

Vilget™

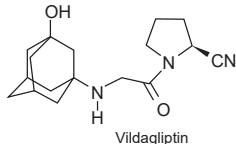
[Vildagliptin+Metformin HCl]

Tablets 50mg + 500mg, 50mg + 850mg, 50mg + 1000mg

DESCRIPTION

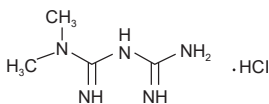
Vilget-M (Vildagliptin + Metformin HCl) combines two antihyperglycemic agents to improve glycaemic control in patients with type 2 diabetes, Vildagliptin and Metformin HCl.

Vildagliptin is an inhibitor of the enzyme dipeptidylpeptidase-4 (DPP-4), which plays a role in regulating insulin secretion. Chemically, vildagliptin is 1-[(3-Hydroxy-adamant-1-ylamino)acetyl]-pyrrolidine-2(S)-carbonitrile. Its molecular formula is $C_{17}H_{25}N_3O_2$ and the structural formula is:



Vildagliptin

Metformin HCl (N,N-dimethylimidodicyanamide hydrochloride) is a member of the biguanide class and not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Its molecular formula is $C_4H_{11}N_5$ HCl and the structural formula is:



Metformin HCl

QUALITATIVE AND QUANTITATIVE COMPOSITION

Vilget-M (Vildagliptin + Metformin HCl) is available for oral administration as:

Vilget-M Tablets 50mg + 500mg
Each film-coated tablet contains:
Vildagliptin...50mg
Metformin HCl USP...500mg

Vilget-M Tablets 50mg + 850mg
Each film-coated tablet contains:
Vildagliptin...50mg
Metformin HCl USP...850mg

Vilget-M Tablets 50mg + 1000mg
Each film-coated tablet contains:
Vildagliptin...50mg
Metformin HCl USP...1000mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Vildagliptin

The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity, resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

Metformin HCl

Metformin HCl decreases hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis, decrease intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin HCl stimulates intracellular glycogen synthesis by acting on glycogen synthase and increase the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

Pharmacokinetics

Vildagliptin

Absorption

Following oral administration in the fasting state, vildagliptin is rapidly absorbed, with peak plasma concentrations observed at 1.7 hours. The absolute bioavailability is 85%.

Effect of Food:

Food slightly delays the time to peak plasma concentration to 2.5 hours, but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased C_{max} (19%).

Distribution

The plasma protein binding of vildagliptin is low (9.3%) and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady-state after intravenous administration (V_{ss}) is 71 litres, suggesting extravascular distribution.

Metabolism

Metabolism is the major elimination pathway for vildagliptin, accounting for 69% of the dose. The major metabolite (LAY 151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the glucuronide (BQS867) and the amide hydrolysis products (4% of dose). Vildagliptin is not metabolised by CYP450 enzymes to any quantifiable extent.

Elimination

Following oral administration of [^{14}C] 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 accounted for 23% of the dose after oral administration. The elimination half-life after oral administration is approximately 3 hours.

Metformin HCl

Absorption

After an oral dose of metformin, the maximum plasma concentration (C_{max}) is achieved after about 2.5 hours. Absolute bioavailability of a 500mg metformin is approximately 50-60% in healthy individuals. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 hours and are generally less than 1µg/ml.

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Effect of Food:

Food slightly delays and decreases the extent of the absorption of metformin. Following administration of a dose of 850mg, the plasma peak concentration was 40% lower. AUC was decreased by 25% and time to peak plasma concentration was prolonged by 35 minutes.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The mean volume of distribution (V_d) ranged between 63-276 litres. The apparent volume of distribution (V/F) of metformin HCl following single oral doses of 850mg averaged 654 ± 358 litres.

Metabolism

Metformin does not undergo hepatic metabolism.

Elimination

Metformin HCl is excreted unchanged in the urine. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of 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.

Special Population

Vildagliptin

Hepatic impairment

The exposure to vildagliptin after a single dose in patients with mild and moderate hepatic impairment was decreased (20% and 8%, respectively), while the exposure to vildagliptin for patients with severe impairment were increased by 22%.

