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PRODUCT MONOGRAPH

ViLACT

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ViLACT

Vildagliptin 50 mg

ViLACT M500

Vildagliptin 50 mg + Metformin HCl 500 mg

ViLACT M850

Vildagliptin 50 mg + Metformin HCl 850 mg

ViLACT M1000

Vildagliptin 50 mg + Metformin HCl 1000 mg

For Oral Administration

Anti-diabetic Agent
(DPP – 4 Inhibitor / DPP – 4 Inhibitor + Metformin HCl)

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ViLACT M1000	**Vildagliptin 50 mg + Metformin HCl 1000 mg**

For Oral Administration

Anti-diabetic Agent (DPP – 4 Inhibitor / DPP – 4 Inhibitor + Metformin HCl)

PART I HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Approved Indications
Oral	**VILACT** Each Tablet Contains: Vildagliptin 50 mg **VILACT M 500** Each Tablet Contains: Vildagliptin 50 mg + Metformin HCl 500 mg **VILACT M 850** Each Tablet Contains: Vildagliptin 50 mg + Metformin HCl 850 mg **VILACT M 1000** Each Tablet Contains: Vildagliptin 50 mg + Metformin HCl 1000 mg	Vildagliptin or Vildagliptin + Metformin HCl is indicated in the treatment of type 2 diabetes mellitus in adults: **As monotherapy** In patients inadequately controlled by diet and exercise alone and for whom Metformin HCl is inappropriate due to contraindications or intolerance. **As dual oral therapy** in combination with -Metformin HCl, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with Metformin HCl. -A sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom Metformin HCl is inappropriate due to contraindications or intolerance. -A thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. **As triple oral therapy** in combination with -A sulphonylurea and Metformin HCl when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Vildagliptin is also indicated for use in combination with insulin (with or without Metformin HCl) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.

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INDICATIONS AND CLINICAL USE

INDICATIONS:
Vildagliptin is indicated in the treatment of type 2 diabetes mellitus in adults:
As monotherapy in patients inadequately controlled by diet and exercise alone and for whom Metformin HCl is inappropriate due to contraindications or intolerance.

As dual therapy in combination with Metformin HCl
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 or Vildagliptin *alone* or who are already treated with the combination of Vildagliptin and Metformin HCl, as separate tablets.

Vildagliptin + Metformin HCl is indicated in combination with a sulfonylurea (SU) (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with Metformin HCl and a sulfonylurea.

Vildagliptin + Metformin HCl is indicated as add-on to insulin as an adjunct to diet and exercise to improve glycemic control in patients when stable doses of insulin and Metformin HCl alone do not provide adequate glycemic control.

CONTRAINDICATIONS

Hypersensitivity
Vildagliptin / Vildagliptin + Metformin HCl are contraindicated in patients with known hypersensitivity to Vildagliptin or Metformin HCl or to any of the excipients.

Patients with Renal Impairment
Vildagliptin + Metformin HCl is contraindicated in patients with severe renal impairment (GFR <30 ml/min).

Congestive Heart Failure
Vildagliptin + Metformin HCl is contraindicated in patients with congestive heart failure requiring pharmacological treatment.

Metabolic Acidosis
Vildagliptin + Metformin HCl is contraindicated in patients with acute or chronic metabolic acidosis, including lactic acidosis or diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Radiologic Studies
Vildagliptin + Metformin HCl should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

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WARNINGS AND PRECAUTIONS

WARNINGS:

General

Vildagliptin / Vildagliptin + Metformin HCl is not a substitute for insulin in patients requiring insulin. Vildagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hepatic Impairment

Vildagliptin is not recommended in patients with hepatic impairment, including patients with a pre-treatment ALT or AST > 2.5 x ULN. Aspartate Aminotransferase (AST) & Alanine Aminotransferase (ALT).

Hepatic 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 tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with Vildagliptin / Vildagliptin + Metformin HCl. LFTs should be monitored during Vildagliptin / Vildagliptin + Metformin HCl treatment 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 to normal. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of therapy with Vildagliptin is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Vildagliptin / Vildagliptin + Metformin HCl and contact their physician immediately. Following withdrawal of treatment with Vildagliptin / Vildagliptin + Metformin HCl and LFT normalization, Vildagliptin / Vildagliptin + Metformin HCl treatment should not be reinitiated.

Renal Impairment

GFR should be assessed before treatment initiation and regularly thereafter. Metformin HCl-containing products (such as Vildagliptin + Metformin HCl) are contraindicated in patients with GFR <30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function. Metformin HCl is known to be substantially excreted by the kidneys, and the risk of Metformin HCl accumulation and lactic acidosis increases with the degree of renal function impairment. Since advancing age is associated with reduced renal function, Metformin HCl-containing products (such as Vildagliptin + Metformin HCl) should be carefully titrated in the elderly to establish the minimum dose for adequate glycemic effect, and renal function should be monitored regularly.

Heart 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 the 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 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.

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.

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 experience dizziness as an adverse reaction should avoid driving vehicles or using machines.

Effects on Fertility
No studies have been conducted with Vildagliptin and Metformin HCl in combination to evaluate potential effects on fertility. Fertility studies have been performed with Vildagliptin in rats at doses producing exposures equivalent to up to 160 times the human dose and have revealed no evidence of impaired male or female fertility or early embryonic development due to Vildagliptin. Fertility of male or female rats was also unaffected by Metformin HCl administration at doses up to 600 mg/kg/day, or approximately 3-times the maximum recommended daily human dose on a body surface area basis.

PRECAUTIONS

Hepatic Impairment
Vildagliptin is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 2.5 x ULN.
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. LFTs should be monitored during Vildagliptin + Metformin HCl treatment 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 up thereafter with frequent liver function tests until the abnormality/abnormalities return to normal. Should an increase in AST or ALT of 3x the ULN or greater persist, withdrawal of therapy with Vildagliptin + Metformin HCl is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Vildagliptin + Metformin HCl and contact their physician immediately. Following withdrawal of treatment with Vildagliptin + Metformin HCl and LFT normalization, Vildagliptin + Metformin HCl should not be reinitiated.
Vildagliptin + Metformin HCl is not recommended in patients with hepatic impairment. Since impaired hepatic function has been associated with some cases of lactic acidosis, a risk associated with Metformin HCl, Metformin HCl-containing products (such as Vildagliptin + Metformin HCl) should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Pregnancy
There is insufficient experience with Vildagliptin / Vildagliptin + Metformin HCl in pregnant women. Embryo-fetal development (teratology) studies have been conducted in rats and rabbits with the combination of Vildagliptin and Metformin HCl in a 1:10 ratio and produced no evidence of teratogenicity in either species.

Vildagliptin + Metformin HCl should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus. Animal studies are not always predictive of human response.

Lactation
No studies have been conducted with the combined components of Vildagliptin / Vildagliptin + Metformin HCl. Metformin HCl is excreted into human breast milk. It is not known whether Vildagliptin is excreted in human milk or not. Vildagliptin + Metformin HCl should not be administered to breast-feeding women.

