**LINAXA M**

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

abbreviated prescribing information for LINAXA M (Linagliptin and Metformin Hydrochloride tablets 2.5 mg +500 mg, 2.5 mg+ 850 mg and 2.5 mg+1000 mg)

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

**PHARMACOLOGICAL PROPERTIES**: Mechanism of Action: 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. Metformin: Metformin hydrochloride is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

**INDICATION:** t is indicated as an adjunct to diet and exercise to improve glycemia control in adults with type II Diabetes Mellitus when treatment with Linagliptin and Metformin is appropriate.

**DOSAGE AND ADMINISTRATION:** As directed by physician.

**CONTRAINDICATION:** Hypersensitivity to the active substances or to any of the excipients listed, Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis), Diabetic pre-coma, Severe renal failure (GFR <30 ml/min), Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock, Hepatic impairment, acute alcohol intoxication, alcoholism.

**WARNINGS & PRECAUTIONS**: *Lactic acidosis*: Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. *Renal function:* GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR<30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function. *Cardiac function:* Patients with heart failure are more at risk of hypoxia and renal impairment. In patients with stable chronic heart failure, Linagliptin and Metformin Hydrochloride tablets may be used with a regular monitoring of cardiac and renal function. *Surgery:* Metformin must be discontinued at the time of surgery under general, spinal or epidural anesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable. *Elderly:* Caution should be exercised when treating patients 80 years and older. *Acute pancreatitis:* Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, Linagliptin and Metformin Hydrochloride tablets should be discontinued; if acute pancreatitis is confirmed, Linagliptin and Metformin Hydrochloride tablets should not be restarted. Caution should be exercised in patients with a history of pancreatitis. *Bullous pemphigoid:* If bullous

pemphigoid is suspected, Linagliptin and Metformin Hydrochloride tablets should be discontinued.

**DRUG INTERACTIONS:** 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. Based on these results and in vivo drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates. In vivo assessment of interactions. Effects of other medicinal products on linagliptin: Clinical data described below suggest that the risk for clinically meaningful interactions by coadministered medicinal products is low. Sulphonylureas: The steady-state pharmacokinetics of 5 mg linagliptin were not changed by concomitant administration of a single 1.75 mg dose glibenclamide (glyburide). Ritonavir: Co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, increased the AUC and Cmax of linagliptin approximately twofold and threefold, respectively. Rifampicin: Multiple co-administration of 5 mg linagliptin with rifampicin, a potent inductor of P-glycoprotein and CYP3A4, resulted in a 39.6% and 43.8% decreased linagliptin steady-state AUC and Cmax respectively, and about 30% decreased DPP-4 inhibition at trough. Metformin Co-administration of multiple daily doses of 10 mg linagliptin with 850 mg metformin hydrochloride, an OCT substrate, had no relevant effect on the pharmacokinetics of metformin in healthy subjects. Therefore, linagliptin is not an inhibitor of OCT-mediated transport. Digoxin: Co-administration of multiple daily doses of 5 mg linagliptin with multiple doses of 0.25 mg digoxin had no effect on the pharmacokinetics of digoxin in healthy subjects. Therefore, linagliptin is not an inhibitor of P-glycoprotein-mediated transport in vivo. Warfarin: Multiple daily doses of 5 mg linagliptin did not alter the pharmacokinetics of S(-) or R(+) warfarin, a CYP2C9 substrate, administered in a single dose. Caution is advised, especially in patients with renal impairment, when Inhibitors of OCT1, Inducers of OCT1, or, Inhibitors of OCT2 are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin. Alcohol: Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment. Iodinated contrast agents: LINAXA M must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable

**ADVERSE REACTIONS:** Nasopharyngitis, Hypersensitivity, Hypoglycaemia. Lactic acidosis Vitamin B12 deficiency, Taste disturbance, Cough, Decreased appetite, Diarrhoea, Nausea,, Pancreatitis, Vomiting, Constipation, Abdominal, Liver function disorders 2, Hepatitis, Angioedema, Urticaria, Erythema, Rash, Pruritus, Bullous pemphigoid, Amylase increased, Lipase increased.

**MARKETED BY:**

TORRENT PHARMACEUTICALS LTD.

**IN/ LINAXA M/2.5 mg+500 mg/ 850 mg/1000 mg/APR-23/01/ABPI**

(Additional information is available on request)