

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

Linagliptin and Metformin Hydrochloride Tablets (2.5 mg/500 mg) & (2.5 mg/1000mg)

Lingretin® M

2.5/500 & 2.5/1000

1. Generic Name

Linagliptin and Metformin Hydrochloride Tablets (2.5 mg/500 mg) & (2.5 mg/1000mg)

2. Quantitative Composition:

Lingretin® M

2.5/500

Each film coated tablet contains:

Linagliptin.....2.5 mg

Metformin Hydrochloride I.P....500 mg

Excipients.....q.s.

Colours: Ferric Oxide USP NF Yellow & Titanium Dioxide I.P.

Lingretin® M

2.5/1000

Each film coated tablet contains:

Linagliptin.....2.5 mg

Metformin Hydrochloride I.P....1000 mg

Excipients.....q.s.

Colours: Titanium Dioxide I.P. & Ferric Oxide USP NF Red

3. Dosage Form & strength

Refer section 1 & 2

4. Clinical particulars

4.1 Therapeutic indication

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.

4.2 Posology and method of administration

Posology:

The dosage of Lingretin® M should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended dosage of 2.5 mg linagliptin/1000 mg metformin hydrochloride (HCl), taken orally twice daily. Lingretin® M should be given twice daily with meals. Dosage escalation should be gradual to reduce the gastrointestinal (GI) side effects associated with metformin use.

Recommended starting dosage:

- In patients currently not treated with metformin HCl, initiate treatment with 2.5 mg linagliptin/500 mg metformin HCl twice daily.
- In patients already treated with metformin HCl, start with 2.5 mg linagliptin and the current dosage of metformin HCl taken at each of the two daily meals (e.g., a patient on metformin HCl 1,000 mg

twice daily would be started on 2.5 mg linagliptin/1,000 mg metformin HCl twice daily with meals).

- Patients already treated with linagliptin and metformin HCl individual components may be switched to Lingretin® M containing the same dosages of each component.

Recommended Dosing in Renal Impairment

Assess renal function prior to initiation of Lingretin® M and periodically thereafter.

- Lingretin® M is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m².
- Initiation of Lingretin® M in patients with an eGFR between 30-45 mL/min/1.73 m² is not recommended.
- In patients taking Lingretin® M whose eGFR later falls below 45 mL/min/1.73 m², assess benefit/risk of continuing therapy.
- Discontinue Lingretin® M if the patient's eGFR later falls below 30 mL/min/1.73 m².

Discontinuation for Iodinated Contrast Imaging Procedures

- Discontinue Lingretin® M at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m²; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, restart Lingretin® M if renal function is stable.

Method of Administration:

Lingretin® M should be given with meals.

4.3 Contraindications

Lingretin® M is contraindicated in patients with:

- severe renal impairment (eGFR below 30 mL/min/1.73 m²).
- acute or chronic metabolic acidosis, including diabetic ketoacidosis.
- hypersensitivity to linagliptin, metformin, or any of the excipients in Lingretin® M, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred with linagliptin.

4.4 Special warnings and precautions for use

Lactic Acidosis

Metformin

There have been post marketing 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 bradyarrhythmia's 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 Lingretin® M. In Lingretin® M-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin 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 Lingretin® M 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 post marketing 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 Lingretin® M, obtain an estimated glomerular filtration rate (eGFR).
- Lingretin® M is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² [see Contraindications (4)].
- Initiation of Lingretin® M is not recommended in patients with eGFR between 30 – 45 mL/min/1.73 m².
- Obtain an eGFR at least annually in all patients taking Lingretin® M. 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 Lingretin® M whose eGFR later falls below 45 mL/min/1.73 m², assess the benefit and risk of continuing therapy.

Drug Interactions: The concomitant use of Lingretin® M with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop Lingretin® M at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m²; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart Lingretin® M if renal function is stable.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Lingretin® M should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the post marketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Lingretin® M.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism, and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving Lingretin® M.

Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of Lingretin® M in patients with clinical or laboratory evidence of hepatic disease.

Pancreatitis

Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. In the CARMELINA trial, acute pancreatitis was reported in 9 (0.3%) patients treated with linagliptin and in 5 (0.1%) patients treated with placebo. Two patients treated with linagliptin in the CARMELINA trial had acute pancreatitis with a fatal outcome. There have been post marketing reports of acute pancreatitis, including fatal pancreatitis, in patients treated with linagliptin.

Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue Lingretin® M 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 Lingretin® M.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin secretagogues and insulin are known to cause hypoglycemia. The risk of hypoglycemia is increased when Lingretin® M is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin. Therefore, a lower dosage of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with Lingretin® M.

Hypersensitivity Reactions

There have been post marketing reports of serious hypersensitivity reactions in patients treated with linagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred predominantly 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 Lingretin® M, assess for other potential causes for the event, and institute alternative treatment for diabetes mellitus.

