PATIENT INFORMATION LEAFLET
For the use of a Registered Medical Practitioner, or a Hospital, or a Laboratory only

Vildagliptin & Metformin Hydrochloride Tablets IP

AMERICAN
VILDAFOX-M 50/500
Tablets

WARNINGS FOR PRODUCTS CONTAING METFORMIN HYDROCHLORIDE

WARNING: LACTIC ACIDOSIS

- Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure.
- Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate.

If acidosis is suspected, discontinue metformin hydrochloride extended-release tablets and hospitalize the patient immediately.

1. GENERIC NAME
Vildagliptin 50 mg and Metformin Hydrochloride 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains:

Vildagliptin	IP	50 mg
Metformin Hydrochloride	IP	500 mg
Excipients		q.s.

Colours: Ferric Oxide Red USP-NF, Ferric Oxide Yellow USP-NF & Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH
Oral dosage form (Tablets),
Vildagliptin and Metformin Hydrochloride Tablets (50 mg+500 mg)

4. CLINICAL PARTICULARS
4.1 Therapeutic indication
For the treatment of type-II diabetes mellitus when single drug therapy along with diet, exercise do not result in adequate glycemic control.

4.2 Posology and Method of administration
Vildagliptin
Posology
Adults :
When used as monotherapy, in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea, or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening.
When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg once daily.
When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.
Doses higher than 100 mg are not recommended.
If a dose of Vildagliptin is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established.
Additional information on special populations
Elderly (≥ 65 years) No dose adjustments are necessary in elderly patients (see also sections 5.1 and 5.2).
Renal impairment
No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). In patients with moderate or severe renal impairment or with end-stage renal disease (ESRD), the recommended dose of Vildagliptin is 50 mg once daily.
Hepatic impairment
Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x the upper limit of normal (ULN).
Paediatric population
Vildagliptin is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of vildagliptin in children and adolescents (< 18 years) have not been established. No data are available.
Metformin Hydrochloride
Adult Dosage
- The recommended starting dose of Metformin Hydrochloride is 500 mg orally twice a day or 850 mg once a day, given with meals.
- Increase the dose in increments of 500 mg weekly or 850 mg every 2 weeks on the basis of glycemic control and tolerability, up to a maximum dose of 2550 mg per day, given in divided doses.
- Doses above 2000 mg may be better tolerated given 3 times a day with meals.

Pediatric Dosage
- The recommended starting dose of Metformin Hydrochloride for pediatric patients 10 years of age and older is 500 mg orally twice a day, given with meals.
- Increase dosage in increments of 500 mg weekly on the basis of glycemic control and tolerability, up to a maximum of 2000 mg per day, given in divided doses twice daily.

Recommendations for Use in Renal Impairment
- Assess renal function prior to initiation of Metformin Hydrochloride and periodically thereafter.
- Metformin Hydrochloride is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
- Initiation of Metformin Hydrochloride in patients with an eGFR between 30 – 45 mL/minute/1.73 m^2 is not recommended.
- In patients taking Metformin Hydrochloride whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy.
- Discontinue Metformin Hydrochloride if the patient's eGFR later falls below 30 mL/minute/1.73 m^2.

Discontinuation for Iodinated Contrast Imaging Procedures
Discontinue Metformin Hydrochloride at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart Metformin Hydrochloride if renal function is stable.

4.3 Contraindication
Vildagliptin
Patients may develop hypersensitivity to the active substance or to any of the excipients.
Metformin Hydrochloride
Metformin Hydrochloride are contraindicated in patients with:
Severe renal impairment (eGFR below 30 mL/min/1.73 m2)
Hypersensitivity to metformin.
Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

