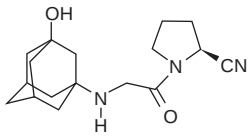
Vilget™

[Vildagliptin Tablets 50mg]

DESCRIPTION
Vilget (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

QUALITATIVE AND QUANTITATIVE COMPOSITION
Vilget (Vildagliptin) is available for oral administration as:

Vilget Tablets 50mg
Each tablet contains:
Vildagliptin …….50mg

CLINICAL PHARMACOLOGY
Mechanism of Action
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).

Pharmacokinetics
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 CYP 450 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 feces. 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.

Special Population
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.

THERAPEUTIC INDICATIONS
Vilget (Vildagliptin) is indicated for the treatment of type 2 diabetes mellitus in adults:

As monotherapy
- In patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

As dual oral therapy in combination with
- Metformin, in patients with insufficient glycemic control despite maximal tolerated dose of monotherapy with metformin.
- Sulfonylurea, in patients with insufficient glycemic control despite maximal tolerated dose of a sulfonylurea and for whom metformin is inappropriate due to contraindications or intolerance.
- Thiazolidinedione, in patients with insufficient glycemic control and for whom the use of a thiazolidinedione is appropriate.

As triple oral therapy in combination with
- Sulfonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycemic control.

Vilget (Vildagliptin) is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycemic control.

DOSAGE AND ADMINISTRATION
The recommended dose of Vilget (Vildagliptin) is 50mg once or twice daily. The maximum dose of Vilget (Vildagliptin) is 100mg. Vilget (Vildagliptin) can be administered orally with or without food.

Adult
When used as monotherapy, in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulfonylurea, or in combination with insulin (with or without metformin), the recommended daily dose of Vilget (Vildagliptin) is 100mg, administered as one dose of 50mg in the morning and one dose of 50mg in the evening.

When used in dual combination with a sulfonylurea, the recommended dose of Vilget (Vildagliptin) is 50mg once daily administered in the morning.

If a dose of Vilget (Vildagliptin) is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

Special Population
Patients with renal impairment
No dose adjustment is required in patients with mild renal impairment (creatinine clearance • 50 ml/min). In patients with moderate or severe renal impairment or with end-stage renal disease (ESRD), the recommended dose of Vilget (Vildagliptin) is 50mg once daily.

Patients with hepatic impairment
Vilget (Vildagliptin) 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).

Pediatrics
Vilget (Vildagliptin) is not recommended for use in children and adolescents (<18 years).

CONTRAINDICATIONS
Vildagliptin is contraindicated in patients with known hypersensitivity to vildagliptin or to any excipient of the product.

PRECAUTIONS
General
Vildagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Renal impairment
Vildagliptin should be used with caution in patients with ESRD or hemodialysis.

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 with vildagliptin at three-month intervals during the first year and periodically thereafter. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue vildagliptin.

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.

Pregnancy
There are no adequate data from the use of vildagliptin in pregnant women. Due to lack of human data, vildagliptin should not be used during pregnancy.

Nursing Mothers
It is unknown whether vildagliptin is excreted in human milk. Animal studies have shown excretion of vildagliptin in milk. Vildagliptin should not be used during breast-feeding.

ADVERSE REACTIONS
The following adverse reactions have been reported during the use of vildagliptin:

Monotherapy
Common: Dizziness.
Uncommon: Hypoglycemia, headache, edema peripheral, constipation & arthralgia.
Very Rare: Upper respiratory tract infection & nasopharyngitis.

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

Combination with Sulfonylurea
Common: Hypoglycemia, tremor, headache, dizziness & asthenia.
Uncommon: Constipation.
Very Rare: Nasopharyngitis.

Combination with Thiazolidinedione
Common: Weight increase & edema peripheral.
Uncommon: Hypoglycemia, headache & asthenia.

Combination with Metformin and Sulfonylurea
Common: Hypoglycemia, dizziness, tremor, hyperhidrosis & asthenia.

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

Drug Interactions
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.

OVERDOSAGE
In the event of an overdose, supportive management is recommended. Vildagliptin cannot be removed by hemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by hemodialysis.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.
Keep out of reach of children.

HOW SUPPLIED
Vilget (Vildagliptin) Tablets 50mg are available in pack of 28's.

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.

Getz pharma (PVT) LIMITED
www.getzpharma.com
A member of The Getz Group, USA.

EXP-200009550

Manufactured by: Getz Pharma (Pvt.) Ltd. 29-30/27, K.I.A., Karachi - 74900, Pakistan.