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 HCl accumulation occurs with acute worsening of renal function and increases the risk of lactic acidosis.
In case of dehydration (e.g. due to severe diarrhea or vomiting, fever or reduced fluid intake), the patient should stop taking Metformin HCl containing products (such as Vildagliptin + Metformin HCl) and seek immediate medical attention.
Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in patients treated with Metformin HCl containing products (such as Vildagliptin + Metformin HCl). Other risk factors for lactic acidosis are excessive alcohol intake, hepatic impairment, 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.
Diagnosis of Lactic Acidosis
Patients and/or caregivers should be informed of the risk of lactic acidosis. Lactic acidosis is characterized by acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. If suspected symptoms occur, the patient should stop taking Metformin HCl containing products (such as Vildagliptin + Metformin HCl) and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (<7.35), increased plasma lactate levels (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with Metformin HCl containing products (such as Vildagliptin + Metformin HCl) should be discontinued and the patient should be immediately hospitalized.

Hypoxic States
Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. If such events occur in patients receiving Metformin HCl containing products (such as Vildagliptin + Metformin HCl), the medication should be promptly discontinued.

Surgical Procedures
Metformin HCl containing products (such as Vildagliptin + Metformin HCl) must be discontinued at the time of surgery under general, spinal or epidural anaesthesia (except minor procedures not associated with restricted intake of food and fluids) and may be restarted no earlier than 48 hours following surgery or until the patient's oral nutrition has resumed and renal function has been re-evaluated and found to be stable.

Alcohol Intake
Alcohol is known to potentiate the effect of Metformin HCl on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving Metformin HCl containing products (such as Vildagliptin + Metformin Hcl). Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Vitamin B12 Levels
Metformin HCl has 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 HCl and/or vitamin B12 supplementation. Measurement of hematological parameters on at least an annual basis is advised for patients receiving Metformin HCl containing products (such as Vildagliptin + Metformin HCl) 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.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes
A patient with type 2 diabetes previously well-controlled on Vildagliptin + Metformin HCl who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should promptly be evaluated for ketoacidosis and/or lactic acidosis. If acidosis of either form occurs, Vildagliptin + Metformin HCl must be stopped immediately and appropriate measures initiated.

Hypoglycemia
Hypoglycemia does not usually occur in patients receiving Vildagliptin + Metformin HCl alone, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or ethanol use. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking drugs.

Loss of Control of Blood Glucose
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, surgery, etc., a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold Vildagliptin + Metformin HCl and temporarily administer insulin. Vildagliptin + Metformin HCl may be reinstituted after the acute episode is resolved.

ADVERSE REACTIONS

Vildagliptin / Vildagliptin + Metformin HCl:

Adverse Drug Reaction Overview
The safety and tolerability of Vildagliptin (50 mg once daily, 50 mg twice daily and 100 mg daily) have been assessed by pooling data from more than 11,000 patients from 36 Phase II and III studies (including 3 open label studies) ranging in duration from 12 to more than 104 weeks. The studies used in this pooled analysis have assessed Vildagliptin as monotherapy, add-on therapy to other oral anti-diabetic agents (Metformin HCl, TZD, SU and Insulin) and as an initial combination therapy with Metformin HCl or Pioglitazone. Patients not receiving Vildagliptin (all comparators group) were taking only Placebo or Metformin HCl, TZD, SU, Acarbose or Insulin. For the calculation of frequency of adverse drug reactions for the individual indications, safety data from a subset of pivotal controlled trials of at least 12 week's duration was considered. Safety data were obtained from patients exposed to Vildagliptin at a daily dose of 50 mg (once daily) or 100 mg (50 mg twice daily or 100 mg daily) who received Vildagliptin as monotherapy or in combination with another agent.
The majority of adverse reactions in these trials were mild and transient, not requiring treatment discontinuations. No association was found between adverse reactions and age, ethnicity, duration of exposure or daily dose.
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 angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing Vildagliptin treatment.
Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were

generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials 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 50 mg daily, Vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

Summary of Adverse Drug Reactions from Clinical Trials

Adverse reactions reported in patients who received Vildagliptin in double-blind studies as monotherapy and add-on therapies, are listed below, for each indication, by MedDRA system organ class and absolute frequency. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Monotherapy

The overall incidence of withdrawal from monotherapy trials due to adverse reactions was no greater for patients treated with Vildagliptin at a dose of 50 mg once daily (0.2%) or Vildagliptin at a dose of 50 mg twice daily (0.1%) than for placebo (0.6%) or comparators (0.5%).

In monotherapy studies, hypoglycemia was uncommon, reported in 0.5% (2 of 409) of patients treated with Vildagliptin 50 mg once daily and 0.3% (4 of 1,373) of patients treated with Vildagliptin 50 mg twice daily compared to 0.2% (2 of 1,082) of patients in the groups treated with an active comparator or Placebo, with no serious or severe events reported. Vildagliptin is weight neutral when administered as monotherapy.

Adverse reactions reported in patients who received Vildagliptin 100 mg daily as Monotherapy in double-blind studies (N=1,855)

Infections and infestations	Very rare (Upper respiratory tract infection & Nasopharyngitis)
Metabolism and nutrition disorders	Uncommon (Hypoglycaemia)
Nervous system disorders	Common (Dizziness) Uncommon (Headache)
Vascular disorders	Uncommon (Peripheral oedema)
Gastrointestinal disorders	Uncommon (Constipation)
Musculoskeletal and connective tissue disorders	Uncommon (Arthralgia)

Long term clinical trials of up to 2 years did not show any additional safety signals or unforeseen risks with Vildagliptin monotherapy.

Combination with Metformin HCl

In clinical trials with the combination of Vildagliptin + Metformin HCl, 0.4% of patients withdrew due to adverse reactions. In the Vildagliptin 50 mg once daily + Metformin HCl treatment group, and no withdrawal due to adverse reactions was reported in either the Vildagliptin 50 mg twice daily + Metformin HCl or the placebo + Metformin HCl treatment groups.

In another clinical trial, the incidence of hypoglycemia was uncommon in patients receiving Vildagliptin 50 mg once daily in combination with Metformin HCl (0.9%) in patients receiving Vildagliptin 50 mg twice daily in combination with Metformin HCl (0.5%) and in patients receiving Placebo + Metformin HCl (0.4%). No severe hypoglycemic events were reported in the Vildagliptin arms.

Vildagliptin is weight neutral when administered in combination with Metformin HCl.

Adverse reactions reported in patients who received Vildagliptin 50 mg once daily (n=233) or 50 mg twice daily (n=183) in combination with Metformin HCl in double-blind studies

Metabolism and nutrition disorders	Common (Hypoglycemia)
Nervous system disorders	Common (Tremor, Headache, Dizziness), Uncommon (Fatigue)
Gastrointestinal disorders	Common (Nausea)

Combination with a Sulfonylurea (SU)
In clinical trials, with the combination of Vildagliptin 50 mg + Glimepiride, the overall incidence of withdrawals due to adverse reactions was 0.6% in the Vildagliptin 50 mg + Glimepiride treatment group versus 0% in the Placebo + Glimepiride treatment group.
In clinical trials, the incidence of hypoglycemia when Vildagliptin 50 mg once daily was added to Glimepiride was 1.2% versus 0.6% for Placebo + Glimepiride. No severe hypoglycemic events were reported in the Vildagliptin arms.
At the recommended dose of 50 mg, Vildagliptin is weight neutral when administered in combination with Glimepiride.