4.4 Special warnings and precautions for use
Vildagliptin
General
Vildagliptin is not a substitute for insulin in insulin-requiring patients. Vildagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
Renal impairment
There is limited experience in patients with ESRD on haemodialysis. Therefore, Vildagliptin should be used with caution in these patients.
Hepatic impairment
Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3x ULN.
Liver enzyme monitoring
Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function test results returned to normal after discontinuation of treatment. Liver function tests should be performed prior to the initiation of treatment with Vildagliptin in order to know the patient's baseline value. Liver function should be monitored during treatment with Vildagliptin 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 abnormalities return to normal. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Vildagliptin therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Vildagliptin. Following withdrawal of treatment with Vildagliptin and LFT normalisation, treatment with Vildagliptin should not be reinitiated.
Cardiac failure
A clinical trial of vildagliptin in patients with New York Heart Association (NYHA) functional class I-III showed that treatment with vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive.
There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class IV and therefore use is not recommended in these patients.
Skin disorders
Skin lesions, including blistering and ulceration have been reported in extremities of monkeys in 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
Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia.
Metformin Hydrochloride
Lactic Acidosis
There have been postmarketing cases of Metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; Metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.
If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Metformin Hydrochloride. In Metformin Hydrochloride treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated Metformin (Metformin Hydrochloride is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.
Educate patients and their families about the symptoms of lactic acidosis and, if these symptoms occur, instruct them to discontinue Metformin Hydrochloride and report these symptoms to their healthcare provider.
For each of the known and possible risk factors for Metformin-associated lactic acidosis, recommendations to reduce the risk of and manage Metformin-associated lactic acidosis are provided below:
- Renal impairment—The postmarketing Metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because Metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include:
  - Before initiating Metformin Hydrochloride, obtain an estimated glomerular filtration rate (eGFR).
  - Metformin Hydrochloride is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.
  - Initiation of Metformin Hydrochloride is not recommended in patients with eGFR between 30-45 mL/min/1.73 m^2.
  - Obtain an eGFR at least annually in all patients taking Metformin Hydrochloride. In patients at risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
  - In patients taking Metformin Hydrochloride whose eGFR falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy.
- Drug interactions — The concomitant use of Metformin Hydrochloride with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance, or increase metformin accumulation. Consider more frequent monitoring of patients.
- Age 65 or greater — The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assesses renal function more frequently in elderly patients.
- Radiological studies with contrast — Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop Metformin Hydrochloride at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart Metformin Hydrochloride if renal function is stable.
- Surgery and other procedures — With holding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension, and renal impairment. Metformin Hydrochloride should be temporarily discontinued while patients have restricted food and fluid intake.
- Hypoxic states — Several of the postmarketing cases of Metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may cause prerenal azotemia. When such an event occurs, discontinue Metformin Hydrochloride.
- Excessive alcohol intake — Alcohol potentiates the effect of Metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving Metformin Hydrochloride.
- Hepatic impairment — Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid using Metformin Hydrochloride in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 Deficiency
In Metformin Hydrochloride clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of Metformin Hydrochloride or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 at 2-to-3-year intervals in patients on Metformin Hydrochloride and manage any abnormalities.
Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. Metformin Hydrochloride may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with Metformin Hydrochloride.
Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Metformin Hydrochloride.

4.5 Drug Interaction
Vildagliptin
Vildagliptin has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate and does not inhibit or induce CYP 450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes.
Combination with pioglitazone, metformin and glyburide
Results from studies conducted with these oral antidiabetics have shown no clinically relevant pharmacokinetic interactions.
Digoxin (Pgp substrate), warfarin (CYP2C9 substrate)
Clinical studies performed with healthy subjects have shown no clinically relevant pharmacokinetic interactions. However, this has not been established in the target population.
Combination with amlodipine, ramipril, valsartan or simvastatin
Drug-drug interaction studies in healthy subjects were conducted with amlodipine, ramipril, valsartan and simvastatin.
In these studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin.
Combination with ACE-inhibitors
There may be an increased risk of angioedema in patients concomitantly taking ACE inhibitors.
As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.
Metformin Hydrochloride
Table 3: Clinically Significant Drug Interactions with Metformin Hydrochloride

Carbonic Anhydrase Inhibitors	
Clinical Impact:	Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gaps, hyperchloremic metabolic acidosis. Concomitant use of these drugs with GLUCOPHAGE/GLUCOPHAGE XR may increase the risk for lactic acidosis.
Intervention:	Consider more frequent monitoring of these patients.
Examples	Topiramate, zonisamide, acetazolamide or dichlorphenamide.
Drugs that Reduce Metformin Hydrochloride Clearance	
Clinical Impact:	Concomitant use of drugs 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) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.
Intervention:	Consider the benefits and risks of concomitant use with Metformin Hydrochloride.
Examples	Ranolazine, vandetanib, dolutegravir, and cimetidine.
Alcohol	
Clinical Impact:	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention:	Warn patients against excessive alcohol intake while receiving Metformin Hydrochloride.
Insulin Secretagogues or Insulin	
Clinical Impact:	Coadministration of Metformin Hydrochloride with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia.
Intervention:	Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.
Drugs Affecting Glycemic Control	
Clinical Impact:	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.
Intervention:	When such drugs are administered to a patient receiving Metformin Hydrochloride, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Metformin Hydrochloride, observe the patient closely for hypoglycemia.
Examples:	Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid.

