SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE PRODUCT

ViPTiN® MET (Vildagliptin + Metformin HCl) 50/500mg Tablets

ViPTiN® MET (Vildagliptin + Metformin HCl) 50/850mg Tablets

ViPTiN® MET (Vildagliptin + Metformin HCl) 50/1000mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ViPTiN® MET 50/500mg Tablets	**ViPTiN® MET 50/850mg Tablets**	**ViPTiN® MET 50/1000mg Tablets**
Each film coated tablet contains:	Each film coated tablet contains:	Each film coated tablet contains:
Vildagliptin MS.....50mg	Vildagliptin MS.....50mg	Vildagliptin MS.....50mg
Metformin HCl BP.....500mg	Metformin HCl BP.....850mg	Metformin HCl BP.....1000mg

3. PHARMACEUTICAL FORM

Tablet.

Appearance:

ViPTiN® MET 50/500mg Tablets: Light peach to peach color oblong shaped film coated tablets, plain on both sides.

ViPTiN® MET 50/850mg Tablets: Peach to dark peach color oblong shaped film coated tablets, engrave "**SAMI**" on both sides.

ViPTiN® MET 50/1000mg Tablets: Light cream to cream color oblong shaped film coated tablets, engrave "**SAMI**" on both sides.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

ViPTiN® MET is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:

- In patients who are inadequately controlled with metformin hydrochloride alone.
- In patients who are already being treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets.
- In combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycemic control.

Limitation of use: **ViPTiN® MET** should not be used in patients with type I diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

Based on the patient's current dose of vildagliptin and/or metformin, **ViPTiN® MET** may be initiated at either the 50mg/500mg or 50mg/850mg or 50mg/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 hydrochloride. Patients receiving vildagliptin and metformin from separate tablets may be switched to **ViPTiN® MET** containing the same doses of each component. In treatment naive patients, **ViPTiN® MET** may be initiated at 50mg/500mg once daily and gradually titrated to a maximum dose of 50mg/1000mg twice daily after assessing the adequacy of therapeutic response. The dose of **ViPTiN® MET** used in combination therapy with sulfonylurea (SU) or insulin would provide vildagliptin dosed as 50mg twice daily (100mg total daily dose) and a dose of metformin similar to the dose already being taken. When used in combination with a sulfonylurea, a lower dose of the sulfonylurea may be considered to reduce the risk of hypoglycaemia. Initial combination therapy or maintenance of combination therapy should be individualized and are left to the discretion of the health care provider. Doses higher than 100mg of vildagliptin are not recommended. The use of antihyperglycaemic therapy in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability. The recommended starting dose of **ViPTiN® MET** should be based on the patient's current regimen of vildagliptin and/or metformin hydrochloride.

Special populations:

Elderly (≥ 65 years): As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking **ViPTiN® MET** should have their renal function monitored regularly.

Renal impairment: A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months. The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR<60ml/min. If no adequate strength of **ViPTiN® MET** is available, individual monocomponents should be used instead of the fixed dose combination.

GFR ml/min	Metformin	Vildagliptin
60-89	Maximum daily dose is 3000mg. Dose reduction may be considered in relation to declining renal function.	No dose adjustment
45-59	Maximum daily dose is 2000mg. The starting dose is at most half of the maximum dose.	Maximal daily dose is 50mg.
30-44	Maximum daily dose is 1000mg. The starting dose is at most half of the maximum dose.	
<30	Metformin is contraindicated.	

Hepatic impairment: **ViPTiN® MET** should not be used in patients with hepatic impairment, including those with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the u pper limit of normal (ULN).

Paediatric population: **ViPTiN® MET** is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of **ViPTiN® MET** in children and adolescents (< 18 years) have not been established. No data are available.

Method of administration:

- Oral use.
- Taking **ViPTiN® MET** with or just after food may reduce gastrointestinal symptoms associated with metformin.

4.3. CONTRAINDICATIONS:

- Hypersensitivity to the active substances or to any of the excipients.
  - Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
  - Diabetic pre-coma
  - Severe renal failure (GFR < 30ml/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
- Breast-feeding.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

General: Vildagliptin + Metformin hydrochloride 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, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis. Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterized by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (> 5mmol/l) and an increased anion gap and lactate/pyruvate ratio.