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 Lingretin® M.

Vitamin B12 Deficiency

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 at 2-to-3-year intervals in patients on Lingretin® M and manage any abnormalities.

Severe and Disabling Arthralgia

There have been post marketing reports of severe and disabling arthralgia in patients taking linagliptin. 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

Bullous pemphigoid was reported in 7 (0.2%) patients treated with linagliptin compared to none in patients treated with placebo in the CARMELINA trial, and 3 of these patients were hospitalized due to bullous pemphigoid. Post marketing 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 Lingretin® M. If bullous pemphigoid is suspected, Lingretin® M should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Heart Failure

An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of Lingretin® M prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic

symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of Lingretin® M.

4.5 Drug Interactions

Carbonic Anhydrase Inhibitors	
Clinical Impact	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 Lingretin® M may increase the risk of lactic acidosis.
Intervention	Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance	
Clinical Impact	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.
Intervention	Consider the benefits and risks of concomitant use.
Alcohol	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention	Warn patients against excessive alcohol intake while receiving Lingretin® M.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when Lingretin® M is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of Lingretin® M with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower dosages of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Drugs Affecting Glycemic Control	
Clinical Impact	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.
Intervention	When such drugs are administered to a patient receiving Lingretin® M, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving Lingretin® M, the patient should be observed closely for hypoglycemia.
Inducers of P-glycoprotein or CYP3A4 Enzymes	
Clinical Impact	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.
Intervention	Use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

Pregnancy

There are no adequate and well controlled studies in pregnant women with Linagliptin and Metformin HCl or its individual components, and some clinical data is available for metformin which indicate that the risk for major malformations was not increased when metformin is taken during the first trimester in pregnancy. In addition, metformin was not associated with increased perinatal complications. Nevertheless, because these clinical data cannot rule out the possibility of harm, Linagliptin and Metformin HCl should be used during pregnancy only if clearly needed.

Breast-feeding

No studies in lactating animals have been conducted with the combined components of Linagliptin and Metformin HCl. In studies performed with the individual components, both linagliptin and metformin were secreted in the milk of lactating rats. It is not known whether linagliptin is excreted in human milk. Metformin is excreted in human milk in low concentrations. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Fertility

The effect of this medicinal product or Linagliptin and Metformin HCl on fertility in humans has not been studied.

Pediatric Use

Safety and effectiveness of Linagliptin and Metformin HCl have not been established in pediatric patients. Effectiveness of linagliptin was not demonstrated in a 26-week randomized, double-blind, placebo-controlled trial (NCT03429543) in 157 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus.

Geriatric Use

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

Linagliptin

In linagliptin studies, 1,085 linagliptin-treated patients were 65 years of age and older and 131 patients were 75 years of age and older. In these linagliptin studies, no overall differences in safety or effectiveness of linagliptin were observed between geriatric patients and younger adult patients.

Metformin

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger 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 HCl is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73.

In the linagliptin treatment arm of the CARMELINA trial, 2,200 (63%) patients had renal impairment (eGFR <60 mL/min/1.73 m²).

Approximately 20% of the population had eGFR $\geq$ 45 to <60 mL/min/1.73 m², 28% of the population had eGFR $\geq$ 30 to <45 mL/min/1.73 m² and 15% had eGFR <30 mL/min/1.73 m². The overall incidence of adverse reactions were generally similar between the linagliptin and placebo treatment arms.

Hepatic Impairment

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

4.7 Effects on ability to drive and use machines

Linagliptin and Metformin HCl have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Lactic Acidosis
- Pancreatitis
- Hypoglycaemia with Concomitant Use with Insulin and Insulin Secretagogues
- Hypersensitivity Reactions
- Vitamin B12 Deficiency
- Severe and Disabling Arthralgia
- Bullous Pemphigoid
- Heart Failure

4.9 Overdose

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.

5. Pharmacological properties

5.1 Mechanism of action

Pharmacotherapeutic group: tablets contain 2 oral antihyperglycemic drugs used in the management of type 2 diabetes mellitus: Linagliptin and Metformin hydrochloride.

ATC Code: A10BD11

Mechanism of action

Linagliptin

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic 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 HCl

Metformin is an antihyperglycemic agent which improves 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 actually decrease.

5.2 Pharmacodynamic Properties

Linagliptin

Linagliptin binds to DPP-4 in a reversible manner and increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4, 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 HCl

In clinical studies, the major non glycemic effect of metformin is either weight stability or modest weight loss.

In humans, independently of its action on glycaemia, immediate release metformin has favorable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

5.3 Pharmacokinetic properties

Linagliptin

Absorption

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 C_{max} 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.

Distribution

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.

Metabolism

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.

Elimination

Linagliptin has a terminal half-life of about 200 hours at steady state, though the accumulation half-life is about 11 hours. Renal clearance at steady state was approximately 70 mL/min.