1.8 Use in Special Populations (such as Pregnant women, Lactating women, Paediatric patients, Geriatric patients etc.)
Vildagliptin
Pregnancy
There are no adequate data from the use of vildagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Due to lack of human data, Vildagliptin should not be used during pregnancy.
Breast-feeding
It is unknown whether vildagliptin is excreted in human milk. Animal studies have shown excretion of vildagliptin in milk. Vildagliptin should not be used during breast-feeding.
Fertility
No studies on the effect on human fertility have been conducted for vildagliptin
Metformin Hydrochloride
Pregnancy
Risk Summary
Limited data with Metformin Hydrochloride in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with Metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes mellitus in pregnancy.
No adverse developmental effects were observed when Metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2- and 5 times, respectively, a 2550 mg clinical dose, based on body surface area.
The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes mellitus with an HbA1C >7 and has been reported to be as high as 20–25% in women with a HbA1C >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.
Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk
Poorly controlled diabetes mellitus in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes mellitus increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.
Data
Human Data
Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.
Animal Data
Metformin Hydrochloride did not adversely affect development outcomes when administered to pregnant rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 5 times a 2550 mg clinical dose based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.
Lactation
Risk Summary
Limited published studies report that Metformin is present in human milk. However, there is insufficient information to determine the effects of Metformin on the breastfed infant and no available information on the effects of Metformin on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Metformin Hydrochloride and any potential adverse effects on the breastfed child from Metformin Hydrochloride or from the underlying maternal condition.
Data
Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.
Females and Males of Reproductive Potential
Discuss the potential for unintended pregnancy with premenopausal women as therapy with Metformin Hydrochloride may result in ovulation in some anovulatory women.
Pediatric Use
Metformin Hydrochloride The safety and effectiveness of Metformin Hydrochloride for the treatment of type 2 diabetes mellitus have been established in pediatric patients 10 to 16 years old. Safety and effectiveness of Metformin Hydrochloride have not been established in pediatric patients less than 10 years old. Use of Metformin Hydrochloride in pediatric patients 10 to 16 years old for the treatment of type 2 diabetes mellitus is supported by evidence from adequate and well-controlled studies of Metformin Hydrochloride in adults with additional data from a controlled clinical study in pediatric patients 10 to 16 years old with type 2 diabetes mellitus, which demonstrated a similar response in glycemic control to that seen in adults.
In this study, adverse reactions were similar to those described in adults. A maximum daily dose of 2000 mg of Metformin Hydrochloride is recommended.
Geriatric Use
Controlled clinical studies of Metformin Hydrochloride did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal functions more frequently in elderly patients.
Renal Impairment
Metformin is substantially excreted by the kidney, and the risk of Metformin accumulation and lactic acidosis increases with the degree of renal impairment. Metformin Hydrochloride is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2.
Hepatic Impairment
Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Metformin Hydrochloride is not recommended in patients with hepatic impairment.

4.7 Effect on ability to drive and use machines
Vildagliptin
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.
Metformin Hydrochloride
Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines. However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulfonylureas, insulin, or meglitinides).

4.8 Undesirable effects
Vildagliptin
Summary of the safety profile
Safety data were obtained from a total of 5451 patients exposed to vildagliptin at a daily dose of 100 mg (50 mg twice daily) in double-blind placebo-controlled trials of at least 12 weeks duration. Of these patients, 4622 patients received vildagliptin as monotherapy and 829 patients received placebo.
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. Hypoglycaemia has been reported in patients receiving vildagliptin concomitantly with sulphonylurea and insulin. The risk of acute pancreatitis has been reported with the use of vildagliptin.
Tabulated list of adverse reactions
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 system organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to<1/10), uncommon (≥ 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.
Table 1 Adverse reactions reported in patients who received vildagliptin as monotherapy or as add-on therapy in controlled clinical studies and in post-marketing experience

