120mm

181mm

Vildamet Tablet

(Vildagliptin + Metformin HCl)

ولڈامیٹ ٹیبلیٹ

(ولڈاگلپٹن + میٹفورمن ایچ سی ایل)

COMPOSITION:

VILDAMET Tablet 50mg/500mg

Each film coated tablet contains:

Vildagliptin.....50mg

Metformin hydrochloride.....500mg

(Innovator's Specification)

VILDAMET Tablet 50mg/850mg

Each film coated tablet contains:

Vildagliptin.....50mg

Metformin hydrochloride.....850mg

(Innovator's Specification)

VILDAMET Tablet 50mg/1000mg

Each film coated tablet contains:

Vildagliptin.....50mg

Metformin HCl.....1000mg

(Innovator's Specification)

DESCRIPTION:

Vildagliptin is a white to slightly yellowish or slightly greyish crystalline powder with a melting point/range of approximately 150°C. It is freely soluble in water.

Metformin is a white crystalline powder which is almost odorless and hygroscopic. It is freely soluble in water, slightly soluble in ethanol (96%), and practically insoluble in chloroform and in ether.

MODE OF ACTION:

Vildagliptin

Vildagliptin, a member of the islet enhancer class, is a high affinity dipeptidyl-peptidase-4

(DPP-4) inhibitor that improves glycemic control.

The administration of vildagliptin results in rapid and near-complete inhibition of DPP-4 activity. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion.

Vildagliptin does not stimulate insulin secretion or reduce glucose levels.

Metformin Hydrochloride

Metformin hydrochloride improves glucose tolerance in patients with T2D, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin hydrochloride does not cause hypoglycaemia in either patients with T2D or normal subjects (except in special circumstances), and does not cause hyperinsulinemia. Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase and increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

DOSAGE & ADMINISTRATION:

Adults

The use of antihyperglycemics therapy in the management of T2D should be individualized on the basis of effectiveness and tolerability. The recommended starting dose of VILDAMET should be based on the patient's current regimen of vildagliptin and/or metformin hydrochloride.VILDAMET should be given with meals to reduce the gastrointestinal side effects associated with metformin hydrochloride. When using VILDAMET the maximum daily dose of vildagliptin (100 mg) should not be exceeded. Starting dose for patients inadequately controlled on metformin hydrochloride monotherapy:

Based on the patient's current dose of metformin hydrochloride, VILDAMET may be initiated at either the 50 mg/500 mg, 50 mg/850 mg tablet strength twice daily.

Starting dose for patients switching from combination therapy of vildagliptin plus metformin hydrochloride as separate tablets:

VILDAMET may be initiated with either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1,000 mg tablet strength based on the dose of vildagliptin or metformin already being taken.

Use in combination with a sulfonylurea or with insulin:

The dose of VILDAMET should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.

INDICATIONS:

For patients with Type2 diabetes mellitus (T2DM):

VILDAMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients whose diabetes is not adequately controlled on metformin hydrochloride alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets. Treatment should not be initiated with this fixed-dose combination.

VILDAMET is indicated in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with metformin and a sulfonylurea.

VILDAMET is indicated as add-on to insulin as an adjunct to diet and exercise to improve glycemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycemic control.

PHARMACOKINETICS:

Absorption

Vildagliptin

Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.75 hours. Co-administration with food slightly decreases the rate of absorption of vildagliptin, as characterized by a 19% decrease in peak concentrations, and a delay in the time to peak plasma concentration to 2.5 hours. There is no change in the extent of absorption, and food does not alter the overall exposure (AUC).

Metformin Hydrochloride

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximate 50 to 60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 mg, and 850 mg to 2,550 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. Food delays the absorption of metformin hydrochloride.

Distribution

Vildagliptin

The plasma-protein binding of vildagliptin is low (9.3%), and vildagliptin distributes equally between plasma and red blood cells.

Metformin Hydrochloride

The apparent volume of distribution (V/F) of metformin hydrochloride following single oral doses of 850 mg averaged 654 ± 358 litres. Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound.

Metabolism

Vildagliptin

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite, LAY151, is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the amide hydrolysis product (4% of the dose).

Metformin Hydrochloride

Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism. In patients with significantly decreased renal function, the plasma half-life of metformin is prolonged and renal clearance is decreased.

Excretion and Elimination

Vildagliptin

Following oral administration of [14C]-vildagliptin, approximately 85% of the dose is excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of the unchanged vildagliptin accounts for 23% of the dose after oral administration.

Metformin Hydrochloride

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.

SIDE EFFECTS:

General side effects include fatigue, tremor, dizziness, headache, chills, nausea, gastroesophageal reflux disease, decreased blood glucose, Diarrhea, flatulence,Hyperhydrosis, Asthenia.

PRECAUTIONS:

General

VILDAMET is not a substitute for insulin in patients requiring insulin. VILDAMET should not be used in patients with T1DM (type 1 diabetes mellitus) or for the treatment of diabetic ketoacidosis.

