200X300 MM

For the use of only a Registered medical Practitioner or a Hospital or a Institution.

Linagliptin 2.5 mg / 5 mg + Metformin Hydrochloride (ER) 500 mg / 500 mg tablet

Linagliptin 2.5 mg / 5 mg + Metformin Hydrochloride (ER) 1000 mg / 1000 mg tablet

LinaNext-M ER

1. *Generic Name

Linagliptin 2.5 mg / 5 mg + Metformin Hydrochloride (ER) 500 mg / 500 mg tablet

Each film coated bilayered tablet contains:
Linagliptin 2.5 mg
Metformin Hydrochloride IP 500 mg
(As Extended Release form)
Excipients q.s.
Colour: Sunset Yellow

Each film coated bilayered tablet contains:
Linagliptin 5 mg
Metformin Hydrochloride IP 500 mg
(As Extended Release form)
Excipients q.s.
Colour: Quinoline Yellow

2. Qualitative and quantitative composition

*Each film coated bilayered tablet contains:
Linagliptin……..2.5 mg / 5 mg
Metformin Hydrochloride IP …… 500 mg / 500 mg
(As Extended Release)

3. Dosage form and strength

Film Coated Bilayered Tablets (2.5 mg / 5 mg + 1000 mg / 1000 mg)

4. Clinical particulars

4.1 Therapeutic indication

Indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type-II diabetes mellitus when treatment with Linagliptin and Metformin is appropriate.

4.2 Posology and method of administration.

Posology: As directed by R.M.P

Method of Administration: To be taken orally.

4.3 Contraindications

Linagliptin + Metformin ER is contraindicated in patients with:
Severe renal impairment (eGFR below 30 mL/min/1.73 m^2)
Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
A history of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity Hypersensitivity to metformin.

4.4 Special warnings and precautions for use

Lactic Acidosis

Metformin

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Linagliptin + Metformin ER. In Linagliptin + Metformin ER-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue Linagliptin + Metformin ER and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include:

- Before initiating Linagliptin and Metformin ER, obtain an estimated glomerular filtration rate (eGFR).
- Linagliptin and Metformin ER is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.
- Initiation of Linagliptin and Metformin ER is not recommended in patients with eGFR between 30 – 45 mL/min/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking Linagliptin and Metformin ER. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking Linagliptin and Metformin ER whose eGFR later falls below 45 mL/min/1.73 m2, assess the benefit and risk of continuing therapy.

Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking linagliptin. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue Linagliptin and Metformin ER and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Linagliptin and Metformin ER.

Use with Medications Known to Cause Hypoglycemia

Linagliptin

Insulin secretagogues and insulin 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 or insulin may be required to reduce the risk of hypoglycemia when used in combination with Linagliptin and Metformin ER.

Metformin

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as SUs and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs.

Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin (one of the components of Linagliptin and Metformin ER). These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue Linagliptin and Metformin ER, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Linagliptin and Metformin ER.

Vitamin B12 Levels

In controlled, 29-week clinical trials of metformin a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia or neurologic manifestations due to the short duration (<1 year) of the clinical trials. This risk may be more relevant to patients receiving long-term treatment with metformin, and adverse hematologic and neurologic reactions have been reported postmarketing. The decrease in vitamin B12 levels appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on Linagliptin and Metformin ER and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurement at 2-to 3-year intervals may be useful.

Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving Linagliptin and Metformin ER. If bullous pemphigoid is suspected, Linagliptin and Metformin ER should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with linagliptin or metformin.

4.5 Drugs interactions

Drug Interactions with Metformin

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Linagliptin and Metformin ER, may increase the risk of 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 Linagliptin and Metformin ER.

Drug Interactions with Linagliptin

Inducers of P-glycoprotein and CYP3A4 Enzymes

Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp inducer or CYP 3A4 inducer. As Linagliptin and Metformin ER is a fixed-dose combination of linagliptin and metformin, use of alternative treatments (not containing linagliptin) is strongly recommended when concomitant treatment with a strong P-gp or CYP 3A4 inducer is necessary.

Insulin Secretagogues or Insulin

Coadministration of Linagliptin and Metformin ER with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

Drugs Affecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Linagliptin and Metformin ER, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving Linagliptin and Metformin ER, the patient should be observed closely for hypoglycemia.