Adverse reactions reported in patients who received Vildagliptin 50 mg in combination with a Sulphonylurea in double-blind studies (N=170)

Infections and infestations	Very rare (Nasopharyngitis)
Metabolism and nutrition disorders	Common (Hypoglycemia)
Nervous system disorders	Common (Tremor, Headache, Dizziness, Asthenia)
Gastrointestinal disorders	Uncommon (Constipation)

Combination with a Thiazolidinedione (TZD)
In clinical trials with the combination of Vildagliptin and a Thiazolidinedione, 0.7% of patients withdrew for adverse reactions in the Vildagliptin 50 mg once daily + Pioglitazone group, and there were no withdrawals due to adverse reactions reported in either the Vildagliptin 50 mg twice daily + Pioglitazone or the Placebo + Pioglitazone treatment groups.
In another clinical trial, no hypoglycemia events were reported in patients receiving Vildagliptin 50 mg once daily + Pioglitazone 45 mg. Hypoglycemia was uncommon in patients receiving Vildagliptin 50 mg twice daily + Pioglitazone 45 mg (0.6%) but common in patients receiving placebo + Pioglitazone 45 mg (1.9%). No severe hypoglycemic events were reported in the Vildagliptin arms.
In the Pioglitazone add-on study, the change in body weight compared to placebo was +0.1 kg and +1.3 kg for Vildagliptin 50 mg daily and Vildagliptin 50 mg twice daily, respectively.
The incidence of peripheral edema when Vildagliptin was added to a maximum dose of background Pioglitazone (45 mg once daily) was 8.2% as 50 mg once daily and 7.0%, as 50 mg twice daily compared to 2.5% for background pioglitazone alone. The incidence of edema when Vildagliptin was added to Pioglitazone as dual initial therapy in drug naïve patients was however less than that for Pioglitazone alone (50 mg once daily 3.5%, 50 mg twice daily 6.1% vs. Pioglitazone 30 mg 9.3%).

Adverse reactions reported in patients who received Vildagliptin 100 mg daily in combination with a Thiazolidinedione in double-blind studies (N=158)

Metabolism and nutrition disorders	Common(Weight increase), Uncommon (Hypoglycemia)
Nervous system disorders	Uncommon (Headache, Asthenia)
Gastrointestinal disorders	Common (Edema peripheral)

Combination with Insulin

In controlled clinical trials using Vildagliptin 50 mg twice daily in combination with Insulin, with or without concomitant Metformin HCl, the overall incidence of withdrawal due to adverse reactions was 0.3% in the Vildagliptin treatment group and there were no cases of withdrawal in the placebo group.

The incidence of hypoglycemia was similar in both treatment groups (14.0% in the Vildagliptin group versus 16.4 % in the placebo group). Two patients reported severe hypoglycemic events in the Vildagliptin group, and 6 patients - in the placebo group.

At the end of the study, the effect on mean body weight was neutral (+0.6 kg change from baseline in the Vildagliptin group and no weight change in the placebo group).

Adverse reactions reported in patients who received Vildagliptin 100 mg daily in combination with Insulin (with or without Metformin HCl) in double-blind studies (N=371)

Metabolism and nutrition disorders	Common (Decreased blood glucose)
Nervous system disorders	Common (Headache chills)
Gastrointestinal disorders	Common (Nausea, gastro-esophageal reflux disease) Uncommon (Diarrhea, flatulence)

Combination with Metformin HCl and SU

There were no cases of withdrawal reported due to adverse reactions in the Vildagliptin + Metformin HCl + Glimepiride treatment group versus 0.6% in the Placebo + Metformin HCl + Glimepiride treatment group.

The incidence of hypoglycemia was common in both treatment groups (5.1% for the Vildagliptin + Metformin HCl + Glimepiride vs. 1.9% for the Placebo + Metformin HCl + Glimepiride). One severe hypoglycemic event was reported in the Vildagliptin group.

At the end of the study, the effect on mean body weight was neutral (+0.6 kg in the Vildagliptin group and -0.1 kg in the placebo group).

Adverse reactions reported in patients who received Vildagliptin 50 mg twice daily in combination with Metformin HCl and a Sulphonylurea (N=157)

Metabolism and nutritional disorders	Common (Hypoglycemia)
Nervous system disorders	Common (Dizziness, tremor)
Skin and subcutaneous tissue disorders	Common (Hyperhidrosis)
General disorders and administration site conditions	Common (Asthenia)

Adverse drug reactions from spontaneous reports and literature cases - Post-Marketing Experience (frequency not known)
The following adverse drug reactions have been derived from post-marketing experience with Vildagliptin via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known.
Adverse drug reactions from spontaneous reports and literature cases - Post-Marketing Experience: Hepatitis reversible upon drug discontinuation, Urticaria, bullous and exfoliative skin lesions, including bullous pemphigoid, Pancreatitis, Arthralgia, sometimes severe.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pvg@panaceabiotec.com, FAX: +91-11-41679069, Telephone number +91-11-41679000.

DRUG INTERACTIONS

Vildagliptin and Other Important Drug- Drug Interactions:
No clinically relevant pharmacokinetic interactions have been observed when Vildagliptin (100 mg daily) was co-administered with Metformin HCl (1000 mg once daily). Drug interactions for each component of Vildagliptin + Metformin HCl has been extensively studied. However, the concomitant use of the active substances in patients in clinical studies and in widespread clinical use has not resulted in any unexpected interactions.
The following statements reflect the information available on the individual active substances.

Vildagliptin
Vildagliptin has low potential for drug interactions. Since Vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit or induce CYP 450 enzymes, it is not likely to interact with co-medications that are substrates, inhibitors or inducers of these enzymes.
Furthermore, Vildagliptin does not affect metabolic clearance of co-medications metabolized by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5. Drug-drug interaction studies were conducted with commonly co-prescribed medications for patients with type 2 diabetes or medications with a narrow therapeutic window. As a result of these studies, no clinically relevant interactions with other oral antidiabetics (Glibenclamide, Pioglitazone, Metformin HCl), Amlodipine, Digoxin, Ramipril, Simvastatin, Valsartan or Warfarin were observed after co-administration with Vildagliptin.

Metformin HCl
Furosemide
Furosemide increased Cmax and blood AUC of Metformin HCl with no change in renal clearance of Metformin HCl. Metformin HCl decreased Cmax, blood AUC of Furosemide, with no change in renal clearance of Furosemide.
Nifedipine
Nifedipine increased absorption, Cmax and AUC of Metformin HCl, and increased excretion of Metformin HCl in urine. Metformin HCl had minimal effects on Nifedipine.
Glyburide
Glyburide produced no changes in Metformin HCl PK/PD parameters. Decreases in Cmax, blood AUC of Glyburide were observed, but were highly variable. Therefore, the clinical significance of this finding was unclear.

