LINAXA E

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

abbreviated prescribing information for LINAXA E (Linagliptin and Empagliflozin Tablets 5 mg + 10 mg, 5 mg + 10 mg)

[Please refer the complete prescribing information available at www.torrentpharma.com]

PHARMACOLOGICAL PROPERTIES: Mechanism of Action: Linagliptin and Empagliflozin combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter (SGLT2) inhibitor, and linagliptin, DPP-4 inhibitor.

Linagliptin: Linagliptin is an inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4) an enzyme which is involved in the inactivation of the incretin hormones GLP-1 and GIP (glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretins are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Linagliptin glucosedependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homeostasis. Linagliptin binds selectively to DPP-4 and exhibits a > 10,000 fold selectivity versus DPP-8 or DPP-9 activity in vitro.

Empagliflozin is a reversible, highly potent (IC50 of 1.3 nmol) and selective competitive inhibitor of SGLT2. Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5 000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

INDICATION: It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

DOSAGE AND ADMINISTRATION: The recommended starting dose is one film-coated tablet of Linagliptin and Empagliflozin 10 mg/5 mg (10 mg empagliflozin plus 5 mg linagliptin) once daily.

In patients who tolerate this starting dose and require additional glycaemic control, the dose can be increased to one film-coated tablet of Linagliptin and Empagliflozin 25 mg/5 mg (25 mg empagliflozin plus 5 mg linagliptin) once daily.

CONTRAINDICATION: Hypersensitivity to the active substances, to any other Sodium-Glucose-Co-Transporter-2 (SGLT2) inhibitor, to any other Dipeptidyl-Peptidase-4 (DPP-4) inhibitor, or to any of the excipients.

WARNINGS & PRECAUTIONS: *Diabetic ketoacidosis*: Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including empagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). It is not known if DKA is more likely to occur with higher doses of empagliflozin Renal function *Renal impairment*: In patients with an eGFR below 60 mL/min/1.73 m2 or CrCl <60 mL/min, the daily dose of empagliflozin/linagliptin is limited to 10 mg/5 mg GFR should be assessed before treatment initiation and regularly thereafter. *Hepatic injury*: Cases of hepatic injury have been

reported with empagliflozin in clinical trials. A causal relationship between empagliflozin and hepatic injury has not been established. *Elevated haematocrit*: Haematocrit increase was observed with empagliflozin treatment. *Chronic kidney disease*: There is experience with empagliflozin for the treatment of diabetes in patients with chronic kidney disease (eGFR ≥30 mL/min/1.73 m2) both with and without albuminuria. Patients with albuminuria may benefit more from treatment with empagliflozin. *Risk for volume depletion*: Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. *Urinary tract infections*: In Linagliptin and Empagliflozin clinical trials, the incidence of urinary tract infections was overall similar between the patients treated with Linagliptin and Empagliflozin and the patients treated with empagliflozin or linagliptin. *Lower limb amputations*: An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical trials with another SGLT2 inhibitor. *Acute pancreatitis*: Use of dipeptidyl peptidase-4 (DPP-4) inhibitors has been associated with a risk of developing acute pancreatitis. *Bullous pemphigoid*: Bullous pemphigoid has been observed in patients taking linagliptin. In the trial, bullous pemphigoid was reported in 0.2% of patients on treatment with linagliptin and in no patient on placebo.

DRUG INTERACTIONS: Pharmacodynamic interactions**:** *Insulin and sulphonylureas:* Insulin and sulphonylureas may increase the risk of hypoglycaemia, Diuretics, rifampicin, ritonavir, Effects of linagliptin on other medicinal products: Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes. Linagliptin is a P-glycoprotein substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency. Effects of other medicinal products on linagliptin: Co-administration of rifampicin decreased linagliptin exposure by 40%, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-glycoprotein (P-gp) or cytochrome P450 (CYP) isozyme CYP3A4 inducer, particularly if these are administed long-term.

ADVERSE REACTIONS: Urinary tract infection (including pyelonephritis and urosepsis), Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections, Nasopharyngitis Necrotising fasciitis of the perineum (Fournier´s gangrene), Hypersensitivity, Angioedema, urticaria, Hypoglycaemia (when used with sulphonylurea or insulin), Thirst Diabetic ketoacidosis, Volume depletion, Cough.

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.

IN/ LINAXA E 10 and 25/1000 mg/Feb-25/01/ABPI

(Additional information is available on request)