4.6 Use in special populations (such as pregnant women, lactating women, Paediatric patients, geriatric patients etc.)

Pregnancy

Risk Summary

The limited data with Linagliptin and Metformin ER and linagliptin use in pregnant women are not sufficient to inform a Linagliptin and Metformin ER-associated or linagliptin-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk [see Data]. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

In animal reproduction studies, no adverse developmental effects were observed when the combination of linagliptin and metformin was administered to pregnant rats during the period of organogenesis at doses similar to the maximum recommended clinical dose, based on exposure.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c>7 and has been reported to be as high as 20-25% in women with HbA1c>10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Linagliptin and metformin, the components of Linagliptin and Metformin ER, were coadministered to pregnant Wistar Han rats during the period of organogenesis. No adverse developmental outcome was observed at doses similar to the maximum recommended clinical dose, based on exposure. At higher doses associated with maternal toxicity, the metformin component of the combination was associated with an increased incidence of fetal rib and scapula malformations at ≥ 9-times a 2000 mg clinical dose, based on exposure.

Linagliptin

No adverse developmental outcome was observed when linagliptin was administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg and 150 mg/kg, respectively. These doses represent approximately 943 times (rats) and 1943 times (rabbits) the 5 mg clinical dose, based on exposure. No adverse functional, behavioral, or reproductive outcome was observed in offspring following administration of linagliptin to Wistar Han rats from gestation day 6 to lactation day 21 at a dose 49 times the 5 mg clinical dose, based on exposure.

Metformin Hydrochloride:

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 6-times a clinical dose of 2000 mg, based on body surface area.

Lactation

Risk Summary There is no information regarding the presence of Linagliptin and Metformin ER or linagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. However, linagliptin is present in rat milk. Limited published studies report that metformin is present in human milk [see Data]. However, there is insufficient information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Linagliptin and Metformin ER and any potential adverse effects on the breastfed child from Linagliptin and Metformin ER or from the underlying maternal condition.

Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

Pediatric Use

Safety and effectiveness of Linagliptin and Metformin ER in pediatric patients under 18 years of age have not been established.

Geriatric Use

Linagliptin is minimally excreted by the kidney; however, metformin is substantially excreted by the kidney.

Linagliptin

There were 4040 type 2 diabetes patients treated with linagliptin 5 mg from 15 clinical trials of linagliptin; 1085 (27%) patients were 65 years and over, while 131 (3%) were 75 years and over. Of these patients, 2566 were enrolled in 12 double-blind placebo-controlled studies; 591 (23%) were 65 years and over, while 82 (3%) were 75 years and over. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients. Therefore, no dose adjustment is recommended in the elderly population. While clinical studies of linagliptin have not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients.

Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Linagliptin and Metformin ER is contraindicated in severe renal impairment: patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2.

If Linagliptin and Metformin ER is discontinued due to evidence of renal impairment, linagliptin may be continued as a single entity tablet at the same total daily dose of 5 mg. No dose adjustment of linagliptin is recommended in patients with renal impairment.

Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Linagliptin and Metformin ER is not recommended in patients with hepatic impairment

4.7 Effects on ability to drive and use machines

Driving and use of machines

While taking Linagliptin + Metformin do not drive or operate machinery unless you are alert.

4.8 Undesirable effects

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Linagliptin/Metformin

The safety of concomitantly administered linagliptin (daily dose 5 mg) and metformin (mean daily dose of approximately 1800 mg) has been evaluated in 2816 patients with type 2 diabetes mellitus treated for ≥12 weeks in clinical trials.

Three placebo-controlled studies with linagliptin + metformin were conducted: 2 studies were 24 weeks in duration, 1 study was 12 weeks in duration. In the 3 placebo-controlled clinical studies, adverse reactions which occurred in ≥5% of patients receiving linagliptin + metformin (n=875) and were more common than in patients given placebo + metformin (n=539) included nasopharyngitis (5.7% vs 4.3%).

Other adverse reactions reported in clinical studies with treatment of linagliptin + metformin were hypersensitivity (e.g., urticaria, angioedema, or bronchial hyperreactivity), cough, decreased appetite, nausea, vomiting, pruritus, and pancreatitis.

