ViPTiN™ MET Tablets

(Vildagliptin + Metformin HCl)

DESCRIPTION:
Vildagliptin, chemical name is (S)-1-[2-(3-hydroxyadamantan-1-yl)(amino)acetyl]pyrrolidine-2-carbonitrile, belongs to a class of oral anti-diabetic drugs and is a selective and reversible inhibitor of dipeptidyl peptidase-4 (DPP-4), the enzyme which inactivates the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), hormones which significantly contribute to the maintenance of glucose homeostasis

Metformin HCl is an established first line treatment for T2DM. Metformin hydrochloride's chemical name is 1,1-dimethylbiguanide monohydrochloride. Metformin is thought to act primarily to increase intestinal glucose utilization and enhance hepatic and peripheral insulin sensitivity

The combination of vildagliptin and metformin is intended for use in patients with T2DM as fixed combination tablets

COMPOSITION:

ViPTiN™ MET 50/500mg Tablets
Each film coated tablet contains:
Vildagliptin MS.....50mg
Metformin HCl BP.....500mg

ViPTiN™ MET 50/850mg Tablets
Each film coated tablet contains:
Vildagliptin MS.....50mg
Metformin HCl BP.....850mg

ViPTiN™ MET 50/1000mg Tablets
Each film coated tablet contains:
Vildagliptin MS.....50mg
Metformin HCl BP.....1000mg

CLINICAL PHARMACOLOGY:
Mechanism of Action: Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor. Metformin acts primarily by decreasing endogenous hepatic glucose production
Pharmacodynamics
Vildagliptin: Vildagliptin acts primarily by inhibiting DPP-4, the enzyme responsible for the degradation of the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide). 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 and GIP
Metformin: Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia or increased weight gain. Metformin may exert its glucose-lowering effect via three mechanisms
- By reduction of hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis
- In muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- By delaying intestinal glucose absorption

Pharmacokinetics
Vildagliptin:
Absorption: Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.7hrs. Food slightly delays the time to peak plasma concentration to 2.5 hrs., but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased C_{max} (19%) compared to dosing in the fasting state. However, the magnitude of change is not clinically significant, so that vildagliptin 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 amide hydrolysis product (4% of dose). DPP-4 contributes partially to the hydrolysis of vildagliptin based on an *in vivo* study using DPP-4 deficient rats. Vildagliptin is not metabolized by CYP 450 enzymes to any quantifiable extent and 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 [^{14}C] vildagliptin, approximately 85% of the dose was excreted into the urine and 15% of the dose was 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/hr., respectively. The mean elimination half-life after intravenous administration is approximately 2 hrs. The elimination half-life after oral administration is approximately 3 hrs.
Metformin
Absorption: After an oral dose of metformin, the maximum plasma concentration (C_{max}) is achieved after about 2.5 hrs. Absolute bioavailability of a 500mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%
After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 hrs. and are generally less than 1μg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4μg/ml, even at maximum doses. 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. The clinical relevance of this decrease is unknown
Distribution: Plasma protein binding is negligible. Metformin partitions into erythrocytes. The mean volume of distribution (Vd) ranged between 63-276 litres
Metabolism: Metformin is excreted unchanged in the urine. No metabolites have been identified in humans
Elimination: Metformin is eliminated by renal excretion. Renal clearance of metformin is > 400ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hrs. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma

THERAPEUTIC INDICATIONS:
Vildagliptin + metformin HCl is indicated in the treatment of type 2 diabetes mellitus:
- Vildagliptin + metformin HCl is indicated in the treatment of adult patients who are unable to achieve sufficient glycemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets
- Vildagliptin + metformin HCl is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulphonylurea
- 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

DOSAGE AND ADMINISTRATION:
Adults: The dose of antihyperglycemic therapy with vildagliptin + metformin HCl should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100mg vildagliptin. Based on the patient's current dose of metformin, vildagliptin + metformin HCl may be initiated at either the 50/500mg or 50/850mg or 50/1000mg tablet strength twice daily, one tablet in the morning and the other in the evening. The recommended daily dose is 100mg vildagliptin plus 2000mg metformin HCl
- Patients receiving vildagliptin and metformin from separate tablets may be switched to vildagliptin + metformin HCl containing the same doses of each component
- For patients inadequately controlled on dual combination with metformin and a sulphonylurea: The doses of 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. When vildagliptin + metformin HCl is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycemia
- For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin: The dose of 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
  Doses higher than 100mg of vildagliptin are not recommended. The maximum recommended daily dose is 3000mg for metformin
  The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established

