SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

CO-NORMOTEN 50/12.5 (Tablet)

CO-NORMOTEN 100/25 (Tablet)

COMPOSITION

Each **CO-NORMOTEN 50/12.5** tablet contains 50 mg losartan potassium and 12,5 mg hydrochlorothiazide.

Each **CO-NORMOTEN 100/25** tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

Each tablet also contains the following inactive ingredients:

Microcrystalline cellulose, lactose monohydrate, pregelatinised maize starch, sodium starch glycolate Type A, magnesium stearate, opadry white with titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION

Pharmacodynamics

CO-NORMOTEN (losartan potassium-hydrochlorothiazide) combines an angiotensin II receptor (type AT_1) antagonist and a diuretic, hydrochlorothiazide.

Losartan

Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system, and a major determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_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.

Hydrochlorothiazide

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

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

Losartan and hydrochlorothiazide

Losartan and hydrochlorothiazide are additive in their antihypertensive efficacy.

Pharmacokinetics

Losartan

Absorption

Following oral administration, losartan undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33 %. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3 – 4 hours, respectively. There is no clinically significant effect on the plasma concentration profile of losartan when administered with a standardised meal.

Distribution

Both losartan and its active metabolite are > 99 % bound to plasma proteins, primarily albumin.

The volume of distribution of losartan is 34 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Metabolism

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

Elimination

Plasma clearance of losartan and its active metabolite is about 600 ml/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 contribute to the elimination of losartan and its metabolites.

Following 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 and hydrochlorothiazide

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

INDICATIONS

CO-NORMOTEN is indicated for the treatment of hypertension in patients established on treatment with identical doses of the individual agents.

CONTRA-INDICATIONS

- Hypersensitivity to any component of this product
- Hypersensitivity to other sulphonamide-derived medicines
- A history of angioedema related to previous therapy with angiotensin receptor blockers (ARBs) or with ACE inhibitors. These patients must never again be given these medicines
- Hereditary or idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Severe renal function impairment (creatinine clearance less than 30 ml/min)
- Anuria – Hydrochlorothiazide may aggravate renal dysfunction
- **CO-NORMOTEN** should not be given to patients with Addison's disease.
- Aortic stenosis
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene and amiloride
- Porphyria
- Lithium therapy: Concomitant administration with **CO-NORMOTEN** may lead to toxic blood levels of lithium
- Pregnancy and lactation- Teratogenicity has been shown in experimental animals. When pregnancy

is detected, **CO-NORMOTEN** should be discontinued as soon as possible. (see **PREGNANCY AND LACTATION**)

- Paediatric use - Safety and efficacy in children has not been established.

**WARNINGS AND SPECIAL PRECAUTIONS **

Use with caution in:-

- Hypotension after cardio-infarction\
- Patients who are sodium- or volume-depleted (e.g. those who have received high-dose diuretics). Thiazide diuretics may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. **CO-NORMOTEN** should be discontinued before carrying out tests for parathyroid function.
- Symptomatic hypotension may occur following the initiation of therapy with **CO**-**NORMOTEN**.
- 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 **CO-NORMOTEN** is recommended.
- Periodic determination of serum electrolytes should be performed at appropriate intervals, as in any patient receiving a diuretic.
- Patients with impaired renal function. The area under the curve (AUC) may be increased by approximately 50 % in patients with moderate renal function impairment. In patients whose renal function is dependent on the renin-angiotensin system, especially those with congestive heart failure, there may be a risk of **CO-NORMOTEN** - induced renal failure. These changes in renal function may be reversible upon discontinuation of therapy.
- Patients with impaired hepatic function – Increased plasma concentrations of **CO- NORMOTEN** may occur. **CO-NORMOTEN** is not indicated since dose titration with losartan is required.
- Patients with diabetes mellitus or hyperglycaemia – Thiazide diuretics 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.
- Losartan, however, decreases uric acid which may attenuate the diuretic-induced hyperuricaemia.
- Systemic lupus erythematosus – Hydrochlorothiazide may exacerbate or activate systemic lupus erythematosus.
- Lapp lactase deficiency or glucose-galactose malabsorption, **CO-NORMOTEN** contains lactose. Patients with rare hereditary problems of galactose intolerance should not take **CO-NORMOTEN.**

Effects on ability to drive and use machines

CO-NORMOTEN has the following side-effects: dizziness, vertigo and transient blurred vision, that may affect the ability to drive and use machines.

Tolerance to **CO-NORMOTEN** should be determined before undertaking tasks that require special attention.

INTERACTIONS

Losartan

No medication interactions of clinical significance have been identified. Compounds which have been studied in clinical pharmacokinetic trials include hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital and ketoconazole.

Hydrochlorothiazide

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

Alcohol, barbiturates, or narcotics: potentiation of orthostatic hypotension may occur.

Antidiabetic medication: (oral agents and insulin): dosage adjustment of the antidiabetic medication may be required.

Other antihypertensive medication: additive effect or potentiation.

Cholestyramine and colestipol resins: absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. **CO-NORMOTEN** should therefore be administered one hour before the intake of the resin.

Corticosteroids, ACTH: 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, nondepolarising: possible increased responsiveness to the muscle relaxant.