Linagliptin

Adverse reactions reported in ≥2% of patients treated with linagliptin 5 mg and more commonly than in patients treated with placebo included: nasopharyngitis (7.0% vs 6.1%), diarrhea (3.3% vs 3.0%), and cough (2.1% vs 1.4%).

Rates for other adverse reactions for linagliptin 5 mg vs placebo when linagliptin was used in combination with specific anti-diabetic agents were: urinary tract infection (3.1% vs 0%) and hypertriglyceridemia (2.4% vs 0%) when linagliptin was used as add-on to sulfonylurea; hyperlipidemia (2.7% vs 0.8%) and weight increased (2.3% vs 0.8%) when linagliptin was used as add-on to pioglitazone; and constipation (2.1% vs 1%) when linagliptin was used as add-on to basal insulin therapy.

Other adverse reactions reported in clinical studies with treatment of linagliptin monotherapy were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity) and myalgia. In the clinical trial program, pancreatitis was reported in 15.2 cases per 10,000 patient year exposure while being treated with linagliptin compared with 3.7 cases per 10,000 patient year exposure while being treated with comparator (placebo and active comparator, sulfonylurea). Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Metformin

The most common adverse reactions due to initiation of metformin are diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.

Hypoglycemia

Linagliptin/Metformin

In a 24-week factorial design study, hypoglycemia was reported in 4 (1.4%) of 286 subjects treated with linagliptin + metformin, 6 (2.1%) of 291 subjects treated with metformin, and 1 (1.4%) of 72 subjects treated with placebo. When linagliptin was administered in combination with metformin and a sulfonylurea, 181 (22.9%) of 792 patients reported hypoglycemia compared with 39 (14.8%) of 263 patients administered placebo in combination with metformin and sulfonylurea. Adverse reactions of hypoglycemia were based on all reports of hypoglycemia. A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflect true hypoglycemia.

Laboratory Tests

Linagliptin

Increase in Uric Acid: Changes in laboratory values that occurred more frequently in the linagliptin group and ≥1% more than in the placebo group were increases in uric acid (1.3% in the placebo group, 2.7% in the linagliptin group).

Increase in Lipase: In a placebo-controlled clinical trial with linagliptin in type 2 diabetes mellitus patients with micro-or macroalbuminuria, a mean increase of 30% in lipase concentrations from baseline to 24 weeks was observed in the linagliptin arm compared to a mean decrease of 2% in the placebo arm. Lipase levels above 3 times upper limit of normal were seen in 8.2% compared to 1.7% patients in the linagliptin and placebo arms, respectively.

Metformin

Decrease in Vitamin B12 Absorption: Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g., megaloblastic anemia).

Postmarketing Experience

The following adverse reactions have been identified during postapproval use. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Linagliptin

- Acute pancreatitis, including fatal pancreatitis
- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions
- Severe and disabling arthralgia
- Bullous pemphigoid
- Rash

• Mouth ulceration, stomatitis

Metformin

• Cholestatic, hepatocellular, and mixed hepatocellular liver injury

4.9 Overdose

In the event of an overdose with Linagliptin + Metformin ER, contact the Poison Control Center. 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 Linagliptin + Metformin ER overdosage is suspected.

Linagliptin

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.

Metformin

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.

5. Pharmacological properties

5.1 Mechanism of Action

Linagliptin + Metformin ER

Linagliptin + Metformin ER combines 2 antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin, a member of the biguanide class.

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.

METFORMIN:

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike SUs, metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.2 Pharmacodynamic properties

LINAGLIPTIN:

Linagliptin binds to DPP-4 in a reversible manner and thus increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in better regulation of glucose homeostasis. Linagliptin binds selectively to DPP-4, and selectively inhibits DPP4 but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100-mg dose. At the 100-mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

METFORMIN:

General effects

Insulin is an important hormone that regulates blood glucose levels.19 Type II diabetes is characterized by a decrease in sensitivity to insulin, resulting in elevations in blood glucose when the pancreas can no longer compensate. In patients diagnosed with type 2 diabetes, insulin is unable to exert adequate effects on tissues and cells (i.e. insulin resistance)19 and insulin deficiency may also be present.