Administration of iodinated contrast agents: Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Renal function: GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR < 30ml/min and should be temporarily discontinued in the presence of conditions that alter renal function. Concomitant medicinal products that may affect renal function, result in significant haemodynamic change, or inhibit renal transport and increase metformin systemic exposure, should be used with caution.
Hepatic impairment: Patients with hepatic impairment, including those with pre-treatment ALT or AST > 3x ULN, should not be treated with Vildagliptin + Metformin hydrochloride.
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 hydrochloride in order to know the patient's baseline value. Liver function should be monitored during treatment with Vildagliptin + Metformin hydrochloride 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 hydrochloride therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Vildagliptin + Metformin hydrochloride. Following withdrawal of treatment with Vildagliptin + Metformin hydrochloride and LFT normalization, treatment with Vildagliptin + Metformin hydrochloride should not be re-initiated.
Skin disorders: Skin lesions, including blistering and ulceration have been reported with vildagliptin in extremities of monkeys in non-clinical 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.
Surgery: Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.
Arthralgia: There have been postmarketing reports of severe and disabling arthralgia in patients taking 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. A subset of 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 joint pain and discontinue drug if appropriate.
Alcohol intake: Alcohol is known to potentiate the effect of metformin hydrochloride on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving metformin-containing products. Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.
Vitamin B12 levels: Metformin been associated with a decrease in serum vitamin B12 levels without clinical manifestations, in approximately 7% of patients. Such a decrease is very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride and/or vitamin B12 supplementation. Measurement of haematological parameters on at least an annual basis is advised for patients receiving metformin-containing products and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (e.g. those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at minimally two-to-three-year intervals may be useful.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:
There have been no formal interaction studies for Vildagliptin + Metformin hydrochloride. The following statements reflect the information available on the individual active substances.
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. Results from clinical trials conducted with the oral antidiabetics pioglitazone, metformin and glyburide in combination with vildagliptin have shown no clinically relevant pharmacokinetic interactions in the target population. Drug-drug interaction studies with digoxin (P-glycoprotein substrate) and warfarin (CYP2C9 substrate) in healthy subjects have shown no clinically relevant pharmacokinetic interactions after co-administration with vildagliptin. 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. However, this has not been established in the target population.
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.
Metformin:
Combinations not recommended: ***Alcohol:*** Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment. ***Iodinated contrast agents:*** Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable
Combinations requiring precautions for use: Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary. Glucocorticoids, beta-2-agonists, and diuretics have intrinsic hyperglycaemic 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 hydrochloride 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 antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation. Concomitant use of medicinal products that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g. organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir and cimetidine) could increase systemic exposure to metformin.
Furosemide: Furosemide increased C_{max} and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreased C_{max}, blood AUC of furosemide, with no change in renal clearance of furosemide.
Nifedipine: Nifedipine increased absorption, C_{max} and AUC of metformin, and increased excretion of metformin in urine. Metformin had minimal effects on nifedipine.
Glyburide: Glyburide produced no changes in metformin PK/PD parameters. Decreases in C_{max}, blood AUC of glyburide were observed, but were highly variable. Therefore the clinical significance of this finding was unclear.

4.6. FERTILITY, PREGNANCY AND LACTATION:
Fertility: No studies on the effect on human fertility have been conducted.
Pregnancy: There are no adequate data from the use of Vildagliptin + Metformin hydrochloride in pregnant women. For vildagliptin studies in animals have shown reproductive toxicity at high doses. For metformin, studies in animals have not shown reproductive toxicity. Studies in animals performed with vildagliptin and metformin have not shown evidence of teratogenicity, but foetotoxic effects at maternotoxic doses. The potential risk for humans is unknown. Vildagliptin + Metformin hydrochloride should not be used during pregnancy.
Breast-feeding: 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 hypoglycaemia related to metformin and the lack of human data with vildagliptin, Vildagliptin + Metformin hydrochloride should not be used during breast-feeding.