System organ class - adverse reaction	Frequency
Infections and infestations	
Nasopharyngitis	Very common
Upper respiratory tract infection	Common
Metabolism and nutrition disorders	
Hypoglycaemia	Uncommon
Nervous system disorders	
Dizziness	Common
Headache	Common
Tremor	Common
Eye disorders	
Vision blurred	Common
Gastrointestinal disorders	
Constipation	Common
Nausea	Common
Gastro-oesophageal reflux disease	Common
Diarrhea	Common
Abdominal pain, including upper	Common
Vomiting	Common
Flatulence	Uncommon
Pancreatitis	Rare
Hepatobiliary disorders	
Hepatitis	Not known
Skin and subcutaneous tissue disorders	
Hyperhidrosis	Common
Rash	Common
Pruritis	Common
Dermatitis	Common
Urticaria	Uncommon
Exfoliative and bullous skin lesions, including bullous pemphigoid	Not known*
Cutaneous vasculitis	Not known*
Musculoskeletal and connective tissue disorders	
Arthralgia	Common
Myalgia	Common
Reproductive system and breast disorders	
Erectile dysfunction	Uncommon
General disorders and administration site conditions	
Asthenia	Common
Oedema peripheral	Common
Fatigue	Uncommon
Chills	Uncommon
Investigations	
Abnormal liver function tests	Uncommon
Weight increase	Uncommon
* Based on post-marketing experience.	

Description of selected adverse reactions
Hepatic impairment
Rare cases of hepatic dysfunction (including hepatitis) have been reported. 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 50 mg once 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.
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 angiotensin converting enzyme inhibitor (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 Hydrochloride
The following adverse reactions are also discussed elsewhere in the labeling:
- Lactic Acidosis
- Vitamin B12 Deficiency
- Hypoglycemia

Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Metformin Hydrochloride
In a U.S. clinical trial of Metformin Hydrochloride in patients with type 2 diabetes mellitus, a total of 141 patients received Metformin Hydrochloride up to 2550 mg per day. Adverse reactions reported in greater than 5% of Metformin Hydrochloride treated patients and that were more common than in placebo-treated patients, are listed in Table 1.
Table 1: Adverse Reactions from a Clinical Trial of Metformin Hydrochloride Occurring >5% and More Common than Placebo in Patients with Type 2 Diabetes Mellitus

	Metformin Hydrochloride (n=141)	Placebo (n=145)
Diarrhea	53%	12%
Nausea/Vomiting	26%	8%
Flatulence	12%	6%
Asthenia	9%	6%
Indigestion	7%	4%
Abdominal Discomfort	6%	5%
Headache	6%	5%

Diarrhea led to discontinuation of Metformin Hydrochloride in 6% of patients. Additionally, the following adverse reactions were reported in ≥1% to ≤5% of Metformin Hydrochloride treated patients and were more commonly reported with GLUCOPHAGE than placebo: abnormal stools, hypoglycemia, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.
In Metformin Hydrochloride clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients.
Pediatric Patients
In clinical trials with Metformin Hydrochloride in pediatric patients with type 2 diabetes mellitus, the profile of adverse reactions was similar to that observed in adults.
Postmarketing Experience
The following adverse reactions have been identified during post approval use of Metformin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Cholestatic, hepatocellular, and mixed hepatocellular liver injury have been reported with postmarketing use of Metformin.
4.9 Overdose
Vildagliptin
Information regarding overdose with vildagliptin is limited.
Symptoms
Information on the likely symptoms of overdose was taken from a rising dose tolerability study in healthy subjects given vildagliptin for 10 days. At 400 mg, 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 600 mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), aspartate aminotransferase (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.
Management
In the event of an overdose, supportive management is recommended. Vildagliptin cannot be removed by haemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by haemodialysis.
Metformin Hydrochloride
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom Metformin overdosage is suspected.
5. Pharmacological Properties
5.1 Mechanism of Action
Vildagliptin
The administration of vildagliptin results in a rapid and complete inhibition of DPP 4 activity, resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).
Metformin hydrochloride
Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.
5.2 Pharmacodynamic properties
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 β (Homeostasis Model Assessment β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.
By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion.
The enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia.
The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptin treatment.
Clinical efficacy and safety
More than 15,000 patients with type 2 diabetes participated in double-blind placebo- or active- controlled clinical trials of up to more than 2 years' treatment duration. In these studies, vildagliptin was administered to more than 9,000 patients at daily doses of 50 mg once daily, 50 mg twice daily or 100 mg once daily. More than 5,000 male and more than 4,000 female patients received vildagliptin 50 mg once daily or 100 mg daily. More than 1,900 patients receiving vildagliptin 50 mg once daily or 100 mg daily

