Linamet™

Linagliptin/Metformin Hydrochloride Tablet

Composition

Linamet 2.5/500 Tablet: Each film coated tablet contains 2.5 mg Linagliptin INN and 500 mg Metformin Hydrochloride BP.

Linamet 2.5/850 Tablet: Each film coated tablet contains 2.5 mg Linagliptin INN and 850 mg Metformin Hydrochloride BP.

Linamet 2.5/1000 Tablet: Each film coated tablet contains 2.5 mg Linagliptin INN and 1000 mg Metformin Hydrochloride BP.

Properties

Pharmacodynamics

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.

Metformin

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. 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.

Pharmacokinetics

Linamet

The results of a bioequivalence study in healthy subjects demonstrated that Linamet (Linagliptin/Metformin Hydrochloride) 2.5 mg/500 mg, 2.5 mg/850 and 2.5 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of Linagliptin and Metformin as individual tablets. There was no change in Metformin AUC; however, mean peak serum concentration of Metformin was decreased by 18% when administered with food. A delayed time-to-peak serum concentrations by 2 hours was observed for Metformin under fed conditions. These changes are not likely to be clinically significant.

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 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.

Metformin

The absolute bioavailability of a Metformin Hydrochloride 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of Metformin tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination

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 [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. 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.

Indications and Usage

Indication

Linamet tablets are 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.

Important Limitations of Use

Linamet should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. Linamet has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using Linamet.

Specific Populations

US-FDA Pregnancy Category B

There are no adequate and well controlled studies in pregnant women 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, Linamet should be used during pregnancy only if clearly needed. Linamet was not teratogenic when administered to Wistar Han rats during the period of organogenesis at doses similar to clinical exposure. At higher maternally toxic doses (9 and 23 times the clinical dose based on exposure), the metformin component of the combination was associated with an increased incidence of fetal rib and scapula malformations.

Nursing Mothers

No studies in lactating animals have been conducted with the combined components of Linamet.

Pediatric Use

Safety and effectiveness of Linamet 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. Considering that aging can be associated with reduced renal function, Linamet should be used with caution as age increases.

Renal Impairment

Linamet

Studies characterizing the pharmacokinetics of Linagliptin and Metformin after administration of Linamet in renally impaired patients have not been performed. Since Metformin is contraindicated in patients with renal impairment, use of Linamet is also contraindicated in patients with renal impairment (e.g., serum creatinine ≥1.5 mg/dL [males] or ≥1.4 mg/dL [females], or abnormal creatinine clearance).

Linagliptin

Under steady-state conditions, Linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In patients with moderate renal impairment under steady-state conditions, mean exposure of Linagliptin increased ($AUC_{T,ss}$ by 71% and Cmax by 46%) compared with healthy subjects. This increase was not associated with a prolonged accumulation half-life, terminal half-life, or an increased accumulation factor. Renal excretion of Linagliptin was below 5% of the administered dose and was not affected by decreased renal function. Patients with type 2 diabetes mellitus and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes mellitus and normal renal function (increase in AUC by 42% and Cmax by 35%). For both type 2 diabetes mellitus groups, renal excretion was below 7% of the administered dose.

Metformin

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of Metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Impairment

Linamet

Studies characterizing the pharmacokinetics of Linagliptin and Metformin after administration of Linamet in hepatically impaired patients have not been performed. However, use of Metformin alone in patients with hepatic impairment has been associated with some cases of lactic acidosis. Therefore, use of Linamet is not recommended in patients with hepatic impairment.

Linagliptin

In patients with mild hepatic impairment (Child-Pugh class A) steady-state exposure ($AUC_{T,ss}$) of Linagliptin was approximately 25% lower and Cmax, ss was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUCss of Linagliptin was about 14% lower and $C_{max,ss}$ was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of Linagliptin in terms of AUC_{0-24} and approximately 23% lower Cmax compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition.

Metformin

No pharmacokinetic studies of Metformin have been conducted in patients with

hepatic impairment.

