VLADIMIR™-M 500/1000

1. **Generic Name**

Vildagliptin

Metformin

2. **Qualitative and Quantitative composition**

Vildagliptin……..50mg

Metformin……..500/1000 mg

3. **Dosage form and strength**

Vladimir is available as tablets of Vildagliptin 50 mg and Metformin-500, 1000mg strength.

4. **Clinical particulars**

4.1 Therapeutic indication

Vladimir M is indicated in the treatment of type 2 diabetes mellitus

The drug product should be used only in patients who have not sufficiently responded to either of the following treatments.

- Diet and/or exercise therapy alone
- Use of sulfonylureas in addition to diet and/or exercise therapy
- Use of thiazolidinedione in addition to diet and/or exercise therapy.

4.2 Posology and method of administration

As directed by physician.

4.3 Contraindication

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

- General

Vladimir is not a substitute for insulin in insulin-requiring patients. Vladimir should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

- Liver enzyme monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function test results returned to normal after discontinuation of treatment. Liver function tests should be performed prior to the initiation of treatment with Vladimir to know the patient's baseline value. Liver function should be monitored during treatment with Vladimir at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return(s) to normal. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Vladimir therapy is recommended.

Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Vladimir.

Following withdrawal of treatment with Vladimir and LFT normalisation, treatment with Vladimir should not be reinitiated.

- Cardiac failure

A clinical trial of vildagliptin in patients with New York Heart Association (NYHA) functional class I-III showed that treatment with vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive.

There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class IV and therefore use is not recommended in these patients.

- Skin disorders

Skin lesions, including blistering and ulceration have been reported in extremities of monkeys in nonclinical toxicology studies. Although skin lesions were not observed at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications. Furthermore, there have been post-marketing reports of bullous and exfoliative skin lesions. Therefore, in keeping with routine care of the 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. Patients should be informed of the characteristic symptom of acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.

- Hypoglycaemia

Sulphonyl ureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonyl urea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonyl urea may be considered to reduce the risk of hypoglycaemia.

4.5 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 CYP 450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes.

- Combination with pioglitazone, metformin and glyburide

Results from studies conducted with these oral antidiabetics have shown no clinically relevant pharmacokinetic interactions.

- Digoxin (Pgp substrate), warfarin (CYP2C9 substrate)

Clinical studies performed with healthy subjects have shown no clinically relevant pharmacokinetic interactions. However, this has not been established in the target population.

- Combination with amlodipine, ramipril, valsartan or simvastatin

Drug-drug interaction studies in healthy subjects were conducted with amlodipine, ramipril, valsartan and simvastatin. In these studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin.

- Combination with ACE-inhibitors

There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors.

- As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

4.6 Use in special population

- Paediatric: Vladimir is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Vladimir in children and adolescents (< 18 years) have not been established. No data are available
- Geriatric: No dose adjustments are necessary in elderly patients
- Liver impairment: Vladimir should not be used in patients with hepatic impairment, including patients with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x the upper limit of normal (ULN)
- Renal failure: There is limited experience in patients with ESRD on haemodialysis. Therefore, Vladimir should be used with caution in these patients
- Pregnancy and lactation: There are no adequate data from the use of vildagliptin in pregnant women. Studies in animals have shown reproductive

toxicity at high doses. The potential risk for humans is unknown. Due to lack of human data, Vladimir should not be used during pregnancy.

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

4.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Vladimir is known.

4.8 Undesirable effects

Serious

- Angioedema marked by swollen face, tongue or throat, difficulty in swallowing, difficulty in breathing, sudden onset rash or hives
- Liver disease (hepatitis)such as yellow skin and eyes, nausea, loss of appetite or dark-coloured urine, which may indicate liver disease (hepatitis)
- Inflammation of the pancreas (pancreatitis) marked by severe and persistent pain in the abdomen (stomach area), which might reach through to your back, as well as nausea and vomiting

Common

- Dizziness

Uncommon

- Headache
- Constipation
- Swollen hands, ankle or feet (oedema)
- Joint pain
- Low blood glucose

4.9 Overdose

There is limited experience of overdose with Vladimir Tablets. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

5. Pharmacological properties

5.1 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).