SIZE : 420X330 MM FOLD SIZE : 105X82.5MM / 54 GSM MAPLITHO PAPER

were ≥ 65 years. In these trials, vildagliptin was administered as monotherapy in drug- naïve patients with type 2 diabetes or in combination in patients not adequately controlled by other antidiabetic medicinal products.
Overall, vildagliptin improved glycaemic control when given as monotherapy or when used in combination with metformin, a sulphonylurea, and a thiazolidinedione, as measured by clinically relevant reductions in HbA1c from baseline at study endpoint.
In clinical trials, the magnitude of HbA1c reductions with vildagliptin was greater in patients with higher baseline HbA1c.
In a 52-week double-blind controlled trial, vildagliptin (50 mg twice daily) reduced baseline HbA1c by -1% compared to -1.6% for metformin (titrated to 2 g/day) statistical non-inferiority was not achieved. Patients treated with vildagliptin reported significantly lower incidences of gastrointestinal adverse reactions versus those treated with metformin.
In a 24-week double-blind controlled trial, vildagliptin (50 mg twice daily) was compared to rosiglitazone (8 mg once daily). Mean reductions were -1.20% with vildagliptin and -1.48% with rosiglitazone in patients with mean baseline HbA1c of 8.7%. Patients receiving rosiglitazone experienced a mean increase in weight (+1.6 kg) while those receiving vildagliptin experienced no weight gain (-0.3 kg). The incidence of peripheral oedema was lower in the vildagliptin group than in the rosiglitazone group (2.1% vs. 4.1% respectively).
In a clinical trial of 2 years' duration, vildagliptin (50 mg twice daily) was compared to gliclazide (up to 320 mg/day). After two years, mean reduction in HbA1c was 0.5% for vildagliptin and -0.6% for gliclazide, from a mean baseline HBA1c of 8.6%. Statistical non-inferiority was not achieved. Vildagliptin was associated with fewer hypoglycaemic events (0.7%) than gliclazide (1.7%).
In a 24-week trial, vildagliptin (50 mg twice daily) was compared to pioglitazone (30 mg once daily) in patients inadequately controlled with metformin (mean daily dose: 2020 mg). Mean reductions from baseline HbA1c of 8.4% were -0.9% with vildagliptin added to metformin and -1.0% with pioglitazone added to metformin. A mean weight gain of +1.9 kg was observed in patients receiving pioglitazone added to metformin compared to +0.3 kg in those receiving vildagliptin added to metformin.
In a clinical trial of 2 years' duration, vildagliptin (50 mg twice daily) was compared to glimepiride (up to 6 mg/day – mean dose at 2 years: 4.6 mg) in patients treated with metformin (mean daily dose: 1894 mg). After 1 year mean reductions in HbA1c were -0.4% with vildagliptin added to metformin and -0.5% with glimepiride added to metformin, from a mean baseline HbA1c of 7.3%. Body weight change with vildagliptin was -0.2 kg vs +1.6 kg with glimepiride. The incidence of hypoglycaemia was significantly lower in the vildagliptin group (1.7%) than in the glimepiride group (16.2%). At study endpoint (2 years), the HbA1c was similar to baseline values in both treatment groups and the body weight changes and hypoglycaemia differences were maintained.
In a 52-week trial, vildagliptin (50 mg twice daily) was compared to gliclazide (mean daily dose: 229.5 mg) in patients inadequately controlled with metformin (metformin dose at baseline 1928 mg/day). After 1 year, mean reductions in HbA1c were -0.81% with vildagliptin added to metformin (mean baseline HbA1c 8.4%) and -0.85% with gliclazide added to metformin (mean baseline HbA1c 8.5%); statistical non inferiority was achieved (95% CI -0.11 – 0.20). Body weight change with vildagliptin was +0.1 kg compared to a weight gain of +1.4 kg with gliclazide.
In a 24-week trial the efficacy of the fixed dose combination of vildagliptin and metformin (gradually titrated to a dose of 50 mg/500 mg twice daily or 50 mg/1000 mg twice daily) as initial therapy in drug-naïve patients was evaluated. Vildagliptin/metformin 50 mg/1000 mg twice daily reduced HbA1c by -1.82%, vildagliptin/metformin 50 mg/500 mg twice daily by -1.61%, metformin 1000 mg twice daily by -1.36% and vildagliptin 50 mg twice daily by -1.09% from a mean baseline HbA1c of 8.6%. The decrease in HbA1c observed in patients with a baseline ≥ 10.0% was greater.
