## LINAXA D /GLUCRETA L

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

Abbreviated Prescribing information for **LINAXA D /GLUCRETA L** (Linagliptin 5 mg and Dapagliflozin 10 mg Tablets) [Please refer the complete prescribing information for details].

**PHARMACOLOGICAL PROPERTIES:**

**MECHANISM OF ACTION: *Dapagliflozin:*** Dapagliflozin is a reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2) that improves glycaemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis). SGLT2 is selectively expressed in the kidney. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Urinary glucose excretion (glucuresis) induced by Dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by Dapagliflozin is also associated with mild diuresis and transient natriuresis. ***Linagliptin:*** Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones 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. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha cells,resulting in a reduction in hepatic glucose output.

**INDICATIONS:** LINAXA D /GLUCRETA L is indicated for the treatment of patients with type 2 diabetes Mellitus, Inadequately Controlled on Metformin Monotherapy.

**DOSAGE AND ADMINISTRATION:** It should be given orally once daily.

**CONTRAINDICATION: *Dapagliflozin:*** History of a serious hypersensitivity reaction to Dapagliflozin, such as anaphylactic reactions or angioedema, Patients who are being treated for glycemic control without established CVD or multiple CV risk factors with severe renal impairment, Patients on dialysis. ***Linagliptin:*** No dose adjustment is recommended for patients with renal impairment and hepatic impairment

**WARNINGS & PRECAUTIONS: *Dapagliflozin: Volume depletion*:** Before initiating, assess volume status and renal function in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy, ***Ketoacidosis in Patients with Diabetes Mellitus*:** Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue medication, evaluate and treat promptly. Before initiating, consider risk factors for ketoacidosis. Patients on dapagliflozin may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. ***Urosepsis and Pyelonephritis*:** Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated. ***Hypoglycemia:*** Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with drug. ***Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):*** Serious, life-threatening cases have occurred in patients with diabetes, both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute

prompt treatment. ***Genital Mycotic Infections*:** Monitor and treat if indicated. ***Linagliptin- Use with Medications Known to Cause Hypoglycemia:*** Insulin secretagogues are known to cause hypoglycemia. The use of Linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with Linagliptin, ***Macrovascular outcome:*** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Linagliptin tablets or any other antidiabetic drug.

**DRUG INTERACTIONS:** ***Dapagliflozin: Positive Urine Glucose Test*** Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control. ***Interference with 1,5-anhydroglucitol (1,5-AG) Assay*** , Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control. ***Carbonic Anhydrase Inhibitors*** ,Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Dapagliflozin and Metformin Hydrochloride Extended release Tablet may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients, ***Drugs that Reduce Metformin Clearance*** Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use, Alcohol ***Alcohol*** is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Dapagliflozin and Metformin Hydrochloride Extended Release Tablet. ***Linagliptin:- Inducers of P-glycoprotein or CYP3A4 Enzymes*** Rifampin decreased linagliptin exposure suggesting that the efficacy of Linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with P-gp or CYP 3A4 inducer. ***In vitro*** **Assessment of Drug Interactions:** Linagliptin is a weak to moderate inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes and is not an inducer of CYP isozymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11. Linagliptin is a P-glycoprotein (P-gp) substrate, and inhibits P-gp mediated transport of digoxin at high concentrations. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates at therapeutic concentrations. ***In vivo*** **Assessment of Drug Interactions:** Inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations. For patients requiring use of such drugs, an alternative to linagliptin is strongly recommended. *In vivo* studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT). No dose adjustment of Linagliptin is recommended based on results of the described pharmacokinetic studies.

**ADVERSE REACTIONS**: Pancreatitis, Diabetic Ketoacidosis, Volume Depletion, Pyelonephritis, Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues Precautions, Necrotising Fasciitis of the Perineum (Fournier's Gangrene), Genital Mycotic Infections, Hypersensitivity Reactions, Severe and Disabling Arthralgia, Bullous Pemphigoid, Heart Failure, Skin reactions (urticaria), skin exfoliation, myalgia, Acute kidney injury, Constipation, Angioedema, Mouth ulceration, Stomatitis, Vulvovaginitis, balanitis and related genital infections, Urinary tract infection, Dysuria Polyuria, Back pain" Dry mouth, Blood creatinine increased during initial treatment, Blood urea increased, Dizziness

**MARKETED BY:**

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**IN/LINAXA D/ GLUCRETAL L 5 mg + 10 mg/Jul-2023/01/ABPI**
(Additional information is available on request)