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:
Adverse reactions reported in patients who received vildagliptin in double-blind clinical trials as monotherapy and add-on therapies are listed below by system organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1 000 to <1/100); rare (≥ 1/10 000 to <1/1 000); very rare (<1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Infections and infestation: ***Common:*** Upper respiratory tract infection, nasopharyngitis.
Metabolism and nutrition disorders: ***Uncommon:*** Hypoglycaemia, loss of appetite. ***Very rare:*** Decrease of vitamin B12 absorption and lactic acidosis.
Nervous system disorders: ***Common:*** Dizziness, headache, tremor. ***Uncommon:*** Metallic taste.
Gastrointestinal disorders: ***Common:*** Diarrhoea, nausea, vomiting, gastro-oesophageal reflux disease, flatulence, constipation, abdominal pain including upper. ***Uncommon:*** Pancreatitis.
Hepatobiliary disorders: ***Uncommon:*** Hepatitis
Skin and subcutaneous tissue disorders: ***Common:*** Hyperhidrosis, pruritus, rash, dermatitis. ***Uncommon:*** Erythema, urticaria. ***Not known:*** Exfoliative and bullous skin lesions, including bullous pemphigoid, cutaneous vasculitis.
Musculoskeletal and connective tissue disorders: ***Common:*** Arthralgia. ***Uncommon:*** Myalgia.
General disorders and administration site conditions: ***Common:*** Asthenia. ***Uncommon:*** Fatigue, chills, oedema peripheral.
Investigations: ***Uncommon:*** Abnormal liver function tests.
Description of selected adverse reactions:
Vildagliptin:
Hepatic impairment: 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 returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials of up to 24 weeks in duration, the incidence of ALT or AST elevations ≥ 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for vildagliptin 50mg once daily, vildagliptin 50mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.
Angioedema: Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an ACE inhibitor. The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.
Hypoglycaemia: Hypoglycaemia was uncommon when vildagliptin (0.4%) was used as monotherapy in comparative controlled monotherapy studies with an active

comparator or placebo (0.2%). No severe or serious events of hypoglycaemia were reported. When used as add-on to metformin, hypoglycaemia occurred in 1% of vildagliptin-treated patients and in 0.4% of placebo-treated patients. When pioglitazone was added, hypoglycaemia occurred in 0.6% of vildagliptin-treated patients and in 1.9% of placebo-treated patients. When sulphonylurea was added, hypoglycaemia occurred in 1.2% of vildagliptin treated patients and in 0.6% of placebo-treated patients. When sulphonylurea and metformin were added, hypoglycaemia occurred in 5.1% of vildagliptin-treated patients and in 1.9% of placebo-treated patients. In patients taking vildagliptin in combination with insulin, the incidence of hypoglycaemia was 14% for vildagliptin and 16% for placebo.

Metformin:

Decrease of vitamin B12 absorption: A decrease in vitamin B12 absorption with decrease in serum levels has been observed very rarely in patients who have been treated with metformin over a long period. Consideration of such aetiology is recommended if a patient presents with megaloblastic anemia.

Liver function: Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.

Gastrointestinal disorders: Gastrointestinal adverse reactions occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 daily doses during or after meals. A slow increase in the dose may also improve gastrointestinal tolerability.

4.9. OVERDOSE:

No data are available with regard to overdose of Vildagliptin + Metformin hydrochloride.

Vildagliptin: Information regarding overdose with vildagliptin is limited.

Symptoms: Information on the likely symptoms of overdose with vildagliptin was taken from a rising dose tolerability study in healthy subjects given vildagliptin for 10 days. At 400mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels. At 600mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), AST, C-reactive protein (CRP) and myoglobin levels. Three other subjects experienced oedema of the feet, with paraesthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product.

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.

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: ViPTiN® MET combines two antihyperglycemic agents with complimentary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: vildagliptin, a member of the islet enhancer class, and metformin hydrochloride, a member of the biguanide class. 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.

5.2. PHARMACOKINETICS:

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 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 (V_{SS}) is 71 liters, 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 metabolised 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/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:

Absorption: After an oral dose of metformin, the maximum plasma concentration (C_{max}) is achieved after about 2.5h. 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 24-48h 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 850 mg, 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 (V_d) ranged between 63-276 liters.

Biotransformation: 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 > 400 ml/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 h. 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.