A 24-week, multi-centre, randomised, double-blind, placebo-controlled trial was conducted to evaluate the treatment effect of vildagliptin 50 mg once daily compared to placebo in 515 patients with type 2 diabetes and moderate renal impairment (N=294) or severe renal impairment (N=221). 68.8% and 80.5% of the patients with moderate and severe renal impairment respectively were treated with insulin (mean daily dose of 56 units and 51.6 units respectively) at baseline. In patients with moderate renal impairment vildagliptin significantly decreased HbA1c compared with placebo (difference of -0.53%) from a mean baseline of 7.9%. In patients with severe renal impairment, vildagliptin significantly decreased HbA1c compared with placebo (difference of -0.56%) from a mean baseline of 7.7%.
A 24-week randomised, double-blind, placebo-controlled trial was conducted in 318 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with metformin (≥ 1500 mg daily) and glimepiride (≥ 4 mg daily). Vildagliptin in combination with metformin and glimepiride significantly decreased HbA1c compared with placebo. The placebo-adjusted mean reduction from a mean baseline HbA1c of 8.8% was -0.76%.
A 24-week randomised, double-blind, placebo-controlled trial was conducted in 449 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with a stable dose of basal or premixed insulin (mean daily dose 41 units), with concomitant use of metformin (N=276) or without concomitant metformin (N=173). Vildagliptin in combination with insulin significantly decreased HbA1c compared with placebo. In the overall population, the placebo-adjusted mean reduction from a mean baseline HbA1c 8.8% was -0.72%. In the subgroups treated with insulin with or without concomitant metformin the placebo-adjusted mean reduction in HbA1c was -0.63% and -0.84%, respectively. The incidence of hypoglycaemia in the overall population was 8.4% and 7.2% in the vildagliptin and placebo groups, respectively. Patients receiving vildagliptin experienced no weight gain (+0.2 kg) while those receiving placebo experienced weight reduction (-0.7 kg).
In another 24-week study in patients with more advanced type 2 diabetes not adequately controlled on insulin (short and longer acting, average insulin dose 80 IU/day), the mean reduction in HbA1c when vildagliptin (50 mg twice daily) was added to insulin was statistically significantly greater than with placebo plus insulin (0.5% vs. 0.2%). The incidence of hypoglycaemia was lower in the vildagliptin group than in the placebo group (22.9% vs. 29.6%).
A 52-week multi-centre, randomised, double-blind trial was conducted in patients with type 2 diabetes and congestive heart failure (NYHA functional class I-III) to evaluate the effect of vildagliptin 50 mg twice daily (N=128) compared to placebo (N=126) on left-ventricular ejection fraction (LVEF). Vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing CHF. Adjudicated cardiovascular events were balanced overall. There were more cardiac events in vildagliptin treated patients with NYHA class III heart failure compared to placebo. However, there were imbalances in baseline cardiovascular risk favouring placebo and the number of events was low, precluding firm conclusions. Vildagliptin significantly decreased HbA1c compared with placebo (difference of 0.6%) from a mean baseline of 7.8% at week 16. In the subgroup with NYHA class III, the decrease in HbA1c compared to placebo was lower (difference 0.3%) but this conclusion is limited by the small number of patients (n=44). The incidence of hypoglycaemia in the overall population was 4.7% and 5.6% in the vildagliptin and placebo groups, respectively.
A five-year multi-centre, randomised, double-blind study (VERIFY) was conducted in patients with type 2 diabetes to evaluate the effect of an early combination therapy with vildagliptin and metformin (N = 998) against standard-of-care initial metformin monotherapy followed by combination with vildagliptin (sequential treatment group) (N = 1 003) in newly diagnosed patients with type 2 diabetes. The combination regimen of vildagliptin 50 mg twice daily plus metformin resulted in a statistically and clinically significant relative reduction in hazard for "time to confirmed initial treatment failure" (HbA1c value ≥ 7%) vs metformin monotherapy in treatment-naïve patients with type 2 diabetes over the 5-year study duration (HR [95%CI]: 0.51 [0.45, 0.58]; p<0.001). The incidence of initial treatment failure (HbA1c value ≥ 7%) was 429 (43.6%) patients in the combination treatment group and 614 (62.1%) patients in the sequential treatment group.