Metformin improves glucose tolerance in patients with type-2 diabetes (NIDDM), 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. Hence, the combination of glimepiride and metformin sustained-release complements each other and provides better glycaemic control in management of type-2 diabetes and probably in the prevention of its associated macrovascular and microvascular complications.

5.2 Pharmacodynamic properties

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. Treatment with vildagliptin 50-100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function including HOMA-β (Homeostasis Model Assessment–β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion.

The enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia.

The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptin treatment.

Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes 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.

5.3 Pharmacokinetic properties

Vildagliptin

- Absorption

Following oral administration in the fasting state, vildagliptin is rapidly absorbed, with peak plasma concentrations observed at 1.7 hours. 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%). However, the magnitude of change is not clinically significant, so that Vladimir can be given with or without food. The absolute bioavailability is 85%.

- 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.

- Biotransformation

Metabolism is the major elimination pathway for vildagliptin in humans, 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). In vitro data in human kidney microsomes suggest that the kidney may be one of the major organs contributing to the hydrolysis of vildagliptin to its major inactive metabolite, LAY151. DPP-4 contributes partially to the hydrolysis of vildagliptin based on an in vivo study using DPP-4 deficient rats. Vildagliptin is not metabolised by CYP 450 enzymes to any quantifiable extent. Accordingly, the metabolic clearance of vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. In vitro studies demonstrated that vildagliptin does not inhibit/induce CYP 450 enzymes. Therefore, vildagliptin is not likely to affect metabolic clearance of co-medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

- Elimination

Following oral administration of [14C] vildagliptin, approximately 85% of the dose was 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. After intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 and 13 l/h, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours.

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500-mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Once absorbed, protein binding in plasma is negligible; the drug is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours after oral doses. Metformin crosses the placenta and is distributed into breast milk in small amounts.

6. Nonclinical properties

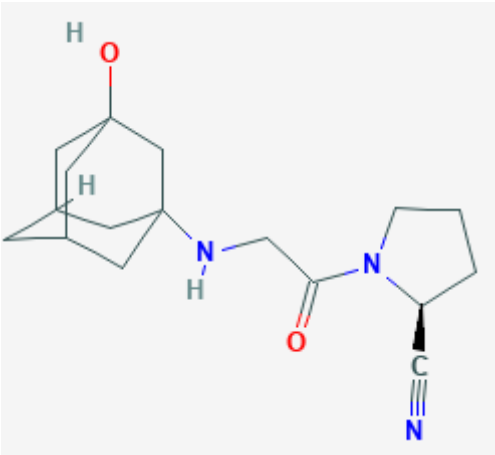
6.1 Animal Toxicology or Pharmacology

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.

7. Description

Vildagliptin

Vildagliptin is a cyanopyrrolidine-based, orally bioavailable inhibitor of dipeptidyl peptidase 4 (DPP-4), with hypoglycemic activity. Its chemical name is (2*S*)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl]pyrrolidine-2-carbonitrile. The empirical formula and molecular weight is $C_{17}H_{25}N_3O_2$ and 303.4 g/mol.



Metformin

Metformin is an agent belonging to the biguanide class of antidiabetics with antihyperglycemic activity. Metformin is associated with a very low incidence of lactic acidosis. Chemical Name is 3-(diaminomethylidene)-1,1-dimethylguanidine Its molecular weight and molecular formula are 129.16 g/mol and $C_4H_{11}N_5$.

8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

36 months.

8.3 Packaging Information

Vladimir is available as pack of 15 tablets.

8.4 Storage and handling instructions

Store in the original package to protect from moisture.

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Manufactured by HETERO LABS LTD.

11. Details of permission or license number with date

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