FINAL PACKAGE INSERT FOR

CIPLAZAR-CO 50/12,5

AND

CIPLAZAR-CO 100/25

SCHEDULING STATUS:

S3

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLAZAR-CO 50/12,5 (Tablet)

CIPLAZAR-CO 100/25 (Tablet)

COMPOSITION:

CIPLAZAR-CO 50/12,5:

Each tablet contains 50 mg losartan potassium and 12,5 mg hydrochlorothiazide.

CIPLAZAR-CO 100/25:

Each tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3. Other hypotensives.

PHARMACOLOGICAL ACTION:

The losartan potassium and hydrochlorothiazide combination combines an angiotensin II receptor (type AT_1) antagonist and a diuretic, hydrochlorothiazide.

Losartan:

Losartan is a synthetic, orally active compound which selectively binds 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.

Angiotensin II is a potent vasoconstrictor, and the primary active hormone of the renin-angiotensin system. It is 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 binds selectively to the AT_1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation.

Hydrochlorothiazide:

Hydrochlorothiazide is a diuretic and an antihypertensive agent. 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. Following oral administration, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Losartan potassium and hydrochlorothiazide:

Losartan and hydrochlorothiazide are additive in their antihypertensive efficacy.

Pharmacokinetics:

Losartan:

Absorption:

After oral administration, losartan undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33 %. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3 – 4 hours, respectively.

Distribution:

Losartan and its active metabolite are 99 % and more bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Metabolism:

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

Elimination:

The plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan potassium is administered orally, about 4 % of the dose is excreted unchanged in the urine, and about 6 % of the dose is excreted in the urine as active metabolite. The pharmacokinetics of

losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6 – 9 hours, respectively. Both biliary and urinary excretion contributes to the elimination of losartan and its metabolites. After an oral dose of ^{14}C 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:

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5,6 and 14,8 hours. Hydrochlorothiazide is not metabolised but is eliminated rapidly 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 and hydrochlorothiazide:

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

INDICATIONS:

CIPLAZAR-CO is indicated in the following:

- For the treatment of hypertension in patients established on identical doses of the individual medicaments.

CONTRA-INDICATIONS:

- Hypersensitivity to **CIPLAZAR-CO** or any of the components of the formulation.
- Hypersensitivity to thiazide diuretics or other sulphonamide-like medicines.
- Anuria or severe renal function impairment (creatine clearance < 30 ml/min) – hydrochlorothiazide may produce cumulative effects or precipitate azotaemia.
- Hepatic function impairment – increased plasma concentrations may occur. **CIPLAZAR-CO** is not recommended since dose titration with losartan is needed.
- Paediatric use – the safety and efficacy of **CIPLAZAR-CO** in paediatric patients have not been established.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs). These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- 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.

- Porphyria.
- Patients with Addison's disease.
- Lithium therapy: concomitant administration with **CIPLAZAR-CO** may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see **"PREGNANCY AND LACTATION"**).

WARNINGS:

CIPLAZAR-CO treatment may cause foetal injury. Should a woman become pregnant while receiving **CIPLAZAR-CO**, the treatment must be stopped promptly and switched to a different medicine. Should a woman contemplate pregnancy, the doctor should consider alternative medication (see **"PREGNANCY AND LACTATION"**).

Hydrochlorothiazide crosses the placental barrier and appears 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. Hydrochlorothiazide does not prevent development of toxaemia of pregnancy and there is no satisfactory evidence that it is useful in the treatment of toxaemia. Women of childbearing age should ensure adequate contraception (see **"CONTRA-INDICATIONS"** and **"PREGNANCY AND LACTATION"**).

Use **CIPLAZAR-CO** with caution in:

- Patients who are sodium- or volume-depleted (e.g. those who have received high-dose diuretics). Symptomatic hypotension may occur following the initiation

of therapy with **CIPLAZAR-CO**. Sodium- or volume-depletion should be corrected before initiating therapy (see **"DOSAGE AND DIRECTIONS FOR USE"**).

- Patients with electrolyte imbalances – the condition may be exacerbated. The correction of electrolyte imbalance prior to administration of **CIPLAZAR-CO** is recommended.
- Patients with diabetes mellitus or hyperglycaemia – hydrochlorothiazide may exacerbate the condition. Dosage adjustments of antidiabetic medicines may be needed.
- Patients with allergy or bronchial asthma – hypersensitivity reactions to hydrochlorothiazide may be more likely in these patients.
- Patients with gout or hyperuricaemia – the condition may be exacerbated by hydrochlorothiazide.
- Systemic lupus erythematosus – hydrochlorothiazide may exacerbate or activate systemic lupus erythematosus.