Renal impairment

Vildagliptin AUC increased on average 1.4, 1.7 and 2-fold in patients with mild, moderate and severe renal impairment, respectively. AUC of the metabolites LAY151 and BQS867 increased on average about 1.5, 3 and 7-fold in patients with mild, moderate and severe renal impairment, respectively. Patients with end stage renal disease (ESRD) have vildagliptin exposure similar to that in patients with severe renal impairment. LAY151 concentrations in ESRD patients were approximately 2-3-fold higher than in patients with severe renal impairment.

Metformin HCl

Elderly

In healthy elderly individuals total plasma clearance of metformin HCl is decreased, the half-life is prolonged and C_{max} is increased, compared to healthy young individuals.

Renal impairment

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

THERAPEUTIC INDICATIONS

Vilget-M (Vildagliptin + Metformin HCl) is indicated for the treatment of patients with Type 2 diabetes mellitus (T2DM):

- Vilget-M (Vildagliptin + Metformin HCl) is indicated as an adjunct to diet and exercise to improve glycaemic control in patients whose diabetes is not adequately controlled on metformin HCl alone or who are already treated with the combination of vildagliptin and metformin HCl, as separate tablets.
- Vilget-M (Vildagliptin + Metformin HCl) is indicated in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulfonylurea.
- Vilget-M (Vildagliptin + Metformin HCl) is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control.

DOSE AND ADMINISTRATION

Adults

The use of antihyperglycemic therapy in the management of T2DM should be individualized on the basis of effectiveness and tolerability. The recommended starting dose of Vilget-M (Vildagliptin + Metformin HCl) should be based on the patient's current regimen of vildagliptin and/or metformin HCl.

Vilget-M (Vildagliptin + Metformin HCl) should be given with meals to reduce the gastrointestinal side effects associated with metformin HCl. When using Vilget-M (Vildagliptin + Metformin HCl) the maximum daily dose of vildagliptin (100mg) should not be exceeded.

Starting dose for patients inadequately controlled on metformin HCl monotherapy:

Based on the patient's current dose of metformin HCl, Vilget-M (Vildagliptin + Metformin HCl) may be initiated at either the 50mg + 500mg, 50mg + 850mg or 50mg + 1000mg tablet twice daily, one tablet in the morning and one tablet in the evening.

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

Vilget-M (Vildagliptin + Metformin HCl) may be initiated with either the 50mg + 500mg, 50mg + 850mg or 50mg + 1000mg tablet based on the dose of vildagliptin or metformin already being taken.

Starting dose for patients inadequately controlled on dual combination with metformin HCl and a sulfonylurea:

The doses of Vilget-M (Vildagliptin + Metformin HCl) should provide vildagliptin as 50mg twice daily (100mg total daily dose) and a dose of metformin similar to the dose already being taken.

Starting dose for patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin HCl:

The dose of Vilget-M (Vildagliptin + Metformin HCl) should provide vildagliptin dosed as 50mg twice daily (100mg total daily dose) and a dose of metformin similar to the dose already being taken.

Special Population

Patients with hepatic impairment

Vilget-M (Vildagliptin + Metformin HCl) should not be used in patients with hepatic impairment, including patients with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN).

Elderly (> 65 years)

Elderly patients taking Vilget-M (Vildagliptin + Metformin HCl) should have their renal function monitored regularly.

Pediatrics

Vilget-M (Vildagliptin + Metformin HCl) is not recommended for use in children and adolescents (< 18 years).

CONTRAINDICATIONS

Vildagliptin + Metformin HCl combination is contraindicated in:

- Patients with known hypersensitivity to vildagliptin or metformin HCl or to any excipient of the product.
- Diabetic ketoacidosis or diabetic pre-coma.
- Renal failure or renal dysfunction defined as creatinine clearance < 60ml/min.
- Acute conditions with the potential to alter renal function, such as dehydration, severe infection, shock, intravascular administration of iodinated contrast agents.
- Acute or chronic disease which may cause tissue hypoxia, such as cardiac or respiratory failure, recent myocardial infarction, shock.
- Hepatic impairment.
- Acute alcohol intoxication, alcoholism.

PRECAUTIONS

General

Vildagliptin + Metformin HCl combination is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes.

Lactic acidosis

Lactic acidosis is a very rare but serious metabolic complication that can occur due to metformin accumulation. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalized immediately.