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 to interact with Metformin HCl by competing for common renal tubular transport systems. Thus, with Cimetidine increases in Metformin HCl plasma/blood concentration and AUC were observed to be 60% and 40% respectively. Metformin HCl had no effect on Cimetidine PK. Although such interactions remain theoretical (except for Cimetidine), careful monitoring of patients and doses of Metformin HCl-containing products (such as Vildagliptin + Metformin HCl) and such medications are recommended.

Administration of Intravascular Iodinated Contrast Materials
Metformin HCl-containing products (such as Vildagliptin + Metformin HCl) should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be stable.

Other
Some drugs can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with Metformin HCl-containing products (such as Vildagliptin + Metformin HCl), close monitoring of renal function is necessary. Certain drugs tend to cause hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Close monitoring of glycemic control and Metformin HCl dose adjustments are recommended when such drugs are administered or withdrawn for these patients.
There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to Metformin HCl. Avoid consumption of alcohol and medicinal products containing alcohol.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Vildagliptin:
- The management of antidiabetic therapy should be individualized. The recommended dose of Vildagliptin is 50 mg once or twice daily. The maximum daily dose of Vildagliptin is 100 mg.
- For monotherapy, and for combination with Metformin HCl, with a TZD or with insulin (with or without Metformin Hcl), the recommended dose of Vildagliptin is 50 mg or 100 mg daily.
- When used in dual combination with a sulfonylurea, the recommended dose of Vildagliptin is 50 mg once daily. In this patient population, Vildagliptin 100 mg daily was no more effective than Vildagliptin 50 mg once daily.
- For triple combination with Metformin HCl and a SU, the recommended dose of Vildagliptin is 100 mg daily.
- If tighter glycemic control is required on the top of the maximum recommended daily dose of Vildagliptin, the addition of other antidiabetic drugs such as Metformin HCl, an SU, a TZD or insulin may be considered.

Renal Impairment
No dosage adjustment of Vildagliptin is required in patients with mild renal impairment. In patients with moderate or severe renal impairment or End Stage Renal Disease (ESRD), the recommended dose of Vildagliptin is 50 mg once daily.

Hepatic Impairment
Vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >2.5x the upper limit of normal (ULN).

Pediatric
Vildagliptin has not been studied in patients under 18 years of age; therefore, the use of Vildagliptin in pediatric patients is not recommended.

Geriatric
In patients treated with Vildagliptin ⩾65 years of age and ⩾75 years of age, no differences were observed in the overall safety, tolerability, or efficacy between this elderly population and younger patients. No dosage adjustments are therefore necessary in the elderly patients.

Vildagliptin + Metformin HCl
The use of antihyperglycemic therapy in the management of T2D should be individualized on the basis of effectiveness and tolerability. The recommended starting dose of Vildagliptin + Metformin HCl should be based on the patient's current regimen of Vildagliptin and/or Metformin HCl. Vildagliptin + Metformin HCl should be given with meals to reduce the gastrointestinal side effects associated with Metformin HCl. When using Vildagliptin + Metformin HCl the maximum daily dose of Vildagliptin (100 mg) should not be exceeded.
Starting Dose for Patients Inadequately Controlled on Vildagliptin Monotherapy
Based on the usual starting doses of Metformin HCl (500 mg twice daily or 850 mg once daily), Vildagliptin + Metformin HCl may be initiated at the 50 mg/500 mg tablet strength twice daily and gradually titrated after assessing the adequacy of therapeutic response.
Starting Dose for Patients Inadequately Controlled on Metformin HCl Monotherapy
Based on the patient's current dose of Metformin HCl, Vildagliptin + Metformin HCl may be initiated at either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1,000 mg tablet strength twice daily.
Starting Dose for Patients Switching from Combination Therapy of Vildagliptin Plus Metformin HCl as Separate Tablets
Vildagliptin + Metformin HCl may be initiated with either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1,000 mg tablet strength based on the dose of Vildagliptin or Metformin HCl already being taken.
Starting Dose for Treatment Naïve Patients
In treatment naïve patients, Vildagliptin + Metformin HCl may be initiated at 50 mg/500 mg once daily and gradually titrated to a maximum dose of 50mg/1000 mg twice daily after assessing the adequacy of therapeutic response.

Use in Combination with SU or With Insulin
The dose of Vildagliptin + Metformin HCl should provide Vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of Metformin HCl similar to the dose already being taken.

Renal Impairment
A GFR should be assessed before initiation of treatment with Metformin HCl containing products (such as Vildagliptin + Metformin HCl) 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 to 6 months.
The maximum daily dose of Metformin HCl should preferably be divided into 2 to 3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of Metformin HCl containing products (such as Vildagliptin + Metformin HCl) in patients with GFR<60 ml/min. Vildagliptin + Metformin HCl is contraindicated in patients with GFR <30 ml/min because of its Metformin HCl component.
The following dosing recommendations apply to Metformin HCl and Vildagliptin, used separately or in combination, in patients with renal impairment. If no adequate strength of Vildagliptin + Metformin HCl is available, individual components should be used instead of the fixed dose combination.

Table 1: Dose adjustments in patients with renal impairment

GFR ml/min	Metformin HCl	Vildagliptin
60-89	Maximum daily dose is 3000 mg*. Dose reduction may be considered if renal function declines.	Maximum daily dose is 100 mg.
45-59	Starting dose should not be more than 1000 mg with a maximum daily dose of 2000 mg*.	Maximum daily dose is 50 mg.
30-44	Starting dose should not be more than 500 mg with a maximum daily dose of 1000 mg.	
<30	Metformin HCl is contraindicated.	

*If Metformin HCl doses higher than those achievable with Vildagliptin + Metformin HCl alone are considered necessary.

Hepatic Impairment
Vildagliptin + Metformin HCl is not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment ALT or AST >2.5 x the ULN (upper limit of normal).

Pediatric
The safety and effectiveness of Vildagliptin + Metformin HCl in pediatric patients have not been established. Therefore, Vildagliptin + Metformin HCl is not recommended for use in children below 18 years of age.

Geriatric
As Metformin HCl is excreted via the kidneys, and elderly patients tend to exhibit decreased renal function, elderly patients taking Metformin HCl containing products (such as 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.

Administration
Vildagliptin
Vildagliptin can be administered with or without meals. The 50 mg dose should be administered once daily in the morning. The 100 mg dose should be administered as two divided doses of 50 mg given in the morning and evening.
Vildagliptin + Metformin HCl
For oral use, Vildagliptin + Metformin HCl should be given with meals to reduce the gastrointestinal side effects associated with Metformin Hcl.

Missed Dose
The missed dose should be taken as soon as possible, unless it is almost time for the next dose. The patient should be advised not to take two doses at the same time.