Body Mass Index (BMI)/Weight
Linagliptin
BMI/Weight had no clinically meaningful effect on the pharmacokinetics of Linagliptin based on a population pharmacokinetic analysis.

Gender
Linagliptin
Gender had no clinically meaningful effect on the pharmacokinetics of Linagliptin based on a population pharmacokinetic analysis.

Metformin
Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of Metformin was comparable in males and females.

Geriatric
Linamet
Studies characterizing the pharmacokinetics of Linagliptin and Metformin after administration of Linamet in geriatric patients have not been performed. Based on the Metformin component, Linamet treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Linagliptin
Age did not have a clinically meaningful impact on the pharmacokinetics of Linagliptin based on a population pharmacokinetic analysis.

Metformin
Limited data from controlled pharmacokinetic studies of Metformin in healthy elderly subjects suggest that total plasma clearance of Metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in Metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric
Studies characterizing the pharmacokinetics of Linagliptin and Metformin after administration of Linamet in pediatric patients have not yet been performed.

Linagliptin
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
Strong 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 OCT. No dose adjustment of Linagliptin is recommended based on results of the described pharmacokinetic studies.

Dosage and Administration
Linamet should be given twice daily with meals. Dose escalation should be gradual to reduce the gastrointestinal (GI) side effects associated with Metformin use. For available dosage forms and strengths.

Recommended starting dose:
• In patients currently not treated with Metformin, initiate treatment with 2.5 mg Linagliptin/500 mg Metformin Hydrochloride twice daily.

• 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 500 mg twice daily would be started on 2.5 mg Linagliptin/500 mg Metformin Hydrochloride twice daily with meals).

• Patients already treated with Linagliptin and Metformin individual components may be switched to Linamet containing the same doses of each component.

• No studies have been performed specifically examining the safety and efficacy of Linamet in patients previously treated with other oral antihyperglycemic agents and switched to Linamet. Any change in therapy of type 2 diabetes mellitus should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin when Linamet is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia.

Warnings and Precautions
Lactic acidosis: Warn against excessive alcohol use. Linamet 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.

• There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue Linamet.

• Temporarily discontinue Linamet 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 an insulin secretagogue (e.g.sulfonylurea or insulin) consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

• There have been postmarketing reports of serious hypersensitivity reactions in patients treated with Linagliptin (one of the components of Linamet) including anaphylaxis, angioedema, and exfoliative skin conditions. In such cases, promptly discontinue Linamet, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes.

• Vitamin B12 deficiency: Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually.

• Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

• Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with Linamet or any other antidiabetic drug.

Contraindications
Linamet 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 anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity.

• Hypersensitivity to Metformin

Drug Interactions
Cationic Drugs
Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with Metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of Linamet and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Carbonic Anhydrase Inhibitors
Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with Linamet, as the risk of lactic acidosis may increase.

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 Linamet 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.

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 Linamet, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving Linamet, the patient should be observed closely for hypoglycemia.

Adverse Reactions
• Adverse reactions reported in ⩾ 5% of patients treated with Linamet and more commonly than in patients treated with placebo are nasopharyngitis and diarrhea.

• Hypoglycemia was more commonly reported in patients treated with the combination of Linamet and SU compared with those treated with the combination of SU and Metformin.

Overdosage
In the event of an overdose with Linamet, 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 Linamet 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.

Storage and Stability
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Protect from exposure to high humidity. Store in a safe place out of reach of children.

How Supplied
Linamet 2.5/500 Tablet: Each box contains 3 x 10 Tablets in Alu-Alu blister pack.

Linamet 2.5/850 Tablet: Each box contains 2 x 10 Tablets in Alu-Alu blister pack.

Linamet 2.5/1000 Tablet: Each box contains 2 x 10 Tablets in Alu-Alu blister pack.

Manufactured by :

POPULAR

POPULAR PHARMACEUTICALS LTD.
TONGI, GAZIPUR, BANGLADESH

PPP22304/01
090817/RGP