Linera M

Linagliptin INN & Metformin Hydrochloride BP

Composition
Linera M 2.5 + 500: Each film coated tablet contains Linagliptin INN 2.5 mg & Metformin Hydrochloride BP 500 mg.
Linera M 2.5 + 850: Each film coated tablet contains Linagliptin INN 2.5 mg & Metformin Hydrochloride BP 850 mg.
Linera M 2.5 + 1000: Each film coated tablet contains Linagliptin INN 2.5 mg & Metformin Hydrochloride BP 1000 mg.

Pharmacology
Linagliptin inhibits dipeptidyl peptidase-4 (DPP-4) enzyme which declines the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon. 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.

Metformin is an anti-hyperglycemic medicine which enhances glucose tolerance in patients with type-2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

Indication and Usage
Linera M is a combination of dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate.

Dosage and Administration
The dosage of **Linera M** should be individualized based on both effectiveness and tolerability, while not exceeding the maximum recommended dose of 2.5 mg linagliptin/1000 mg metformin twice daily with meals. Dose escalation should be gradual to reduce the gastrointestinal (GI) side effects associated with metformin use. In patients currently not treated with metformin, initiate treatment with 2.5 mg linagliptin/500 mg metformin twice daily with meals. In patients already treated with metformin, start with 2.5 mg linagliptin and the current dose of metformin taken at each of the two daily meals (e.g., a patient on metformin 1000 mg twice daily would be started on 2.5 mg linagliptin/1000 mg metformin twice daily with meals). Patients already treated with linagliptin and metformin individual components may be switched to linagliptin & metformin combination containing the same doses of each component.

Contraindication
Linera M is contraindicated in patients with
* Renal impairment (e.g., serum creatinine ≥1.5 mg/dL for men, ≥1.4 mg/dL for women, or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
* Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
* A history of hypersensitivity reaction to linagliptin (such as urticaria, angioedema, or bronchial hyperreactivity) or metformin.

Warning and Precaution
* *Lactic acidosis*: **Linera M** is not recommended in hepatic impairment or hypoxic states and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter.
* Temporarily discontinue **Linera M** in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids.
* *Hypoglycemia*: When used with a sulfonylurea (SU), a lower dose of the SU may be required to reduce the risk of hypoglycemia.
* *Vitamin B12 deficiency*: Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually.
* *Macrovascular outcomes*: No conclusive evidence of macrovascular risk reduction with **Linera M** or any other antidiabetic drug.

Side Effect
Side effects reported in 5% of patients treated with **Linera M** more commonly than in patients treated with placebo are nasopharyngitis and diarrhea. Hypoglycemia was more commonly reported in patients treated with the **Linera M** along with SU compared with those treated with the combination of SU and metformin.

Use in Pregnancy and Lactation
Pregnancy category B. There are no adequate and well-controlled studies in pregnant women. **Linera M** should be used during pregnancy only if clearly needed. Caution should be exercised when **Linera M** is administered to a lactating woman.

Use in Children and Adolescents
The safety and effectiveness of **Linera M** in children and adolescents has not yet been established.

Drug Interaction
* Cationic drugs (e.g., Digoxin, Morphin etc) that are eliminated via the proximal renal tubular system may interact with metformin. So careful patient monitoring and dose adjustment of **Linera M** or interfering drugs is recommended in patients taking cationic medications.
* Use Carbonic Anhydrase Inhibitors (e.g., Topiramate) with caution in patients treated with Linatec M, as the risk of lactic acidosis may increase.
* The efficacy of **Linera M** may be reduced when administered in combination with a strong P-glycoprotein/ CYP3A4 inducer (e.g., Rifampicin). Use of alternative treatments (not containing linagliptin) is strongly recommended.

Overdose
In the event of an overdose with **Linera M**, employ the usual supportive measures (e.g. remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom **Linera M** overdosage is suspected.

During controlled clinical trials in healthy subjects, with single doses of up to 600 mg of linagliptin (equivalent to 120 times the recommended daily dose), there were no dose-related clinical adverse drug reactions. There is no experience with doses above 600 mg in humans.

Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases.

Storage
Do not store above 25ºC. Protect from light. Keep all medicines out of the reach of children.

Packaging
Linera M 2.5 + 500: Each box contains 4x8's tablets in blister pack.
Linera M 2.5 + 850: Each box contains 4x8's tablets in blister pack.
Linera M 2.5 + 1000: Each box contains 4x8's tablets in blister pack.

Manufactured by
ZISKA PHARMA
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