Use in Special Population:
General
Vildagliptin + Metformin HCl is not a substitute for insulin in patients requiring insulin. Vildagliptin + Metformin HCl should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Females and Males of Reproductive Potential
No studies on the effect on human fertility have been conducted for Vildagliptin. Fertility studies have been performed in rats at doses up to 200 times the human dose and have revealed no evidence of impaired fertility or early embryonic development due to Vildagliptin.

Pregnancy and Lactation

There is insufficient experience with Vildagliptin in pregnant women. Vildagliptin was not teratogenic in either rats or rabbits. Vildagliptin should not be used during pregnancy unless the benefit to the mother outweighs the potential risk to the fetus.

As it is not known whether Vildagliptin is excreted in human milk, it should not be administered to breast-feeding women.

Gender: No differences in the pharmacokinetics of Vildagliptin were observed between male and female subjects with a diverse range of age and body mass index (BMI). DPP-4 inhibition by Vildagliptin was unaffected by gender.

There is insufficient experience with Vildagliptin + Metformin HCl in pregnant women. Embryo-fetal development (teratology) studies have been conducted in rats and rabbits with the combination of Vildagliptin and Metformin HCl in a 1:10 ratio and produced no evidence of teratogenicity in either species. Vildagliptin + Metformin HCl should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Animal studies are not always predictive of human response.

Obesity

BMI does not show any impact on the pharmacokinetic parameters of Vildagliptin. DPP-4 inhibition by Vildagliptin was unaffected by BMI.

Hepatic Impairment

The effect of impaired hepatic function on the pharmacokinetics of Vildagliptin was studied in subjects with mild, moderate and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison to subjects with normal hepatic function. The exposure to Vildagliptin (100 mg) after a single dose in subjects with mild and moderate hepatic impairment was decreased (20% and 8%, respectively) while the exposure to Vildagliptin for subjects with severe impairment was increased by 22%. The maximum change (increase or decrease) in the exposure to Vildagliptin is ~30%, which is not considered to be clinically relevant. There was no correlation between the severity of hepatic function impairment and changes in exposure to Vildagliptin.

The use of Vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST > 2.5 x ULN.

Renal Impairment

The AUC of Vildagliptin increased on average 1.4, 1.7 and 2-fold in patients with mild, moderate and severe renal impairment, respectively, compared to normal healthy subjects. The AUC of the metabolites LAY151 increased 1.6, 3.2 and 7.3-fold and that of BQS867 increased 1.4, 2.7 and 7.3-fold in patients with mild, moderate and severe renal impairment, respectively, compared to healthy volunteers. Limited data from patients with end stage renal disease (ESRD) indicate that Vildagliptin exposure is similar to that in patients with severe renal impairment. LAY151 concentrations in ESRD patients were approximately 2 to 3-fold higher than in patients with severe renal impairment. Dosage adjustment may be required in patients with renal impairment. Vildagliptin was removed by hemodialysis to a limited extent (3% over a 3 to 4 hour hemodialysis session starting 4 hours post dose).

Geriatric

In otherwise healthy elderly subjects (⩾70 years), the overall exposure to Vildagliptin (100 mg once daily) was increased by 32% with an 18% increase in peak plasma concentration compared to younger healthy subjects (18 to 40 years). These changes are not considered to be clinically relevant. DPP-4 inhibition by Vildagliptin is not affected by age in the age groups studied.

Pediatric

No pharmacokinetic data available.

Ethnicity
There was no evidence that ethnicity affects the pharmacokinetics of Vildagliptin.

OVERDOSAGE

Vildagliptin
In healthy subjects (seven to fourteen subjects per treatment group), Vildagliptin was administered in once-daily doses of 25, 50, 100, 200, 400, and 600 mg for up to 10 consecutive days. Doses up to 200 mg were well tolerated. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paresthesia, fever, edema and transient increase in lipase levels (2x ULN). At 600 mg, one subject experienced edema of the hands and feet and an excessive increase in creatine phosphokinase (CPK) levels, accompanied by elevations of aspartate aminotransferase (AST), C-reactive protein, and myoglobin. Three additional subjects in this dose group presented with edema of both feet, accompanied by paresthesia in two cases. All symptoms and laboratory abnormalities resolved after study drug discontinuation. Vildagliptin is not dialyzable, however the major hydrolysis metabolite (LAY151) can be removed by hemodialysis.

Metformin HCl
Overdose of Metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with Metformin HCl has been established. Lactic acidosis has been reported in approximately 32% of Metformin HCl overdose cases. Metformin HCl is dialyzable with a clearance of up to 170 ml/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of the accumulated drug from patients in whom Metformin HCl overdosage is suspected. In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

ACTION AND CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY

Mechanism of Action

Vildagliptin
The glucagon-like peptide-1 (GLP-1) is secreted from alimentary canal, in response to meal. This promotes insulin secretion from pancreas and regulates blood glucose post meal by controlling glucagon secretion. Vildagliptin exhibits a hypoglycemic effect by controlling the degradation of GLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4) activity. Thus increases blood concentration of active GLP-1.

Metformin HCl
Metformin HCl is an anti-hyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin HCl is a biguanide derivative producing an anti-hyperglycemic effect which is observed in diabetic patients or in diabetic animals. Its pharmacologic mechanisms of action are different from other classes of oral anti-hyperglycemic agents. Metformin HCl may decrease hepatic glucose production, decrease intestinal absorption of glucose, and improve insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike Sulfonylureas, Metformin HCl does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With Metformin HCl therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacodynamics

Vildagliptin

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-ß (Homeostasis Model Assessment–ß), 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 HCl