Cardiovascular risk

A meta-analysis of independently and prospectively adjudicated cardiovascular events from 37 phase III and IV monotherapy and combination therapy clinical studies of up to more than 2 years duration (mean exposure 50 weeks for vildagliptin.
and 49 weeks for comparators) was performed and showed that vildagliptin treatment was not associated with an increase in cardiovascular risk versus comparators. The composite endpoint of adjudicated major adverse cardiovascular events (MACE) including acute myocardial infarction, stroke or cardiovascular death was similar for vildagliptin versus combined active and placebo comparators [Mantel–Haenszel risk ratio (M-H RR) 0.82 (95% CI 0.61-1.11)]. A MACE occurred in 83 out of 9,599 (0.86%) vildagliptin-treated patients and in 85 out of 7,102 (1.20%) comparator-treated patients. Assessment of each individual MACE component showed no increased risk (similar M-H RR). Confirmed heart failure (HF) events defined as HF requiring hospitalisation or new onset of HF were reported in 41 (0.43%) vildagliptin-treated patients and 32 (0.45%) comparator treated patients with M-H RR 1.08 (95% CI 0.68-1.70).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with vildagliptin in all subsets of the paediatric population with type 2 diabetes mellitus.

Metformin hydrochloride

Metformin hydrochloride is a biguanide anti-hyperglycemic agent, which is widely used for the treatment of type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus [NIDDM]. Metformin improves glycemic control by enhancing insulin sensitivity in liver and muscle, and reducing gastrointestinal glucose absorption and hepatic glucose production. However it does not stimulate insulin secretion and, therefore, is not associated with hypoglycemia. Improved metabolic control with metformin does not induce weight gain and may cause weight loss. It has been demonstrated that the favorable effects of metformin also include improvements in factors associated with cardiovascular risk including lipids, fibrinolysis and body weight.

5.3 Pharmacokinetic Properties

Vildagliptin

Absorption

Absorption Following oral administration in the fasting state, vildagliptin is rapidly absorbed, with peak plasma concentrations observed at 1.7 hours. Food slightly delays the time to peak plasma concentration to 2.5 hours but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased Cmax (19%). However, the magnitude of change is not clinically significant, so that Vildagliptin can be given with or without food. The absolute bioavailability is 85%.

Distribution

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

Biotransformation

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite (LAY 151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the glucuronide (BQS867) and the amide hydrolysis products (4% of dose). In vitro data in human kidney microsomes suggest that the kidney may be one of the major organs contributing to the hydrolysis of vildagliptin to its major inactive metabolite, LAY151. DPP-4 contributes partially to the hydrolysis of vildagliptin based on an in vivo study using DPP-4 deficient rats. Vildagliptin is not metabolized by CYP 450 enzymes to any quantifiable extent. Accordingly, the metabolic clearance of vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. In vitro studies demonstrated that vildagliptin does not inhibit/induce CYP 450 enzymes. Therefore, vildagliptin is not likely to affect metabolic clearance of co-medications metabolized by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

Elimination

Following oral administration of [14C] vildagliptin, approximately 85% of the dose was excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of the unchanged vildagliptin accounted for 23% of the dose after oral administration. After intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 and 13 l/h, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours.

Linearity/non-linearity

The Cmax for vildagliptin and the area under the plasma concentrations versus time curves (AUC) increased in an approximately dose proportional manner over the therapeutic dose range.

Characteristics in specific groups of patients

Gender

No clinically relevant differences in the pharmacokinetics of vildagliptin were observed between male and female healthy subjects within a wide range of age and body mass index (BMI). DPP-4 inhibition by vildagliptin is not affected by gender.

Elderly

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

Hepatic impairment

The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in patients with mild, moderate and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison with healthy subjects. The exposure to vildagliptin after a single dose in patients with mild and moderate hepatic impairment was decreased (20% and 8%, respectively), while the exposure to vildagliptin for patients with severe impairment 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 the hepatic disease and changes in the exposure to vildagliptin.