Renal Impairment

VILDAMET should not be used in patients with renal failure or renal dysfunction, e.g. serum creatinine levels ⩾ 1.5 mg/dL (> 135 micromol/L) in males and ⩾ 1.4 mg/dL (> 110 micromol/L) in females.

Monitoring of Renal Function

Metformin hydrochloride is known to be substantially excreted by the kidney and the risk of metformin hydrochloride accumulation and lactic acidosis increases with the degree of renal function impairment. Patients with serum creatinine levels above the ULN for their age should not receive VILDAMET. Since advancing age is associated with reduced renal function, VILDAMET should be carefully given in the elderly to establish the minimum dose for adequate glycaemic effect, and renal function should be monitored regularly.

VILDAMET should be discontinued if evidence of renal impairment is present.

Concomitant Medications that May Affect Renal Function or Metformin Hydrochloride Disposition

Concomitant medications that may affect renal function, result in significant hemodynamic change or interfere with the disposition of metformin hydrochloride, such as cationic drugs that are eliminated by renal tubular secretion should be used with caution Cardiac failure VILDAMET is contraindicated in patients with congestive heart failure requiring pharmacologic treatment, which may potentially interact with metformin hydrochloride.

Hepatic Impairment

Vildagliptin, and hence VILDAMET is not recommended in patients with clinical or laboratory evidence of hepatic impairment, including patients with pre-treatment ALT or AST >2.5x the ULN.

Since impaired hepatic function has been associated with some cases of lactic acidosis (a risk associated with metformin hydrochloride), VILDAMET should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Liver Enzyme Monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with VILDAMET.

Lactic Acidosis

Lactic acidosis is a very rare but serious metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors, such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia Lactic acidosis is characterised by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5mmol/L and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient is hospitalizedimmediately .

Pediatric use

The safety and effectiveness of VILDAMET in paediatric patients have not been established. Therefore, VILDAMET is not recommended for use in children below 18 years of age.

Use in the Elderly (⩾ 65 Years)

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking VILDAMET should have their renal function monitored regularly. VILDAMET should only be used in elderly patients with normal renal function

Effects on fertility

No studies have been conducted with vildagliptin and metformin in combination to evaluate potential effects on fertility. Fertility studies have been performed with vildagliptin in rats at doses producing exposures equivalent to up to 160 times the human dose and have revealed no evidence of impaired male or female fertility or early embryonic development due to vildagliptin. Fertility of male or female rats was also unaffected by metformin administration at doses up to 600 mg/kg/day, or approximately 3-times the maximum recommended daily human dose on a body surface area basis.

DRUG INTERACTIONS:

Vildagliptin has low potential for drug interactions. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit or induce CYP 450 enzymes, it is not likely to interact with co-medications that are substrates, inhibitors or inducers of these enzymes. Furthermore, vildagliptin does not affect metabolic clearance of co-medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5. Drug-drug interaction studies were conducted with commonly co-prescribed medications for patients with T2DM or medications with a narrow therapeutic window. As a result of these studies no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, metformin hydrochloride), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.

Metformin Hydrochloride Furosemide: Furosemide increased Cmax and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreased Cmax, blood AUC of furosemide, with no change in renal clearance of furosemide. Nifedipine Nifedipine increased absorption, Cmax and AUC of metformin, and increased excretion of metformin in urine. Metformin had minimal effects on nifedipine. Glyburide Glyburide produced no changes in metformin PK/PD parameters. Decreases in Cmax, blood AUC of glyburide were observed, but were highly variable. Therefore the clinical significance of this finding was unclear.

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 to interact with metformin by competing for common renal tubular transport systems. Thus, with cimetidine increases in metformin plasma/blood concentration and AUC were observed to be 60% and 40% respectively. Metformin had no effect on cimetidine PK. Although such interactions remain theoretical (except for cimetidine), careful monitoring of patients and doses of metformin and such medications are recommended. Other Certain drugs tend to cause 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. Close monitoring of glycemic control and metformin dose adjustments are recommended when such drugs are administered or withdrawn for these patients. There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to metformin. Consumption of alcohol and medicinal products containing alcohol should be avoided.

CONTRAINDICATIONS:

- VILDAMET is contraindicated in patients with known hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients
- VILDAMET is contraindicated in patients with renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ⩾1.5 mg/dL (>135 micromol/L) in males and ⩾ 1.4 mg/dL (> 110 micromol/L) in females or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia
- VILDAMET is contraindicated in patients with congestive heart failure requiring pharmacologic treatment
- VILDAMET is contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
- VILDAMET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

STORAGE & INSTRUCTIONS:

Store between 15-25°C. Protect from heat, sunlight and moisture. Keep away from the reach of children.

To be sold on prescription of registered medical practitioner only.

HOW SUPPLIED:

VILDAMET Tablet 50mg/500mg
14's Tablets

VILDAMET Tablet 50mg/850mg
14's Tablets

VILDAMET Tablet 50mg/1000mg
14's, 28's Tablets

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Manufactured by:
PHARMASOL PRIVATE LIMITED
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.