Metformin HCl molecular mechanisms underlying action appear to be complex and remain a topic of considerable debate. However, there is general agreement that the administration of Metformin HCl results in the phosphorylation and activation of AMP-activated protein kinase (AMPK) in the liver, which in turn may lead to diverse pharmacologic effects, including inhibition of glucose and lipid synthesis. Although the specific route of AMPK phosphorylation is not yet clear, the molecular components LKB1/STK11 and ATM have been shown to play a role in the phosphorylation of AMPK in the presence of Metformin HCl. However, ATM, LKB1, and AMPK are not the direct targets of Metformin HCl. A recent study using liver-specific AMPK-knockout mice has shown that inhibition of hepatic glucose production by Metformin HCl is preserved, suggesting that Metformin HCl may inhibit hepatic gluconeogenesis in an LKB1-independent and AMPK-independent manner.
The findings from this study are yet to be replicated, and therefore, the role of AMP kinase in the inhibition of gluconeogenesis can still be considered. In a separate study in Oct-1-knockout mice, Metformin HCl both activated AMPK and reduced gluconeogenesis. A separate group has also concluded that Metformin HCl inhibits hepatic gluconeogenesis through AMPK-dependent regulation of small heterodimer partner (SHP). Therefore, a reduction in gluconeogenesis may occur both ways, in an AMPK-dependent and an AMPK-independent manner.
Although the direct target is not fully elucidated, Metformin HCl specifically inhibits complex I of the mitochondrial respiratory chain, suggesting that this inhibition may activate AMPK by increasing the cellular AMP: ATP ratio. AMPK is a major cellular regulator of lipid and glucose metabolism. The activated AMPK phosphorylates and inactivates HMG-CoA reductase (encoded by gene HMGCR), MTOR (target of rapamycin); ACC-2 (encoded by gene ACACB); ACC (encoded by gene ACACA), glycerol-3-phosphate acyltransferase (encoded by gene GPAM); and carbohydrate response element-binding protein. The activation of AMPK by Metformin HCl also suppresses the expression of SREBP-1 (encoded by gene SREBF1), a key lipogenic transcription factor. Phosphorylated AMPK also activates SiRT1 and increases Pgc-1a (encoded by gene PPARGC1A) expression in the nucleus, leading to the downstream activation of mitochondrial biogenesis.
Metformin HCl disrupts the coactivation of PXR with SRC1, resulting in the downregulation of CYP3A4 gene expression. Finally, activated AMPK results in an increase in glucose uptake in skeletal muscle by increasing the GLUT4 (encoded by gene SLC2A4) translocation activity. The overall pharmacological effect of AMPK activation in the liver includes the stimulation of fatty acid oxidation with inhibition of cholesterol and triglyceride synthesis. Peripheral effects include the stimulation of fatty acid oxidation and glucose uptake in skeletal muscle as well as a systemic increase in insulin sensitivity. However, the role of Metformin HCl in insulin-mediated glucose uptake has been debated.

Pharmacokinetics

Absorption

Vildagliptin
Following oral administration in the fasting state, Vildagliptin is rapidly absorbed with an absolute bioavailability of 85%. Peak plasma concentrations for Vildagliptin and the area under the plasma concentration versus time curve (AUC) increased in an approximately dose-proportional manner over the therapeutic dose range. Peak plasma concentrations for Vildagliptin was observed at 1.75 hours. Co-administration with food slightly decreases the rate of absorption of Vildagliptin, as characterized by a 19% decrease in peak concentrations, and a delay in the time to peak plasma concentration to 2.5 hours. There is no change in the extent of absorption and food does not alter the overall exposure (AUC).

Metformin HCl
The absolute bioavailability of a 500 mg Metformin HCl tablet given under fasting conditions is approximately 50 to 60%. Studies using single oral doses of Metformin HCl tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of Metformin HCl, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of the time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of Metformin HCl with food, compared to the same tablet strength administered under fasting conditions. The clinical relevance of these decreases is unknown.

Vildagliptin + Metformin HCl
In the bioequivalence studies of Vildagliptin + Metformin HCl at three dose strengths (50 mg/500 mg, 50 mg/850 mg and 50 mg/1,000 mg), versus free combination of Vildagliptin and Metformin HCl tablets at the corresponding doses, the area under the curve (AUC) and maximum concentration (Cmax) of both the Vildagliptin component and the Metformin HCl component of the Vildagliptin + Metformin HCl tablets were demonstrated to be bioequivalent to that of free combination tablets.

Food does not affect the extent and rate of absorption of Vildagliptin from Vildagliptin + Metformin HCl. The Cmax and AUC of the Metformin HCl component from Vildagliptin + Metformin HCl were decreased by 26% and 7%, respectively when given with food. The absorption of Metformin HCl was also delayed as reflected by the Tmax (2.0 to 4.0 hours) when given with food. These changes in Cmax and AUC are consistent but lower than those observed when Metformin HCl was given alone under fed conditions. The effects of food on the pharmacokinetics of both the Vildagliptin component and Metformin HCl component of Vildagliptin + Metformin HCl were similar to the pharmacokinetics of Vildagliptin and Metformin HCl when given alone with food.

Distribution

Vildagliptin
The plasma-protein binding of Vildagliptin is low (9.3%), and Vildagliptin is distributed equally between plasma and red blood cells. The mean volume of distribution of Vildagliptin at steady state after intravenous administration (Vss) is 71 liters, suggesting extravascular distribution.

Metformin HCl
The apparent volume of distribution (V/F) of Metformin HCl following single oral doses of 850 mg averaged 654 ± 358 liters. Metformin HCl is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin HCl partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Metformin HCl, steady state plasma concentrations of

Metformin HCl are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical studies of Metformin HCl, maximum Metformin HCl plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

Vildagliptin
Metabolism is the major elimination pathway for Vildagliptin in humans, accounting for 69% of the dose. The major metabolite, LAY151, 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 the dose). DPP-4 contributes partially to the hydrolysis of Vildagliptin as shown in an in vivo study using DPP-4 deficient rats. Vildagliptin is not metabolized by cytochrome P450 enzymes to any quantifiable extent. In vitro studies demonstrated that Vildagliptin does not inhibit or induce cytochrome P450 enzymes.

Metformin HCl
Metformin HCl is excreted unchanged in the urine. No metabolites have been identified in humans.

Excretion

Vildagliptin
Following oral administration of 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 accounts for 23% of the dose after oral administration. After an intravenous administration to healthy subjects, the total plasma and renal clearances of Vildagliptin are 41 liters/hour and 13 liters/hour, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours and is independent of the dose.

Metformin HCl
Intravenous single-dose studies in normal subjects demonstrate that Metformin HCl is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. 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.

STORAGE AND STABILITY

Store between 15°C and 30°C

SPECIAL HANDLING INSTRUCTIONS

No special instruction. Keep out of reach of children

DOSAGE FORMS, COMPOSITION AND PACKAGING

VILACT:
Each tablet of VILACT contains Vildagliptin 50 mg.

VILACT M 500:
Each tablet of VILACT M 500 contains Vildagliptin 50 mg + Metformin HCl 500 mg.

VILACT M 850:
Each tablet of VILACT M 850 contains Vildagliptin 50 mg + Metformin HCl 850 mg.

VILACT M 1000:
Each tablet of VILACT M 1000 contains Vildagliptin 50 mg + Metformin HCl 1000 mg.

Each strip of VILACT, VILACT M 500, VILACT M 850 and VILACT M 1000 contains 10 tablets.

