranderinge in bloedsamestelling en dehidrasie veroorsaak.

Indien u vergeet om ANNIN CO te neem:

Indien u vergeet om 'n dosis te neem, neem dit so gou as wat u onthou, tensy dit amper tyd is vir u volgende dosis. Moenie 'n dubbeldosis neem om op te maak vir vergete individuele dosisse nie.

4. Moontlike newe-effekte

ANNIN CO kan newe-effekte hê.

Nie alle newe-effekte wat vir **ANNIN CO** aangemeld is, is in hierdie pamflet ingesluit nie. Indien u algemene gesondheid agteruitgaan of indien u enige ongewensde effekte ervaar terwyl u **ANNIN CO** neem, raadpleeg asseblief u gesondheidsorgverskaffer vir advies.

Indien enige van die volgende gebeur, hou op om **ANNIN CO** te neem en vertel u dokter onmiddellik of gaan na die ongevalle-afdeling van u naaste hospitaal:

- 'n Ernstige allergiese reaksie (uitslag, jeuk, swelling van die gesig, lippe, mond of keel, wat moeilike sluk of asemhaling kan veroorsaak).

Hierdie is 'n ernstige newe-effek. U benodig moontlik dringende mediese behandeling of hospitalisasie.

Hierdie is almal baie ernstige newe-effekte. Indien u dit ervaar, het u moontlik 'n ernstige allergiese reaksie vir **ANNIN CO**. U benodig moontlik dringende mediese behandeling of hospitalisasie.

Vertel u dokter indien u enige van die volgende opmerk:

Die volgende newe-effekte kan gereeld voorkom:

- Hoes, boonste lugweginfeksie, kongestie in die neus, sinusitis, sinusversteuring
- Diarree, abdominale pyn, naarheid, slegte spysvertering
- Spierpyn of krampe, beenpyn, rugpyn
- Slapeloosheid, hoofpyn, duiseligheid
- Swakheid, moegheid, borspyn
- Verhoogde kaliumvlakke (wat abnormale hartritme kan veroorsaak), verlaagde hemoglobienvlakke
- Veranderinge in nierfunksie, insluitend nierversaking
- Te lae suiker in die bloed (hipoglisemie)
- Lae bloeddruk, wag geassosieer kan word met veranderinge in postuur (voel lighoofig of swak wanneer u opstaan, angina (borspyn), abnormale hartklop, serebrovaskulêre ongeluk (TIA, "mini-beroerte"), hartaanval, palpitasies
- Onbehoorlike hartklop, hetsy onreëlmatig, te vinnig of te stadig.

Die volgende newe-effekte kom minder gereeld voor:

- Bloedarmoede, rooi of bruinerige kolle op die vel (soms veral op die voete, bene, arms en boude, met gewrigspyn, swelling van die hande en voete en maagpyn), kneusing, vermindering in witbloedselle, stollingsprobleme
- Verlies aan eetlus, verhoogde uriensuurvlakke of jig, verhoogde bloedsuikervlakke, abnormale bloedelektrolietvlakke
- Angs, senuweeagtigheid, paniekversteuring (herhalende paniekaanvalle), verwarring, depressie, abnormale drome, slaapversteurings, slaperigheid, geheue inkorting
- Dowwe visie, brand of steek in die oë, konjunktivitis, verergering van sig, sien dinge in geel
- Gelui, gons, brul of klik in die ore, vertigo
- Inflammasie van die bloedvate, wat dikwels geassosieer word met 'n veluitslag of kneusing
- Seer keel, asemloosheid, brongitis, longontsteking, water op die longe (wat moeilike asemhaling veroorsaak), neusbloeding, loopneus, kongestie
- Hardlywigheid, opstipasie, wind, maagongesteldheid, maagsmarsas, braking, droë mond, inflammasie van die speekselklier, tandpyn
- Geelsug (vergeling van die oë en vel), inflammasie van die pankreas
- Jeuk, inflammasie van die vel, uitslag, rooiheid van die vel, sensitiwiteit vir lig, droë vel, blosing, sweet, haarverlies
- Pyn in die arms, skouers, heupe, knieë of ander gewrigte, gewrigswelling, styfheid, spierswakheid
- Gereelde urinering insluitend snags, abnormale nierfunksie insluitend inflammasie van die niere, urienweginfeksie, suiker in die urine
- Swelling van die gesig, gelokaliseerde swelling (edeem), koors
- Spelde en naalde of soortgelyke sensasies, pyn in die ledemate, bewing, migrain, floute
- Verhoogde ureum- en kreatinienvlakke, verhoogde lewerensieme