Lithium: should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with **CO-NORMOTEN**. (see **CONTRA-INDICATIONS**)

Non-steroidal anti-inflammatory medication: In some patients, the administration of a non steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

PREGNANCY AND LACTATION

CO-NORMOTEN is contra-indicated during pregnancy. See (CONTRA-INDICATIONS). Women of childbearing age should ensure adequate contraception. Should a woman become pregnant while taking CO-NORMOTEN, the treatment should be discontinued promptly and switched to different medicine. Should a woman contemplate pregnancy , the doctor should consider alternative medication.

CO-NORMOTEN is contra-indicated during lactation. See (CONTRA-INDICATIONS).

DOSAGE AND DIRECTIONS FOR USE

Adults: The usual starting and maintenance dose of **CO-NORMOTEN 50/12.5** is one tablet once daily. For patients who do not respond adequately to **CO-NORMOTEN 50/12.5**, the dosage many be increased to two tablets once daily, or one **CO-NORMOTEN 100/25** tablet daily.

No initial dosage adjustment is necessary for elderly patients.

The maximum antihypertensive effect is attained within three weeks after initiation of therapy.

CO-NORMOTEN may be administered with other antihypertensive agents, particularly calcium channel blockers and beta-blockers.

CO-NORMOTEN may be administered with or without food.

CO-NORMOTEN should not be initiated in patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics). See (WARNINGS).

SIDE-EFFECTS

Side effects

Losartan

Metabolic and nutritional disorders:

Less frequent: Hyperkalaemia

Nervous system disorders:

Frequent: Headache

Less frequent: Dizziness, fatigue, insomnia

Incidence unknown: Asthenia

Cardiac disorders:

Less frequent: Palpitations, tachycardia

Incidence unknown: Chest pain

Vascular disorders:

Less frequent: Orthostatic hypotension (dose-related), oedema

Respiratory, thoracic and mediastinal disorders:

Less frequent: Upper respiratory infection, nasal congestion, pharyngitis, sinus disorder, cough

Gastrointestinal disorders:

Less frequent: Diarrhoea

Incidence unknown: Abdominal pain, dyspepsia, nausea

Hepato-biliary disorders:

Less Frequent: Elevations of alanine amino transferase (ALT

Skin and subcutaneous tissue disorders:

Less Frequent: Rash

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Muscle cramps or pain, back pain

Renal and urinary disorders:

Incidence unknown: Impaired renal function

Immune disorders:

Less Frequent: Angioedoema (involving swelling of the face, lips and/or tongue)

Hydrochlorothiazide

Blood and lymphatic system disorders:

Less frequent: Agranulocytosis, leukopenia, thrombocytopenia, aplastic anaemia, haemolytic anaemia

Metabolic and nutritional disorders:

~~F~~*requent:* Electrolyte disturbances, hypokalaemia, hyponatraemia, hypochloraemia

Less Frequent: Hyperuricaemia

Incidence unknown: Hyperglycaemia, glycosuria

Nervous system disorders:

Incidence unknown: Vertigo, paraesthesias, headache, weakness, restlessness

Eye disorders:

Incidence unknown: Xanthopsia, transient blurred vision

Vascular disorders:

Less frequent: Orthostatic hypotension

Gastrointestinal disorders:

Less frequent: Anorexia, gastric irritation, cramping, diarrhoea, nausea, vomiting, pancreatitis

Incidence unknown: Sialadenitis

Hepato-biliary disorders:

Less Frequent: Cholecystitis

Musculoskeletal, connective tissue and bone disorders:

Incidence unknown: Muscle spasm

Renal and urinary disorders:

Incidence unknown: Renal dysfunction, interstitial nephritis, renal failure

Hypersensitivity:

Less frequent: Skin rash

Incidence unknown: Urticaria, purpura, necrotizing angiitis (vasculitis), (cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions

Investigations:

Incidence unknown: Increases in cholesterol and triglyceride levels

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Losartan

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 hemodialysis.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion & hypokalaemia, hypochloraemia, 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.

IDENTIFICATION

CO-NORMOTEN 50/12.5: Light yellow coloured, oval shaped, biconvex film coated tablet with break line in both sides

CO-NORMOTEN 100/25: Yellow coloured, oval shaped, biconvex film coated tablets with break line on both sides

PRESENTATION

CO-NORMOTEN 50/12.5: 11.2 mm X 6.0 mm bioconvex film coated tablets are packed in blister pack using a white opaque Triplex film sealed with printed aluminium lidding foil of 30 tablets. Each carton box contains 3 cards of blister and each card contains 10 tablets

CO-NORMOTEN 100/25: 15.5 mm X 8.7 mm bioconvex film coated tablets are packed in blister pack using a white opaque Triplex film sealed with printed aluminium lidding foil of 30 tablets. Each carton box contains 3 cards of blister and each card contains 10 tablets

STORAGE INSTRUCTIONS

Store at or below 25 °C in a dry place.

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

Keep out of reach of children.

REGISTRATION NUMBER

CO-NORMOTEN 50/12.5: A42/7.1.3/0857

CO-NORMOTEN 100/25: A42/7.1.3/0858

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