Metformin reduces hepatic production of glucose, decreases the intestinal absorption of glucose, and enhances insulin sensitivity by increasing both peripheral glucose uptake and utilization. In contrast with drugs of the sulfonylurea class, which lead to hyperinsulinemia, the secretion of insulin is unchanged with metformin use.

Effect on fasting plasma glucose (FPG) and Glycosylated hemoglobin (HbA1c)

HbA1c is an important periodic measure of glycemic control used to monitor diabetic patients. Fasting plasma glucose is also a useful and important measure of glycemic control. In a 29-week clinical trial of subjects diagnosed with type II diabetes, metformin decreased the fasting plasma glucose levels by an average of 59 mg/dL from baseline, compared to an average increase of 6.3 mg/dL from baseline in subjects taking a placebo. Glycosylated hemoglobin (HbA1c) was decreased by about 1.4% in subjects receiving metformin, and increased by 0.4% in subjects receiving placebo only.

5.3 Pharmacokinetic properties

Linagliptin + Metformin ER

Administration of Linagliptin + Metformin ER with a high-fat meal resulted in up to 7-22% decrease in overall exposure (AUC_{0-72}) of linagliptin; this effect is not clinically relevant. For metformin extended-release, high-fat meals increased systemic exposure ($AUC_{0-\infty}$) by approximately 54-71% relative to fasting, while C_{max} is increased up to 11%. Meals prolonged T_{max} by approximately 3 hours.

Absorption

Linagliptin

The absolute bioavailability of linagliptin is approximately 30%. Following oral administration, plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. However, the prolonged elimination does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady state plasma concentrations of linagliptin 5 mg are reached by the third dose, and Cmax and AUC increased by a factor of 1.3 at steady-state compared with the first dose. Plasma AUC of linagliptin increased in a less than dose-proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes.

Metformin

Following a single oral dose of 1000 mg (2 x 500 mg tablets) metformin extended-release after a meal, the time to reach maximum plasma metformin concentration (T_{max}) is achieved at approximately 7 to 8 hours. In both single-and multiple-dose studies in healthy subjects, once daily 1000 mg (2 x 500 mg tablets) dosing provides equivalent systemic exposure, as measured by AUC, and up to 35% higher C_{max} of metformin relative to the immediate-release given as 500 mg twice daily.

Single oral doses of metformin extended-release from 500 mg to 2500 mg resulted in less than proportional increase in both AUC and C_{max}. Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from metformin extended-release tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected.

Distribution

Linagliptin

The mean apparent volume of distribution at steady state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 L, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent decreasing from about 99% at 1 nmol/L to 75% to 89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Metformin

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

Linagliptin

Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Metformin

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion

Linagliptin

Following administration of an oral [^{14}C] linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.

Metformin

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Linagliptin + Metformin ER

No animal studies have been conducted with the combined products in Linagliptin + Metformin ER to evaluate carcinogenesis, mutagenesis, or impairment of fertility. General toxicity studies in rats up to 13 weeks were performed with linagliptin/metformin coadministered.

The following data are based on the findings in studies with linagliptin and metformin individually.

Linagliptin

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18, and 60 mg/kg. The highest dose of 60 mg/kg is approximately 418 times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors in mice in a 2-year study at doses up to 80 mg/kg (males) and 25 mg/kg (females), or approximately 35 and 270 times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215 times the clinical dose based on AUC exposure.

Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an in vivo micronucleus assay.

In fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility, or bearing live young up to the highest dose of 240 mg/kg (approximately 943 times the clinical dose based on AUC exposure).

Metformin Hydrochloride

Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1200 mg/kg/day in females. These doses are both approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of the maximum recommended human daily dose of 2000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses of up to 2000 mg/kg/day applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and in vivo mouse micronucleus tests were negative.

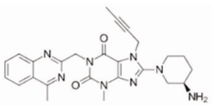
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the MRHD based on body surface area comparisons.