PART II SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance : Vildagliptin

Chemical name : (2S)-1-{2-[(3-hydroxy-1-adamantyl)amino]acetyl} pyrrolidine-2-carbonitrile

Molecular formula : $C_{17}H_{25}N_3O_2$

Molecular mass : 303.19

Structural formula :

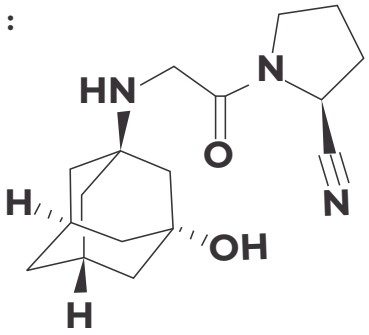

Fig 1: Chemical Structure of Vildagliptin

Drug Substance : Metformin

Proper Name : Metformin hydrochloride

Chemical Name : N,N-Dimethylimidodicarbonimidic diamide

Molecular Formula : $C_4H_{11}N_5 \cdot HCl$

Molecular Mass : 165.63

Structural Formula :

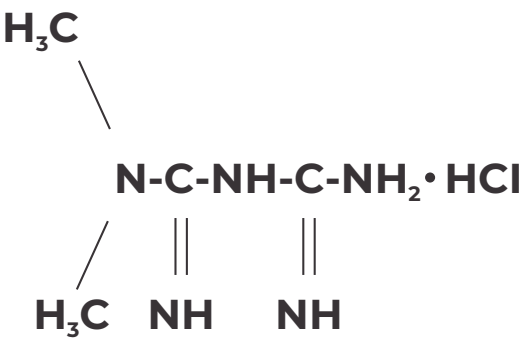

Fig 2: Chemical Structure of Metformin HCl

CLINICAL TRIALS

1) Effectiveness and tolerability of second-line therapy with Vildagliptin vs. other oral agents in Type 2 diabetes: A real-life worldwide observational study (EDGE)
Int J Clin Pract, October 2013, 67, 10, 947–956.

Abstract
Aim: Real-life studies are needed to confirm the clinical relevance of findings from randomised controlled trials (RCTs). This study aimed to assess the effectiveness and tolerability of Vildagliptin add-on vs. other oral antihyperglycaemic drugs (OADs) added to OAD monotherapy in a real-life setting, and to explore the advantages and limitations of large-scale 'pragmatic' trials.
Methods: EDGE was a prospective, 1-year, worldwide, real-life observational study in which 2957 physicians reported on the effects of second-line OADs in 45,868 patients with T2DM not reaching glycemic targets with monotherapy. Physicians could add any OAD, and patients entered either Vildagliptin or (pooled) comparator cohort. The primary effectiveness and tolerability end-point (PEP) evaluated proportions of patients decreasing HbA1c > 0.3%, without hypoglycemia, weight gain, peripheral oedema or gastrointestinal side effects. The most clinically relevant secondary endpoint (SEP 3) was attainment of end-point HbA1c < 7% without hypoglycemia or ⩾3% increase in body weight.
Results: In this large group of T2DM patients, a second OAD was added at mean HbA1c of 8.2 ± 1.3% with no baseline HbA1c difference between cohorts. Second-line OAD therapy attained the PEP in the majority of patients, with higher attainment in those prescribed a Vildagliptin based regimen. The adjusted odds ratio was 1.49 (95% CI: 1.42, 1.55; p < 0.001). In patients with baseline HbA1c ⩾7%, SEP 3 was achieved by 35% of patients on a Vildagliptin-based combination and by 23% of those receiving comparator combinations. The adjusted odds ratio was 1.96 (95% CI: 1.85, 2.07; p < 0.001). Safety events were reported infrequently and safety profiles of Vildagliptin and other OADs were consistent with previous data.
Conclusion: EDGE demonstrates that in a 'real-life' setting, Vildagliptin as second OAD can lower HbA1c to target without well-recognised OAD side effects, more frequently than comparator OADs. In addition, EDGE illustrates that conducting large-scale, prospective, real-life studies poses challenges but yields valuable clinical information complementary to RCTs.

2) Effectiveness and Tolerability of Vildagliptin in Indian Patients with Type 2 Diabetes Mellitus: Results from EDGE–A Real-World Observational Study.
Indian Journal of Clinical Practice, Vol. 24, No. 6, November 2013.

Abstract
Objective: To assess the effectiveness and tolerability of Vildagliptin in combination with another oral antidiabetic drug (OAD) versus any other two-agent OAD combinations in Indian patients with type 2 diabetes mellitus (T2DM) in a real-world setting.
Study design: This was a post-hoc analysis of 472 multicenter, prospective, 1-year, observational EDGE study for 11057 patients enrolled in India. The primary efficacy endpoint of the study was proportion of patients achieving glycosylated hemoglobin (HbA1c) reduction of >0.3% without peripheral edema, hypoglycemic event, discontinuation due to a gastrointestinal event or weight gain. One of the secondary efficacy endpoints was proportion of patients achieving HbA1c <7% without hypoglycemia and weight gain.
Results: The mean age, body mass index, HbA1c and duration of T2DM were 51.8 years, 26.6 kg/m^2, 8.6% and 4.3 years, respectively. The proportion of patients achieving the efficacy endpoints was significantly higher in the Vildagliptin cohort compared with the comparator cohort (p < 0.0001). The Vildagliptin cohort showed a numerically greater reduction in HbA1c than the comparator cohort (1.4 vs 1.1%; analysis not pre-specified). Adverse events were comparable in both groups (4.2% vs 4.9%).
Conclusion: In India, in a real-world setting, Vildagliptin showed better overall clinical benefits compared with comparator OADs in patients with T2DM.

3) Effectiveness and tolerability of second-line treatment with Vildagliptin versus other oral drugs for type 2 diabetes in a real-world setting in the Middle East: results from the EDGE study.
Vascular Health and Risk Management 2015:11 149–155

Abstract

Background: Type 2 diabetes mellitus (T2DM) is a chronic progressive disease that requires treatment intensification with antihyperglycemic agents due to progressive deterioration of B-cell function. A large observational study of 45,868 patients with T2DM across 27 countries (EDGE) assessed the effectiveness and safety of Vildagliptin as add-on to other oral antidiabetic drugs (OADs) versus other comparator OAD combinations. Here, we present results from the Middle East countries (Bahrain, Jordan, Kuwait, Lebanon, Oman, Palestine, and the United Arab Emirates).

Methods: Patients inadequately controlled with OAD monotherapy were eligible after the add-on treatment was chosen by the physician based on clinical judgment and patient need. Patients were assigned to either Vildagliptin or comparator OADs (sulfonylureas, thiazolidinediones, glinides, alpha-glucosidase inhibitors or Metformin HCl, except incretin-based therapies) based on the add-on therapy. The primary endpoint was the proportion of patients achieving a glycated hemoglobin (HbA1c) reduction of > 0.3% without peripheral edema, hypoglycemia, discontinuation due to a gastrointestinal event, or weight gain 5%. One of the secondary endpoints was the proportion of patients achieving HbA1c < 7% without hypoglycemia or weight gain. Change in HbA1c from baseline to study endpoint and safety were also assessed.

Results: Of the 4,780 patients enrolled in the Middle East, 2,513 received Vildagliptin and 2,267 received other OADs. Overall, the mean (± standard deviation) age at baseline was 52.1±10.2 years, mean HbA1c was 8.5%±1.3%, and mean T2DM duration was 4.2±4.0 years. The proportion of patients achieving the primary (76.1% versus 61.6%, P< 0.0001) and secondary (54.8% versus 29.9%, P< 0.0001) endpoints was higher with Vildagliptin than with the comparator OADs. The unadjusted odds ratios for the primary and secondary endpoints were 1.98 (95% confidence interval 1.75 – 2.25) and 2.8 (95% confidence interval 2.5 – 3.2), respectively, in favor of Vildagliptin. Vildagliptin achieved a numerically greater reduction in HbA1c (1.7%) from baseline versus comparator OADs (1.4%). The overall incidence of adverse events was comparable between studied cohorts.