5.3. PRECLINICAL SAFETY DATA:

Animal studies of up to 13-week duration have been conducted with the combined substances in Vildagliptin + Metformin hydrochloride. 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 no-effect dose of 15mg/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 25mg/kg (5-fold human exposure based on AUC) and in mice 750mg/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. Embryofetal 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 75mg/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 50mg/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 ≥ 150mg/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 900mg/kg (approximately 200 times human exposure at the maximum recommended dose). No increases in tumor incidence attributable to vildagliptin were observed. Another two-year carcinogenicity study was conducted in mice at oral doses up to 1000mg/kg. An increased incidence of mammary adenocarcinomas and haemangiosarcomas was observed with a no-effect dose of 500mg/kg (59-fold human exposure) and 100mg/kg (16-fold human exposure), respectively. The increased incidence of these tumors 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 tumors only in one species, and the high systemic exposure ratios at which tumors were observed. In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at doses ≥ 5mg/kg/day. These were consistently located on the extremities (hands, feet, ears and tail). At 5mg/kg/day (approximately equivalent to human AUC exposure at the 100mg 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 ≥ 20mg/kg/day (approximately 3 times human AUC exposure at the 100mg dose). Necrotic lesions of the tail were observed at ≥ 80mg/kg/day. Skin lesions were not reversible in the monkeys treated at 160mg/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:

ViPTiN® MET 50/500mg Tablets:

Core:

- Pregelatinized starch
- Croscarmellose sodium
- Maize starch
- Poly vinyl pyrrolidone
- Sodium starch glycolate
- Red iron oxide color
- Yellow iron oxide color
- Magnesium stearate
- Purified water

Coating:

- Hydroxypropyl methyl cellulose
- Polyethylene glycol
- Poly vinyl pyrrolidone
- Titanium dioxide
- Talcum powder
- Red iron oxide color
- Yellow iron oxide color
- Purified water
- Isopropyl alcohol

ViPTiN® MET 50/850mg Tablets:

Core:

- Pregelatinized starch
- Croscarmellose sodium
- Maize starch
- Poly vinyl pyrrolidone
- Sodium starch glycolate
- Red iron oxide color
- Magnesium stearate
- Purified water

Coating:

- Hydroxypropyl methyl cellulose
- Polyethylene glycol
- Poly vinyl pyrrolidone
- Titanium dioxide
- Talcum powder
- Red iron oxide color
- Purified water
- Isopropyl alcohol

SUMMARY OF PRODUCT CHARACTERISTICS

ViPTiN® MET 50/1000mg Tablets:
Core:
● Pregelatinized starch ● Croscarmellose sodium ● Maize starch ● Poly vinyl pyrrolidone ● Sodium starch glycolate ● Yellow iron oxide color ● Magnesium stearate ● Purified water
Coating:
● Hydroxypropyl methyl cellulose ● Polyethylene glycol ● Poly vinyl pyrrolidone ● Titanium dioxide ● Talcum powder ● Yellow iron oxide color ● Purified water ● Isopropyl alcohol

6.2. INCOMPATIBILITIES:
Not applicable.

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and humidity. Store between 15 to 30°C. Improper storage may deteriorate the medicine.
Keep out of reach of chlildren.

6.5. NATURE AND CONTENTS OF CONTAINER:
ViPTiN® MET 50/500mg Tablets: Alu/Alu Blister, pack size is 14's.
ViPTiN® MET 50/850mg Tablets: Alu/Alu Blister, pack size is 14's.
ViPTiN® MET 50/1000mg Tablets: Alu/Alu Blister, pack size is 14's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:
ViPTiN® MET 50/500mg Tablets: Innovator's Specs.
ViPTiN® MET 50/850mg Tablets: Innovator's Specs.
ViPTiN® MET 50/1000mg Tablets: Innovator's Specs.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

8. MARKETING AUTHORISATION NUMBER(S)
ViPTiN® MET 50/500mg Tablets: 085604
ViPTiN® MET 50/850mg Tablets: 085602
ViPTiN® MET 50/1000mg Tablets: 085605

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
ViPTiN® MET 50/500mg Tablets: 18th December, 2017
ViPTiN® MET 50/850mg Tablets: 18th December, 2017
ViPTiN® MET 50/1000mg Tablets: 18th December, 2017

10. DATE OF REVISION OF THE TEXT

وِپٹن® میٹ ٹیبلٹ

(وِلڈاگلپٹن + میٹفورمن ہائیڈروکلورائیڈ)

ہدایات:

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