FINAL PROPOSED PACKAGE

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

NORMOTEN 50 (Tablet)

NORMOTEN 100 (Tablet)

COMPOSITION

NORMOTEN 50 - Each tablet contains 50 mg losartan potassium (4,24 mg ~ 0,108 mmol potassium)

NORMOTEN 100 - Each tablet contains 100 mg losartan potassium (8,48 mg ~ 0,216 mmol potassium)

NORMOTEN contains the following inactive ingredients:

Lactose anhydrous, starch pregelatinized, magnesium stearate, microcrystalline cellulose, talc, colloidal silicon dioxide, hypromellose, hydroxy propyl cellulose and titanium dioxide

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION

Pharmacodynamics

Losartan is an oral specific angiotensin II antagonist with antihypertensive activity, mainly due to the selective blockade of AT_1 receptors and the consequent reduced pressor effect of angiotensin II.

Angiotensin II is a potent vasoconstrictor and is the primary active hormone of the rennin angiotensin-aldosterone system (RAAS) 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. 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. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT_1 receptor such as bradykinin-mediated effects are not associated with losartan.

During losartan administration, removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to a 2-3 fold increase in angiotensin II in plasma. However, antihypertensive activity and suppression of plasma aldosterone concentration were apparent, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin II levels declined to untreated levels within 3 days.

Pharmacokinetics

Absorption

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

Distribution

Both losartan and its active metabolite are 99 % 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 the active metabolite.

Elimination

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

The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg.

The terminal elimination half-lives of losartan and its active metabolite are 1,5 – 2,5 hours and 3 – 9 hours, respectively.

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

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

Pharmacokinetics in special patient groups

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were 5-fold and 1,7-fold greater respectively, than those seen in young male volunteers.

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. If compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in patients undergoing haemodialysis. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the metabolite can be removed by haemodialysis.

INDICATIONS

NORMOTEN is indicated for the treatment of hypertension.

CONTRA-INDICATIONS

- Hypersensitivity to any of the components of **NORMOTEN**
- 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).
- Severe renal function impairment (creatinine clearance less than 30 ml/min)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney

- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene,
- amiloride.
- Porphyria
- Lithium therapy: Concomitant administration with **NORMOTEN** may lead to toxic blood
- concentrations of lithium.
- Pregnancy and lactation (see **PREGNANCY AND LACTATION**).
- Paediatric use - Safety and effectiveness in children have not been established.

WARNINGS AND SPECIAL PRECAUTIONS

Use 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 **NORMOTEN.**
- Sodium- or volume-depletion should be corrected before initiating therapy or a lower starting

dose is recommended. See DOSAGE AND DIRECTIONS FOR USE.

- With impaired hepatic function. Increased plasma concentrations may occur and lower doses are recommended in these patients. See DOSAGE AND DIRECTIONS FOR USE.

With impaired renal function. The area under the curve (AUC) may be increased by approximately 50 % in patients with moderate renal function impairment. However, dosage adjustments are not necessary unless the patient is volume-depleted. In patients whose renal function is dependent on the renin-angiotensin system, especially those with congestive heart failure, there may be a risk of **NORMOTEN** - induced renal failure.

- With bilateral renal artery stenosis or stenosis of the artery to a solitary kidney – There is an increased risk of renal function impairment in these patients.
- Since hyperkalaemia has been reported (serum potassium greater than 5.5 mEq), serum potassium levels should be monitored, especially in the elderly and in patients with renal function impairment. Discontinuation of **NORMOTEN** due to hyperkalaemia is not usually necessary. (See CONTRA-INDICATIONS)

NORMOTEN contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take **NORMOTEN**.

INTERACTIONS

- Concomitant use of **NORMOTEN** with a diuretic may cause symptomatic hypotension when initiating therapy with **NORMOTEN** A lower starting dose of **NORMOTEN** is recommended for the patient taking a diuretic.

PREGNANCY AND LACTATION

NORMOTEN is contraindicated in pregnancy. See **CONTRAINDICATIONS**. Women of childbearing age should ensure adequate contraception. **NORMOTEN** should be discontinued if pregnancy occurs.

NORMOTEN is contraindicated in lactation. See **CONTRAINDICATIONS**. It is not known whether **NORMOTEN** is distributed into human breast milk. However, **NORMOTEN** and its active metabolite have been identified in significant concentrations in the milk of rats.

The antihypertensive effects of **NORMOTEN** may be potentiated when taken together with other antihypertensive medicines.

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

DOSAGE AND DIRECTIONS FOR USE

Adults: The usual starting and maintenance dose is 50 mg once daily for most patients.

The maximal antihypertensive effect is attained 3 - 6 weeks after initiation of therapy. The dose may be increased to 100 mg once daily, if necessary.

Volume-depleted patients and patients with impaired hepatic function:

Adults: The usual starting dose is 25 mg once daily

No dosage adjustment is required for elderly patients or for patients with impaired renal function, including patients on dialysis, unless the patient is volume-depleted.

A lower dose should be considered for patients with a history of hepatic impairment. Based on pharmacokinetic data, which demonstrate significantly increased plasma concentrations of losartan in cirrhotic

patients, halving of the dose should be considered for patients with a history of hepatic impairment. (see WARNINGS AND SPECIAL PRECAUTIONS).

NORMOTEN may be administered with other antihypertensive agents.

NORMOTEN may be administered with or without food.

SIDE EFFECTS

Metabolic and nutritional disorders:

Incidence unknown: Hyperkalaemia

Nervous system disorders:

Frequent: Headache

Less frequent: Dizziness, asthenia, fatigue, migraine, insomnia

Cardiac disorders:

Incidence unknown: Chest pain, palpitations, tachycardia

Vascular disorders:

Incidence unknown: Orthostatic hypotension (dose-related), oedema

Respiratory, thoracic and mediastinal disorders:

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

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, urticarial

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Muscle cramps or pain, back pain

Immune disorders:

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

Effects on ability to drive and use machines:

There are no data to suggest that **NORMOTEN** interferes with the ability to drive or use machines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms of overdose:

Limited data are available. The most likely symptoms of overdose include hypotension and tachycardia. Bradycardia may occur following parasympathetic (vagal) stimulation. (See SIDE EFFECTS). Neither **NORMOTEN** nor its active metabolite can be removed by haemodialysis.

Treatment of overdose:

Treatment is symptomatic and supportive.

IDENTIFICATION

NORMOTEN 50 - White colour, oval shaped, biconvex, dimensions (3.70 thickness, 10.45 length, 5.60 width), film coated tablet with break line on both sides.

NORMOTEN 100 – White colour, oval shaped, biconvex**,** dimensions (4.60 thickness, 13.20 length, 7.20 width), film coated tablet with break line on both sides.

PRESENTATION

NORMOTEN -50 and -100 tablets are available in white opaque triplex film (PVC/LDPE/PVDC) sealed with aluminium foil blister packs of 30’s packed in outer carton.

STORAGE INSTRUCTIONS

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

Protect from light.

KEEP THE BLISTERS IN THE CARTON UNTIL REQUIRED FOR USE.

Keep out of reach of children.

REGISTRATION NUMBERS

NORMOTEN 50 – 42/7.1.3/0437

NORMOTEN 100 – 42/7.1.3/0438

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DATE OF PUBLICATION OF THIS PACKAGE INSERT

August 2014