Die volgend newe-effekte kom minder dikwels voor:

- Hepatitis (inflammasie van die lewer), abnormale lewerfunksietoetse

Die volgende newe-effekte kom voor met onbekende frekwensie:

- Trombositopenie ('n lae aantal plaatjies in die bloed)
- Pankreatitis (inflammasie van die pankreas)
- Griepagtige simptome soos koors, kouekoors, spierpyne, hoes, kongestie, loopneus, hoofpyn en moegheid
- Lewerprobleme
- Rabdomiolise ('n Afbraak van spierweefsel wat spierpyn veroorsaak met donker (teekleurige) urine)
- Verminderde seksdrang of impotensie
- Ortostatiese hipotensie ('n Vorm van lae bloeddruk wat plaasvind wanneer u opstaan van sit of lê)
- Hiponatremie ('n Toestand wat voorkom wanneer die vlak van natrium in die bloed te laag is)
- Vel- en lipkanker (Nie-melanoom velkanker)

Indien u enige newe-effekte opmerk wat nie in hierdie pamflet genoem word nie, lig asseblief u dokter of apteker in.

Aanmelding van newe-effekte

Indien u newe-effekte ervaar, praat met u dokter, apteker of verpleegster. Dit sluit enige moontlike newe-effekte in wat nie in hierdie pamflet gelys is nie. U kan newe-effekte ook aan SAHPRA rapporteer via die 6.04 Adverse Drug Reaction Reporting Form, wat aanlyn onder SAHPRA se publikasies verskyn: https://www.sahpra.org.za/Publications/Index/8. Deur newe-effekte aan te meld, kan u meer inligting verskaf oor die veiligheid van hierdie medisyne.

5. Hoe om ANNIN CO te berg

Hou buite die sig en bereik van kinders.

Berg by of benede 25 °C.

Berg in die oorspronklike verpakking om te beskerm teen lig en vog.

Moenie **ANNIN CO** gebruik na die vervaldatum wat op die verpakking aangedui is nie. Die vervaldatum verwys na die laaste dag van daardie maand,

Indien u tablette verkleur of enige ander tekens van verswakking toon, raadpleeg u dokter of apteker wat u sal vertel wat om te doen.

Medisyne moet nie via afvalwater of huishoudelike afval weggegooi word nie. Vra u apteker hoe om van medisyne ontslae te raak wat nie meer nodig is nie. Hierdie maatreëls sal help om die omgewing te beskerm.

BERG ALLE MEDISYNE BUITE BEREIK VAN KINDERS.

Neem alle ongebruikte medisyne terug na u apteker.

Moenie ongebruikte medisyne in dreine of rioolsisteme (bv. toilette) weggooi nie.

6. Inhoud van die verpakking en ander inligting

Wat ANNIN CO bevat:

Daar is twee aktiewe bestanddele in **ANNIN CO.** Dit is losartankalium en hidrochloortiasied.

ANNIN CO 50/12,5 mg

Elke filmbedekte tablet bevat 50 mg losartankalium en 12,5 mg hidrochloortiasied.

ANNIN CO 100/25 mg

Elke filmbedekte tablet bevat 100 mg losartankalium en 25 mg hidrochloortiasied.