7. Description

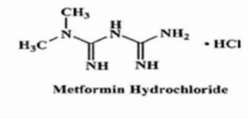
Linagliptin tablets contain, as the active ingredient, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

Linagliptin is described chemically as 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2quinazolinyl)methyl]-

The empirical formula is C25H28N8O2 and the molecular weight is 472.54 g/mol. The structural formula is:



Metformin hydrochloride tablet is an oral antihyperglycemic medication used in the management of type 2 diabetes. Metformin hydrochloride (N,Ndimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. The structural formula of metformin hydrochloride (metformin HCl) is as shown:



Metformin Hydrochloride

8.Pharmaceutical particulars

8.1 Incompatibilities

No incompatibility study has been found.

8.2 Shelf-life

Refer to pack

8.3 Packaging Information

One Blister containing 10 tablets in one carton

8.4 Storage

Store protected from light and moisture at a temperature not exceeding 30°C.

9. Patient Counselling Information

Medication Guide

Instruct patients to read the Medication Guide before starting Linagliptin + Metformin ER therapy and to reread each time the prescription is renewed. Instruct patients to inform their doctor if they develop any bothersome or unusual symptoms, or if any symptom persists or worsens.

Inform patients of the potential risks and benefits of Linagliptin + Metformin ER and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Lactic Acidosis

Inform patients of the risks of lactic acidosis due to the metformin component, its symptoms, and conditions that predispose to its development. Advise patients to discontinue Linagliptin + Metformin ER immediately and to notify their doctor promptly if unexplained hyperventilation, malaise, myalgia, unusual somnolence, slow or irregular heartbeat, sensation of feeling cold (especially in the extremities), or other nonspecific symptoms occur. GI symptoms are common during initiation of metformin treatment and may occur during initiation of Linagliptin + Metformin ER therapy; however, advise patients to consult their doctor if they develop unexplained symptoms. Although GI symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to metformin-induced lactic acidosis or other serious disease.

Pancreatitis

Inform patients that acute pancreatitis has been reported during postmarketing use of linagliptin. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue Linagliptin + Metformin ER promptly and contact their physician if persistent severe abdominal pain occurs.

Monitoring of Renal Function

Inform patients about the importance of regular testing of renal function and hematological parameters when receiving treatment with Linagliptin + Metformin ER.

Instruct patients to inform their doctor that they are taking Linagliptin + Metformin ER prior to any surgical or radiological procedure, as temporary discontinuation of Linagliptin + Metformin ER may be required until renal function has been confirmed to be normal.

Hypoglycemia

Inform patients that the risk of hypoglycemia is increased when Linagliptin + Metformin ER is used in combination with an insulin secretagogue (e.g., sulfonylurea), and that a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia.

Hypersensitivity Reactions

Inform patients that serious allergic reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported during postmarketing use of linagliptin (one of the components of Linagliptin + Metformin ER). If symptoms of allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking Linagliptin + Metformin ER and seek medical advice promptly.

Missed Dose Instruct patients to take Linagliptin + Metformin ER only as prescribed. If a dose is missed, advise patients not to double their next dose.

Alcohol Intake

Warn patients against excessive alcohol intake, either acute or chronic, while receiving.

Administration Instructions

Inform patients taking Linagliptin + Metformin ER that the tablets must be swallowed whole and never split, crushed, dissolved, or chewed and that incompletely dissolved Linagliptin + Metformin ER tablets may be eliminated in the feces. Patients should be told that, if they see tablets in feces, they should report this finding to their healthcare provider.

Blood Glucose and A1C Monitoring

Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C levels, with a goal of decreasing these levels toward the normal range. A1C monitoring is especially useful for evaluating long-term glycemic control.

Renal Function and Other Hematologic Parameters Monitoring

Inform patients that initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (e.g., eGFR) should be performed, at least on an annual basis.

Severe and Disabling Arthralgia

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs.

Bullous Pemphigoid

Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur.

Pregnancy

Inform female patients that treatment with metformin may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation.

Other General Warnings

Talk to your doctor if

- You experience any allergic reactions after taking Linagliptin + Metformin.
- You have any pre-existing medical conditions such as heart disorder, liver or kidney problem, thyroid, etc.
- You are getting suicidal thoughts after taking this medicine, talk to your doctor immediately.
- You are experiencing vision problems or dizziness and sleepiness

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