Renal impairment

Vildagliptin + Metformin HCl combination should not be used in patients with renal failure or renal dysfunction, e.g. serum creatinine levels $\geq 1.5\text{mg/dL}$ ($> 135\text{micromol/L}$) in males and $\geq 1.4\text{mg/dL}$ ($> 110\text{micromol/L}$) in females. Treatment should be discontinued if evidence of renal impairment is present.

Liver enzyme monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported. Liver function tests should be performed prior to the initiation of treatment. Liver function should be monitored during treatment at three-month intervals during the first year and periodically thereafter.

Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue therapy with vildagliptin + metformin HCl combination.

Cardiac failure

Vildagliptin use is not recommended in patients with NYHA functional class IV.

Skin disorders

In diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.

Acute pancreatitis

Use of vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued and if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.

Hypoglycemia

Sulfonylureas are known to cause hypoglycemia. Patients receiving vildagliptin in combination with a sulfonylurea may be at risk for hypoglycemia. Therefore, a lower dose of sulfonylurea may be considered to reduce the risk of hypoglycemia.

Surgery

Treatment with metformin should be discontinued 48 hours before elective surgery with general anesthesia and should not usually be resumed earlier than 48 hours afterwards.

Administration of iodinated contrast agent

Treatment with metformin should be discontinued prior to or at the time of, the test and not reinstated until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

Pregnancy

There are no adequate and well controlled studies in pregnant women. Therefore Vildagliptin + Metformin HCl combination should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Metformin is excreted into human breast milk. It is not known whether vildagliptin is excreted in human milk or not. Vildagliptin + Metformin HCl combination should not be administered to nursing mothers.

ADVERSE REACTIONS

Vildagliptin in combination with Metformin

Common: Hypoglycemia, tremor, headache, dizziness & nausea.
Uncommon: Fatigue.

Vildagliptin in combination with Metformin and Sulfonylurea

Common: Hypoglycemia, dizziness, tremor, hyperhidrosis & asthenia.

Vildagliptin in combination with Insulin

Common: Decreased blood glucose, headache, chills, nausea, gastro-esophageal reflux disease.
Uncommon: Diarrhea & flatulence.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

DRUG INTERACTIONS

Vildagliptin

Vildagliptin has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate and does not inhibit or induce CYP450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes. As with other oral antidiabetic medicinal products the hypoglycemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

Metformin HCl

Furosemide

Furosemide increases C_{max} and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreases C_{max} , blood AUC of furosemide, with no change in renal clearance of furosemide.

Nifedipine

Nifedipine increases absorption, C_{max} and AUC of metformin, and increases excretion of metformin in urine. Metformin has minimal effects on nifedipine.

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. Careful monitoring of patients and doses of metformin and such medicinal products are recommended.

Other

Certain drugs i.e. thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs and isoniazid tend to produce hyperglycemia and may lead to loss of glycoemic control. Close monitoring of glycoemic control and metformin dose adjustments are recommended when such drugs are administered or on its discontinuation.

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the metformin. Consumption of alcohol and medicinal products containing alcohol should be avoided.

OVERDOSAGE

Information regarding overdose with vildagliptin is limited. A large overdose of metformin (or co-existing risk of lactic acidosis) may lead to lactic acidosis, which is a medical emergency and must be treated in hospital. The most effective method of removing metformin is hemodialysis. However, vildagliptin cannot be removed by hemodialysis, although the major hydrolysis metabolite (LAY 151) can be removed by hemodialysis. Supportive management is recommended.

STORAGE

Store at 25°C (Excursions permitted between 15°C - 30°C).
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Vilget-M (Vildagliptin + Metformin HCl) Tablets 50mg + 500mg is available in pack of 14's.

Vilget-M (Vildagliptin + Metformin HCl) Tablets 50mg + 850mg is available in pack of 14's.

Vilget-M (Vildagliptin + Metformin HCl) Tablets 50mg + 1000mg is available in pack of 14's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

**Please read the contents carefully before use.
This package insert is continually updated from time to time.**

Manufactured by:

 **Getz**
pharma
(PVT) LIMITED
www.getzpharma.com

29-30/27,
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