Excretion

Following administration of an oral [¹⁴C] 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.

Metformin Hydrochloride

Absorption

After an oral dose of metformin, t_{max} is reached in 2.5 h. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean V_d ranged between 63-276 l.

Biotransformation

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with the combination of linagliptin and metformin HCl.

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 HCl

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2,000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed

with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following in vitro tests: Ames test (*Salmonella typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also 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.

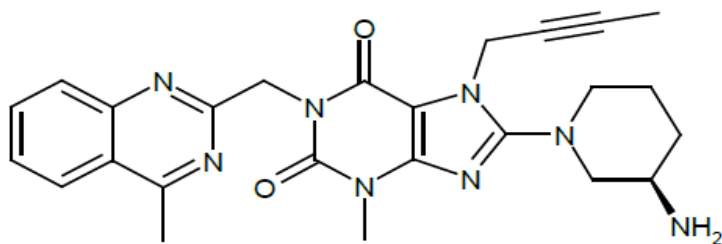
7. Description

Linagliptin

Linagliptin is 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]

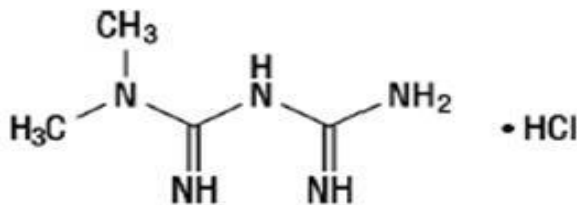
The empirical formula is $C_{25}H_{28}N_8O_2$ and the molecular weight is 472.54 g/mol. The structural formula is:



Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water (0.9 mg/mL). Linagliptin is soluble in methanol (ca. 60 mg/mL), sparingly soluble in ethanol (ca. 10 mg/mL), very slightly soluble in isopropanol (<1 mg/mL), and very slightly soluble in acetone (ca. 1 mg/mL).

Metformin Hydrochloride

Metformin hydrochloride (N, N- dimethylimidodi carbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63 g/mol. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:



8. Pharmaceutical particulars

8.1 Incompatibilities

Not Applicable

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

10 tablets in a blister pack.

8.4 Storage and handling instructions

Store at a temperature not exceeding 30°C.

Medicine: Keep out of reach of children.

9. Patient Counseling Information

Lactic Acidosis

Inform patients of the risks of lactic acidosis due to metformin, its symptoms, and conditions that predispose to its development. Advise patients to discontinue Lingretin® M immediately and to notify their healthcare provider promptly if unexplained hyperventilation, malaise, myalgia, unusual somnolence, or other nonspecific symptoms occur. Counsel patients against excessive alcohol intake and inform patients about importance of regular testing of renal function while receiving Lingretin® M. Instruct patients to inform their healthcare provider that they are taking Lingretin® M prior to any surgical or radiological procedure, as temporary discontinuation may be required until renal function has been confirmed to be normal.

Pancreatitis

Inform patients that acute pancreatitis has been reported during 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 Lingretin® M promptly and contact their healthcare provider if persistent severe abdominal pain occurs.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Inform patients that the risk of hypoglycemia is increased when Lingretin® M is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin.

Hypersensitivity Reactions

Inform patients that serious allergic reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported during post marketing use of linagliptin (one of the components of Lingretin® M). 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 Lingretin® M and seek medical advice promptly.

Vitamin B12 Deficiency

Inform patients about the importance of regular hematological parameters while receiving Lingretin® M. 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 has been reported during use of linagliptin. Instruct patients to seek medical advice if blisters or erosions occur.

Heart Failure

Inform patients of the signs and symptoms of heart failure. Before initiating Lingretin® M, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Instruct patients to contact their healthcare provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet.

Patients of Reproductive Potential

Inform patients that treatment with metformin may result in ovulation in some premenopausal anovulatory patients, which may lead to unintended pregnancy.

Missed Dose

Instruct patients to take Lingretin® M only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

10. Details of manufacturer

Manufactured by:

Exemed Pharmaceuticals

Plot No.: 133/1 & 133/2, Selvas Road,

Vapi, Dist: Valsad-396195, Gujarat, India.

Marketed by:

Abbott Healthcare Pvt. Ltd.

Angel Space, Bldg. D-4, Gala No. 1 to 6 &

11 to 16 Ground Floor, 101 to 106 &

111 to 116 First Floor, 201 to 206 & 211 to 216

2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India.

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11. Details of permission or licence number with date

Lingretin M (2.5/500) Mfg. License No. G/25/2011, dated 05.04.2023

Lingretin M (2.5/1000) Mfg. License No. G/25/2011, dated 02.06.2023

12. Date of revision

Version 1.0, dated 21/07/2023

For Product Complaints/Adverse events or Queries please write to webmasterindia@abbott.com