OR
As directed by the physician

Specific Populations:
Renal Impairment: Vildagliptin + metformin HCl should not be used in patients with creatinine clearance <60ml/min.
Hepatic Impairment: Vildagliptin + metformin HCl should not be used in patients with hepatic impairment, including those with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN)
Elderly (≥ 65 years): As metformin is excreted via the kidneys and elderly patients tend to exhibit decreased renal function, elderly patients taking vildagliptin + metformin HCl should have their renal function monitored regularly. The dosage of vildagliptin+metformin HCl for elderly patients should be adjusted based on renal function Metformin treatment should not be initiated in patients ≥ 80 years of age. Metformin should be used with caution in patients <80 years of age
Paediatric population (<18 years): Vildagliptin + metformin HCl is not recommended for use in children and adolescents. The safety and efficacy of vildagliptin + metformin HCl in children and adolescents (<18 years) have not been established
Method of Administration: Oral use: Taking vildagliptin + metformin HCl with or just after food may reduce gastrointestinal symptoms associated with metformin

CONTRAINDICATIONS:
- Hypersensitivity to the active substances or to any of the excipients
- Diabetic ketoacidosis or diabetic pre-coma
- Severe renal failure or renal dysfunction, eGFR <30ml/min/1.73m^2
- 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
- Lactation
- Metformin are contraindicated in patients with: Serum creatinine levels ≥1.5mg/dL in males, ≥1.4mg/dL in females

WARNINGS AND PRECAUTIONS:
General: Vildagliptin + metformin HCl is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes

210 mm

120mm

Lactic acidosis: Lactic acidosis is a very rare but serious metabolic complication that most often occurs with acute worsening of renal function, or cardiorespiratory illness or sepsis. metformin accumulation occurs with acute worsening of renal function and increases the risk of lactic acidosis
The risks of metabolic acidosis (e.g. lactic acidosis) caused by metformin should be explained to patients. Patients should be advised to discontinue metformin immediately and to promptly notify their health practitioner, if lactic acidosis symptoms occur

Renal impairment: eGFR should be assessed before treatment initiation and regularly thereafter. Metformin-containing products (such as vildagliptin + metformin HCl) are contraindicated in patients with eGFR <30ml/min/1.73m^2 and should be temporarily discontinued in the presence of conditions that alter renal function
As metformin is excreted by the kidney, serum creatinine concentrations should be monitored regularly:
- At least once a year in patients with normal renal function
- At least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients

Renal impairment in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID
Hepatic impairment: Patients with hepatic impairment, including those with pre-treatment ALT or AST > 3x ULN, should not be treated with vildagliptin + metformin HCl
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 vildagliptin + metformin HCl in order to know the patient's baseline value. Liver function should be monitored during treatment with vildagliptin + metformin HCl 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 LFTs until the abnormality(ies) return(s) to normal. Should an increase in AST or in ALT of 3x ULN or greater persist, withdrawal of vildagliptin + metformin HCl therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue vildagliptin + metformin HCl
Following withdrawal of treatment with vildagliptin + metformin HCl and LFT normalisation, treatment with vildagliptin + metformin HCl should not be re-initiated
Skin disorders: During routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended
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
Hypoglycemia: Sulphonylureas are known to cause hypoglycemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycemia
Surgery: Metformin-containing products (such as vildagliptin + metformin HCl) must be discontinued at the time of surgery under general, spinal or epidural anesthesia (except minor procedures not associated with restricted intake of food and fluids) and may be restarted no earlier than 48hrs. following surgery or until the patient's oral nutrition has resumed and renal function has been re-evaluated and found to be stable
Administration of iodinated contrast agent: The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure. Therefore, due to the metformin active substance, vildagliptin + metformin HCl should be discontinued prior to, or at the time of, the test and not reinstituted until 48 hrs. afterwards, and only after renal function has been re-evaluated and found to be stable
- Metformin should not be restarted until renal function has been evaluated as normal
- Patients taking metformin should have their renal function monitored periodically