Conclusion: In real life, treatment with Vildagliptin was associated with a higher proportion of patients with T2DM achieving better glycemic control without tolerability issues in the Middle East.

TOXICOLOGY

Vildagliptin:
Intra-cardiac impulse conduction delays were observed in dogs with a no-effect dose of 15 mg/kg (7- fold human exposure based on Cmax).
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. Embryo-foetal 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 1,000 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 (16-fold 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 HCl:
Preclinical data on Metformin HCl reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. Long-term carcinogenicity studies with Metformin HCl have been performed in rats (dosing duration 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons. No evidence of carcinogenicity with Metformin HCl was found in either male or female mice. Similarly, there was no tumourigenic potential observed with Metformin HCl in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day. There was no evidence of mutagenic potential of Metformin HCl in the following in vitro tests: Ames test (*S. typhimurium*), and gene mutation test (mouse lymphoma cells) or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative.

SOURCE

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11. GalvusMet Product Monograph, Novartis New Zealand Limited (Rev August 2018).

VILACT

Panacea Biotec
Innovation in support of life

PART III ABRIDGED PRESCRIBING INFORMATION

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

VILACT Tablets
(Vildagliptin 50 mg)

VILACT M 500 Tablets
(Vildagliptin 50 mg + Metformin HCl 500 mg)

VILACT M 850 Tablets
Tablets (Vildagliptin 50 mg + Metformin HCl 850 mg)

VILACT M 1000 Tablets
(Vildagliptin 50 mg + Metformin HCl 1000 mg)

Composition: Each **VILACT** Tablet contains Vildagliptin 50 mg. Each **VILACT M 500** Tablet contains Vildagliptin 50 mg and Metformin HCl 500 mg. Each **Vilact M 850** Tablet contains Vildagliptin 50 mg and Metformin HCl 850 mg. Each **VILACT M 1000** Tablet contains Vildagliptin 50 mg and Metformin HCl 1000 mg. **Indications: VILACT** is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with Type 2 Diabetes Mellitus (T2DM). **VILACT M 500**, **VILACT M 850** & **VILACT M 1000** is indicated in patients with T2DM whose diabetes is not adequately controlled on Metformin HCl or Vildagliptin alone or who are already treated with the combination of Vildagliptin and Metformin HCl, as separate tablets. **Mechanism of Action:** Vildagliptin inhibits dipeptidyl peptidase-4 (DPP-4) enzyme, which degrades the active incretins GLP-1 (Glucagon like peptide-1) and GIP (Glucose-dependent insulinotropic peptide). By preventing GLP-1 and GIP degradation, Vildagliptin is able to increase the secretion of insulin by beta-cells and suppress the release of glucagon by alpha-cells of the pancreas. Metformin HCl decreases hepatic glucose production, decrease intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. **Dosage and Administration: Vildagliptin:** 50 mg twice daily administered with or without meals. Maximum recommended dose is 100 mg daily administered as two divided doses of 50 mg given in the morning and evening. No dosage adjustment is required in patients with mild renal impairment. In patients with moderate or severe renal impairment or End Stage Renal Disease (ESRD), the recommended dose is 50 mg once daily. Not recommended in patients with hepatic impairment, including patients with a pre-treatment ALT or AST >2.5 x the ULN. **VILACT M 500**, **VILACT M 850** & **VILACT M 1000**: Starting dose for Patients Inadequately Controlled on Vildagliptin Monotherapy: Based on the usual starting doses of Metformin Hcl (500 mg twice daily or 850 mg once daily), Vildagliptin + Metformin HCl may be initiated at the 50 mg/500 mg tablet strength twice daily and gradually titrated after assessing the adequacy of therapeutic response.

Starting Dose for Patients Inadequately Controlled on Metformin HCl Monotherapy: Based on the patient's current dose of Metformin HCl, Vildagliptin + Metformin HCl may be initiated at either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily. Starting Dose for Patients Switching from Combination Therapy of Vildagliptin Plus Metformin HCl as Separate Tablets: Vildagliptin + Metformin HCl may be initiated with either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1000 mg tablet strength based on the dose of Vildagliptin or Metformin HCl already being taken. Starting Dose for Treatment Naïve Patients: In treatment naïve patients, Vildagliptin + Metformin HCl may be initiated at 50 mg/500 mg once daily and gradually titrated to a maximum dose of 50mg/1000 mg twice daily after assessing the adequacy of therapeutic response. Use in Combination with SU or With Insulin: The dose of Vildagliptin + Metformin HCl should provide Vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of Metformin HCl similar to the dose already being taken.

Not recommended in patients with hepatic impairment, including patients with a pre-treatment ALT or AST >2.5 x the ULN. **Contraindications:** History of hypersensitivity to Vildagliptin / Metformin HCl or to any of its excipients. Patients with severe Renal Impairment, Congestive Heart Failure. Also contraindicated in conditions such patients with acute or chronic metabolic acidosis, including lactic acidosis or diabetic ketoacidosis, with or without coma. **Warnings and Precautions:** For allergic or hypersensitive reaction, seek emergency medical attention. Possible symptoms such as difficulty in breathing, difficulty in swallowing, swelling, chest tightness, skin rashes, and hives might occur. Vildagliptin should be discontinued if associated with acute pancreatitis. In patients taking Metformin HCl, lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis. Lactic acidosis is a medical emergency that must be treated. Warn patients against excessive alcohol intake due to high risk of lactic acidosis. **Pregnancy and Lactation:** The safety of Vildagliptin / Metformin HCl in pregnant and nursing women is not known. **Drug Interaction:** No clinically relevant pharmacokinetic interaction was observed when Vildagliptin was co-administered with Metformin HCl. Patients might suffer from hypoglycemia if Vildagliptin is given along with other hypoglycemic agents. Metformin HCl may cause an increased risk of lactic acidosis in acute alcohol intoxication. **Adverse Effect:** Vildagliptin studies reported few adverse reactions such as hypoglycaemia, constipation and arthralgia. Vildagliptin + Metformin HCl commonly cause adverse effects, such as nausea, tremor, headache, dizziness, fatigue and hypoglycaemia.

Packaging: **VILACT, VILACT M 500, VILACT M 850** and **VILACT M 1000** each is available as a strip of 10 tablets.

Dated: Dec 2019

Panacea Biotec
Innovation in support of life

VILACT

Vildagliptin 50 mg

VILACT M500

Vildagliptin 50 mg + Metformin HCl 500 mg

VILACT M850

Vildagliptin 50 mg + Metformin HCl 850 mg

VILACT M1000

Vildagliptin 50 mg + Metformin HCl 1000 mg

For Oral Administration

Anti-diabetic Agent

(DPP – 4 Inhibitor / DPP – 4 Inhibitor + Metformin HCl)

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