Ander bestanddele:

Sellulose, mikrokristallyne Ph.Eur (Avicel PH 101)

Sellulose, mikrokristallyne Ph.Eur (Avicel PH 200)

Stysel, pre-gelatiniseerd Ph.Eur (Starch 1500)

Watervrye kolloïdale silika Ph.Eur (Aerosil® 200 Pharma)

Magnesiumstearaat Ph.Eur

Bestanddele van die Bedekkingsmateriaal:

Opadry Geel 20A52067

Hoe ANNIN CO lyk en inhoud van die verpakking

ANNIN CO 50/12,5 mg

Geelkleurige, ovaalvormige, skuinsrand, bikonvekse filmbedekte tablette gegraveer met 'E' aan die een kant en '48' aan die ander kant.

ANNIN CO 100/25 mg

Geelkleurige, ovaalvormige, skuinsrand, bikonvekse filmbedekte tablette gegraveer met 'E' aan die een kant en '49' aan die ander kant.

ANNIN CO 50/12,5 mg en ANNIN CO 100/25 mg:

<u>**Stulpverpakking**</u>

<u>PVC / Aclar</u>

Stulpverpakking bestaan uit 250 mikron wit ondeursigtige PVC-film gelamineer met 50 mikron aclar as die vormingsmateriaal en 25 mikron aluminiumfoelie met 7 gsm hitteseëllak as die dekselmateriaal.

<u>PVC / PE / PVdc</u>

Stulpverpakking bestaan uit 250 mikron wit ondeursigtige PVC-film gelamineer met 25 mikron PE, bedek met 90 gsm PVdc as die vormingsmateriaal en 25 mikron aluminiumfoelie met 7 gsm hitteseëllak as die dekselmateriaal.

Verpakkingsgrootte: 30's. Elke karton bevat 3 stulpstroke met 10 tablette elk.

HDPE

Wit, ondeursigtige ronde 40 mL HDPE-houer met 'n nekafwerking van 33 mm gesluit met 33 mm - 400 RS wit, ondeursigtige polipropileen geribde sluiting met watte en induksie seëlvoering.

Verpakkingsgrootte: 30's: Elke HDPE-houer bevat 30 tablette elk.

Houer van die Registrasiesertifikaat

AUROGEN SOUTH AFRICA (EDMS.) BPK
Woodhillkantoorpark
Gebou 1, Eerste Vloer,
Philip Engelbrechtlaan 53
Meyersdal, Uitbr. 12, 1448,
Johannesburg
Suid-Afrika

Registrasienommer

ANNIN CO 50/12,5 mg: 45/7.1.3/1054

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

Hierdie pamflet is laas hersien in

24 Februarie 2023

P1534375

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 unknown
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

<u>Immune system disorders</u>

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.

<u>Skin and subcutaneous tissue disorders</u>

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

c. <u>Paediatric Use</u>

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.

<u>**Hydrochlorothiazide**</u>

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: C09DA01

Mechanism of action

<u>**Pharmacodynamic properties**</u>

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

<u>**Losartan**</u>

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, 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$_1$ 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$_1$ 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.

<u>**Hydrochlorothiazide**</u>

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.

<u>**Losartan potassium - Hydrochlorothiazide**</u>

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

<u>**Losartan**</u>

<u>Absorption</u>

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.

<u>Distribution</u>

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.

<u>Metabolism</u>

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

<u>Elimination</u>

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.

<u>**Hydrochlorothiazide**</u>

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.

<u>**Losartan potassium - Hydrochlorothiazide**</u>

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 50/12,5 mg and ANNIN CO 100/25 mg

<u>**Blister pack**</u>

<u>PVC / Aclar</u>

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.

<u>PVC / PE / PVdc</u>

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.

<u>HDPE</u>

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 NUMBERS

ANNIN CO 50/12,5 mg: 45/7.1.3/1054

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 February 2023