Joint pain: There have been post marketing reports of severe and disabling joint pain in patients taking dipeptidyl peptidase-4 (DPP-4 inhibitors). The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. Some patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe and persistent joint pain, and consider discontinuation of therapy with this class of drugs
Pregnancy: There is insufficient experience with vildagliptin + metformin HCl in pregnant women. Therefore, vildagliptin + metformin HCl should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus
Breastfeeding: Studies in animals have shown excretion of both metformin and vildagliptin in milk. It is unknown whether vildagliptin is excreted in human milk, but metformin is excreted in human milk in low amounts. Due to both the potential risk of neonate hypoglycemia related to metformin and the lack of human data with vildagliptin, vildagliptin + metformin HCl should not be used during lactation

ADVERSE REACTIONS
Vildagliptin in combination with metformin:
Common: Hypoglycemia, tremor, headache, dizziness and nausea
Uncommon: Fatigue
Vildagliptin in combination with metformin and sulfonylurea:
Common: Hypoglycemia, dizziness, tremor, hyperhidrosis and asthenia
Vildagliptin in combination with insulin:
Common: Decreased blood glucose, headache, chills, nausea, gastroesophageal reflux disease
Uncommon: Diarrhoea and flatulence
Vildagliptin as mono-therapy:
Common: Dizziness
Uncommon: Upper respiratory tract infection, nasopharyngitis, hypoglycemia, headache, oedema peripheral, constipation, arthralgia
For metformin component:
Common: Decreased appetite, dysgeusia, flatulence, nausea, vomiting, diarrhoea, abdominal pain
Uncommon: Lactic acidosis, hepatitis, erythema, pruritus, urticaria, decrease of vitamin B_{12} absorption, liver function test abnormal

Drug Interactions
Vildagliptin: Vildagliptin has a low potential for interactions with coadministered 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: Combinations not recommended. There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the metformin active substance of vildagliptin + metformin HCl. Consumption of alcohol and medicinal products containing alcohol should be avoided

Cationic active substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems and hence delay the elimination of metformin, which may increase the risk of lactic acidosis. A study in healthy volunteers showed that cimetidine, administered as 400mg twice daily, increased metformin systemic exposure (AUC) by 50%. Therefore, close monitoring of glycemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered

Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation with the risk of lactic acidosis. Metformin-containing products (such as vildagliptin + metformin HCl) should be discontinued prior to, or at the time of the test and not reinstituted until 48hrs. afterwards and only after renal function has been re-evaluated and found to be stable

Combinations requiring precautions for use: Glucocorticoids, beta-2-agonists, and diuretics have intrinsic hyperglycemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dosage of vildagliptin + metformin HCl may need to be adjusted during concomitant therapy and on its discontinuation

Angiotensin converting enzyme (ACE) inhibitors may decrease the blood glucose levels. If necessary, the dosage of the antihyperglycemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation
Other: Some drugs can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclooxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin containing products (such as vildagliptin + metformin HCl), close monitoring of renal function is necessary

OVERDOSAGE:
No data are available with regard to overdose of vildagliptin + metformin HCl
Vildagliptin: Information regarding overdose with vildagliptin is limited
Metformin: 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
Management: The most effective method of removing metformin is haemodialysis. However, vildagliptin cannot be removed by haemodialysis, although the major hydrolysis metabolite (LAY 151) can. Supportive management is recommended

STABILITY:
See expiry on the pack

PRESENTATION:
ViPTiN MET 50/500mg tablets in a pack of 14's
ViPTiN MET 50/850mg tablets in a pack of 14's
ViPTiN MET 50/1000mg tablets in a pack of 14's

INSTRUCTIONS:
Keep out of reach of children. Avoid exposure to heat, light and humidity
Store between 15 to 30°C. Improper storage may deteriorate the medicine

وِپٹن™ میٹ ٹیبلٹ
(ولڈاگلپٹن + میٹفورمن ہائیڈروکلورائیڈ)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

R.N-02/HA/0318-T/C

210 mm

120mm