1. Name of the medicinal product

VILGET-M 50/1000MG Tablet

VILGET-M 50/500MG Tablet

2. Qualitative and quantitative composition

Each film-coated tablet contains Vildagliptin 50mg and Metformin HCl USP 1000mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form

White colored, oblong shaped, film coated tablet, engraved GETZ on one side and bisect line on other side.

4. Clinical particulars

4.1 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 glycemic 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 glycemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycemic control.

4.2 Posology and method of administration

<u>Adults</u>

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, VilgetM (Vildagliptin + Metformin HCl) may be initiated at either the 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 + 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).

4.3 Contraindications

Vildagliptin + Metformin HCl combination is contraindicated in:

- Patients with known hypersensitivity to vildagliptin or to any excipient of the product.

- Diabetic ketoacidosis or diabetic pre-coma.

4.4 Special warnings and precautions for use

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 ≥ 1.5mg/dL (> 135micromol/L) in males and ≥ 1.4mg/dL (> 110micromol/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 reinstituted until 48 hours afterwards and only after renal function has been reevaluated and found to be normal.

4.5 Interaction with other medicinal products and other forms of interaction

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 CYP 450 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 Cmax and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreases Cmax, blood AUC of furosemide, with no change in renal clearance of furosemide.

Nifedipine
Nifedipine increases absorption, Cmax 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 glycemic

control. Close monitoring of glycemic 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.

4.6 Fertility, pregnancy and lactation

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.

Lactation
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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who may experience dizziness as an adverse reaction should avoid driving vehicles or using machines.

4.8 Undesirable effects

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, gastroesophageal reflux disease.
Uncommon: Diarrhea & flatulence.

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.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

There is no experience of overdose with vonoprazan. Vonoprazan is not removed from the circulation by hemodialysis. If overdose occurs, treatment should be symptomatic and supportive.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD08

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).

5.2 Pharmacokinetic properties

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 Cmax (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 (Vss) 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 metabolized 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.

Metformin HCI
Absorption
After an oral dose of metformin, the maximum plasma concentration (Cmax) 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 feces 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.

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 (Vd) 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 7fold 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 Cmax 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.

5.3 Preclinical safety data

Animal studies of up to 13-week duration have been conducted with the combined substances in Vildagliptin/Metformin. No new toxicities associated

with the combination were identified. The following data are findings from studies performed with vildagliptin or metformin individually.

Vildagliptin
Intra-cardiac impulse conduction delays were observed in dogs with a noeffect dose of 15 mg/kg (7-fold human exposure based on C_{max}).

Accumulation of foamy alveolar macrophages in the lung was observed in rats and mice. The no-effect dose in rats was 25 mg/kg (5-fold human exposure based on AUC) and in mice 750 mg/kg (142-fold human exposure).
Gastrointestinal symptoms, particularly soft faeces, mucoid faeces, diarrhoea and, at higher doses, faecal blood were observed in dogs. A no-effect level was not established.

Vildagliptin was not mutagenic in conventional *in vitro* and *in vivo* tests for genotoxicity.

A fertility and early embryonic development study in rats revealed no evidence of impaired fertility, reproductive performance or early embryonic development due to vildagliptin. Embryofoetal toxicity was evaluated in rats and rabbits. An increased incidence of wavy ribs was observed in rats in association with reduced maternal body weight parameters, with a no-effect dose of 75 mg/kg (10-fold human exposure). In rabbits, decreased foetal weight and skeletal variations indicative of developmental delays were noted only in the presence of severe maternal toxicity, with a no-effect dose of 50 mg/kg (9-fold human exposure). A pre- and postnatal development study was performed in rats. Findings were only observed in association with maternal toxicity at ≥ 150 mg/kg and included a transient decrease in body weight and reduced motor activity in the F1 generation.

A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times human exposure at the maximum recommended dose). No increases in tumour incidence attributable to vildagliptin were observed. Another two-year carcinogenicity study was conducted in mice at oral doses up to 1000 mg/kg. An increased incidence of mammary adenocarcinomas and haemangiosarcomas was observed with a no-effect dose of 500 mg/kg (59-fold human exposure) and 100 mg/kg (16fold human exposure), respectively. The increased incidence of these tumours in mice is considered not to represent a significant risk to humans based on the lack of genotoxicity of vildagliptin and its principal metabolite, the occurrence of tumours only in one species, and the high systemic exposure ratios at which tumours were observed.

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at doses ≥ 5 mg/kg/day. These were consistently located on the extremities (hands, feet, ears and tail). At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), only blisters were observed. They were reversible despite continued treatment and were not

associated with histopathological abnormalities. Flaking skin, peeling skin, scabs and tail sores with correlating histopathological changes were noted at doses ≥ 20 mg/kg/day (approximately 3 times human AUC exposure at the 100 mg dose). Necrotic lesions of the tail were observed at ≥ 80 mg/kg/day. Skin lesions were not reversible in the monkeys treated at 160 mg/kg/day during a 4-week recovery period.

Metformin
Non-clinical data on metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:
Microcrystalline Cellulose (Avicel PH-101)
Hydroxypropyl cellulose (Klucel LF)
Croscarmellose Sodium
Magnesium Stearate
Purified Water

Coat:
Opadry AMB White 80W68912
Purified Talc
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C. Protect from sunlight and moisture. The expiration date refers to the product correctly stored at the required conditions.

6.5 Nature and contents of container

Vilget-M (Vildagliptin + Metformin HCl) Tablets 50mg + 1000mg are available in Alu-Alu blister packs of 5 x 7 tablets in a unit carton along with a package insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7. Marketing authorisation holder and manufacturing site addresses

Marketing authorisation holder

Getz Pharma (Private) Limited,
29-30/27, Korangi Industrial Area Karachi 74900,
Pakistan

Manufacturing Site Address

Getz Pharma (Private) Limited
29-30, Sector 27, Korangi Industrial Area,
Karachi-74900, Pakistan
Tel.: (92-21) 111-111-511
Website: www.getzpharma.com http://www.getzpharma.com/
Fax: (92-21) 5057592
E-mail: info@getzpharma.com

8. Marketing authorisation number(s)

H2024/CTD10287/21211 VILGET-M 50/1000MG Tablet

9. Date of first authorisation/renewal of the authorisation

Date of first authorization: 16-Feb-2024

10. Date of revision of the text

Nov-2024