INTERACTIONS:

The antihypertensive effect of **CIPLAZAR-CO** may be potentiated when taken together with other antihypertensive medicine.

Losartan potassium:

An additive hyperkalaemic effect is possible with potassium supplements, potassium-sparing diuretics, e.g. spironolactone, triamterene, amiloride and other medicines that can cause hyperkalaemia.

Rifampicin increases metabolism of losartan and its active metabolite.

Fluconazole reduces levels of the active metabolite of losartan.

Non-steroidal anti-inflammatory agents (NSAIDS) may attenuate the antihypertensive effect of losartan.

Hydrochlorothiazide:

The following medicines, when administered concurrently, may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics:

The potentiation of orthostatic hypotension may occur, when concurrently used with hydrochlorothiazides.

Antidiabetic medication (oral agents and insulin):

Hydrochlorothiazide may increase blood glucose concentrations. Dosage adjustment of the antidiabetic medicine may be required.

Other antihypertensive medication:

Additive effect or potentiation.

Cholestyramine and colestipol resins:

The 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 percent, respectively. **CIPLAZAR-CO** should therefore be administered one hour before the intake of the resin.

Corticosteroids, ACTH:

Concurrent use with hydrochlorothiazide may aggravate electrolyte depletion, particularly hypokalaemia.

Sympathomimetics:

Concurrent use may decrease the response to sympathomimetic agents.

Neuromuscular blocking agents:

Concurrent use of hydrochlorothiazide may enhance the blockade of non-depolarising neuromuscular blocking agents.

Lithium:

Diuretic agents, such as hydrochlorothiazide, reduce the renal clearance of lithium and add a high risk of lithium toxicity (see **"CONTRA-INDICATIONS"**).

Non-steroidal anti-inflammatory medication:

The administration of a non-steroidal anti-inflammatory agent may reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

PREGNANCY AND LACTATION:

The use of **CIPLAZAR-CO** during pregnancy and lactation is contra-indicated as

safety has not been established (see **"CONTRA-INDICATIONS"** and **"WARNINGS"**).

Losartan is contra-indicated in pregnancy since it has been associated with foetal toxicity in animal studies, and other medicines that act on the renin-angiotensin system have been associated with foetal toxicity in humans. Hydrochlorothiazide crosses the placenta and can cause foetal harm.

DOSAGE AND DIRECTIONS FOR USE:

The usual starting and maintenance dose of **CIPLAZAR-CO 50/12,5** is one tablet once daily. For patients who do not respond adequately to **CIPLAZAR-CO 50/12,5**, the dosage may be changed to one tablet of **CIPLAZAR-CO 100/25** once daily or two tablets of **CIPLAZAR-CO 50/12,5** once daily. The maximum dose is one tablet of **CIPLAZAR-CO 100/25** once daily or two tablets of **CIPLAZAR-CO 50/12,5** once daily. The maximum antihypertensive effect is attained within three weeks after initiation of therapy. **CIPLAZAR-CO** should not be initiated in patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics). **CIPLAZAR-CO** is not recommended for patients with severe renal impairment or for patients with hepatic impairment (see **"Special Precautions"**). No initial dosage adjustment is necessary for elderly patients. **CIPLAZAR-CO** may be administered with other antihypertensive agents, particularly calcium channel blockers and beta-blockers. **CIPLAZAR-CO** may be administered with or without food.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

The following side-effects may occur with the use of **CIPLAZAR-CO:**

Losartan potassium:

Immune system disorders:

The following side-effects have been reported and frequencies are unknown:

Angioedema (including swelling of the face, lips and/or tongue).

Psychiatric disorders:

Less frequent: Insomnia.

Nervous system disorders:

Less frequent: Dizziness, headache.

Cardiac disorders:

Less frequent: Palpitations, tachycardia.

Vascular disorders:

The following side-effects have been reported and frequencies are unknown:

Orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

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

Gastrointestinal disorders:

Less frequent: Diarrhoea, dyspepsia, nausea, abdominal pain.

Skin and subcutaneous tissue disorders:

The following side-effects have been reported and frequencies are unknown:

Rash, urticaria.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Back pain, muscle cramps.

***General disorders*:**

Frequent: Asthenia/fatigue, chest pain, oedema/swelling.

Investigations:

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

Hydrochlorothiazide:

The following side-effects may occur with hydrochlorothiazide:

Immune system disorders:

The following side-effects have been reported and frequencies are unknown:

Hypersensitivity reactions, including purpura, photosensitivity, rash, urticaria, necrotising angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress, including pneumonitis and pulmonary oedema, and anaphylactic reactions.

Metabolism and nutrition disorders:

The following side-effects have been reported and frequencies are unknown:

Hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance, hyperkalaemia.

Blood and the lymphatic system disorders:

The following side-effects have been reported and frequencies are unknown:

Leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia.

Nervous system disorders:

The following side-effects have been reported and frequencies are unknown:

Vertigo, paraesthesia, headache,

xanthopsia.

Vascular disorders:

The following side-effects have been reported and frequencies are unknown:

Hypotension, including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive medicines).

Gastrointestinal disorders:

The following side-effects have been reported and frequencies are unknown:

Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhoea, constipation, pancreatitis, sialadenitis.

Hepatobiliary disorders:

The following side-effects have been reported and frequencies are unknown:

Jaundice (intrahepatic cholestatic jaundice).

Renal and urinary disorders:

The following side-effects have been reported and frequencies are unknown:

Renal dysfunction, interstitial nephritis, renal failure.

General disorders:

The following side-effects have been reported and frequencies are unknown:

Muscle spasm, weakness, restlessness, transient blurred vision.

Investigations:

In controlled clinical trials with **CIPLAZAR-CO**, hyperkalaemia (serum potassium more than 5,5 mmol/L) occurred in 0,7 % of patients, but in these trials, discontinuation of **CIPLAZAR-CO** due to hyperkalaemia was not necessary. Elevations of alanine amino transferase (ALT) have occurred but usually resolved upon discontinuation of therapy.

The following additional adverse reactions have been reported in post-marketing experience with **CIPLAZAR-CO**:

Immune system disorders:

Hypersensitivity:

Angioedema (involving swelling of the face, lips, pharynx and/or tongue) has been reported in patients treated with **CIPLAZAR-CO**; some of whom previously experienced angioedema with other medicines, including angiotensin converting enzyme (ACE) inhibitors.

Gastrointestinal disorders:

Hepatitis has been reported in patients treated with losartan, and diarrhoea.

Special Precautions:

Hepatic and renal impairment:

CIPLAZAR-CO is not recommended for patients with hepatic impairment or severe renal impairment (see **"DOSAGE AND DIRECTIONS FOR USE"**). 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 be reversible upon discontinuation of therapy.

Medicines which affect the renin-angiotensin system, including **CIPLAZAR-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 **"CONTRA-INDICATIONS"**). Similar effects have been reported with losartan; these changes in renal function may be reversible upon discontinuation of therapy.

Hypotension and electrolyte/fluid imbalance:

In patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of **CIPLAZAR-CO**, or a lower starting dose should be used (see **"DOSAGE AND DIRECTIONS FOR USE"**). Periodic determination of serum electrolytes should be performed at appropriate intervals as in any patient receiving diuretics, including **CIPLAZAR-CO**.

Metabolic and endocrine effects:

Hydrochlorothiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see **"INTERACTIONS"**).

Hydrochlorothiazide may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. **CIPLAZAR-CO** should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with hydrochlorothiazide diuretic therapy. Hydrochlorothiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricaemia.

Other:

In patients receiving hydrochlorothiazide, sensitivity 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 hydrochlorothiazide.

CIPLAZAR-CO contains lactose. Patients who are lactose intolerant and who take **CIPLAZAR-CO** may experience unwanted side-effects, such as nausea, cramping, bloating, diarrhoea, and flatulence. **CIPLAZAR-CO** should not be taken by patients with rare hereditary problems or a history of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Losartan potassium:

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, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

Treatment of overdose with **CIPLAZAR-CO** is symptomatic and supportive.

IDENTIFICATION:

CIPLAZAR-CO 50/12,5:

Yellow, and oval-shaped, film-coated tablets with breakline on one side.

CIPLAZAR-CO 100/25:

Yellow, and oval-shaped, film-coated tablets.

PRESENTATION:

HDPE bottle:

CIPLAZAR-CO 50/12,5:

White HDPE plastic bottle containing 100 tablets.

CIPLAZAR-CO 100/25:

White HDPE plastic bottle containing 100 tablets.

Blister strip:

CIPLAZAR-CO 50/12,5:

Aluminium blister strip containing 10 tablets packed in 100's.

CIPLAZAR-CO 100/25:

Aluminium blister strip containing 10 tablets packed in 100's.

STORAGE INSTRUCTIONS:

HDPE Bottle:

Store at or below 25 °C. Keep well closed.

KEEP OUT OF REACH OF CHILDREN.

Blister Strip:

Store at or below 25 °C.

Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:
42/7.1.3/0723
42/7.1.3/0724