Renal impairment

A multiple-dose, open-label trial was conducted to evaluate the pharmacokinetics of the lower therapeutic dose of vildagliptin (50 mg once daily) in patients with varying degrees of chronic renal impairment defined by creatinine clearance (mild: 50 to <80 ml/min, moderate: 30 to < 50 ml / min and severe:< 30 ml / min) compared to normal healthy control subjects.
Vildagliptin AUC 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. AUC of the metabolites LAY151 and BQS867 increased on average about 1.5, 3 and 7-fold in patients with mild, moderate and severe renal impairment, respectively. 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 were approximately 2-3-fold higher than in patients with severe renal impairment.
Vildagliptin was removed by hemodialysis to a limited extent (3% over a 3-4 hour hemodialysis session starting 4 hours post dose).

Ethnic group

Limited data suggest that race does not have any major influence on vildagliptin pharmacokinetics.

Metformin Hydrochloride

Absorption

The absolute bioavailability of a Metformin Hydrochloride 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of Metformin Hydrochloride 500 to 1500 mg and 850 to 2550 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. At usual clinical doses and dosing schedules of Metformin Hydrochloride, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 µg/mL.
Peak plasma levels are approximately 20% lower dose of Metformin Hydrochloride; however, the extent of absorption (as measured by AUC) is comparable to Metformin Hydrochloride.

Effect of food:

Food decreases the extent of absorption and slightly delays the absorption of metformin, 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 time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of Metformin Hydrochloride with food, compared to the same tablet strength administered fasting.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of Metformin Hydrochloride 500 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Metabolism

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

Elimination

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin 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.

Renal Impairment

In patients with decreased renal function the plasma and blood half-life of metformin is prolonged, and the renal clearance is decreased.

Hepatic Impairment

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Geriatrics

Limited data from controlled pharmacokinetic studies of Metformin Hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. It appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Specific Populations

Renal Impairment

In patients with decreased renal function the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased.

Hepatic Impairment

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Geriatrics

Limited data from controlled pharmacokinetic studies of Metformin Hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. It appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatrics

After administration of a single oral Metformin Hydrochloride 500 mg tablet with food, geometric mean metformin Cmax and AUC differed less than 5% between pediatric type 2 diabetic patients (12-16 years of age) and gender-and weight-matched healthy adults (20-45 years of age), all with normal renal function.

Gender

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender (males=19, females=16).

Race

No studies of metformin pharmacokinetic parameters according to race have been performed.

6 Non – Clinical Properties

6.1 Animal Toxicology or Pharmacology

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 to 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.

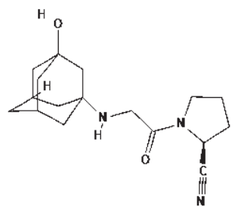
Metformin Hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 3 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin 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 a mutagenic potential of metformin in the following in vitro tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative. Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons.

7. Description

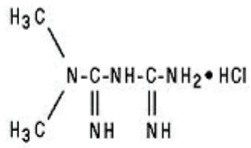
Vildagliptin

Vildagliptin is an oral anti-hyperglycemic agent (anti-diabetic drug) of the dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. Vildagliptin inhibits tee inactivation of GLP-1 and GIP byDPP-4, allowing GLP-1 and GIP to potentiate the secretion of insulin in the beta cells and suppress glucagon release by tee alpha cells of the islets of Langerhans in the pancreas. Vildagliptin has been shown to reduce hyperglycemia in type 2 diabetes mellites. Vildagliptin is identified by the chemical formula $C_{17}H_{25}N_3O_2$, molecular weight of 303.406 g/mol. The structure formula is



Metformin Hydrochloride

Metformin Hydrochloride contains the antihyperglycemic agent metformin, which is a biguanide, in the form of monohydrochloride. The chemical name of metformin hydrochloride is N,N-dimethylimidodicarbonimidic diamide hydrochloride. The structural formula is as shown below:



Metformin Hydrochloride molecular formula is C4H11N5 HCl and a molecular weight of 165.63. It is freely soluble in water and is practically insoluble in acetone, ether, and chloroform.

8. Pharmaceutical particulars

8.1 INCOMPATIBILITIES

Not Applicable

8.2 SHELF LIFE

Please refer details on blister/carton.

8.3 PACKAGING INFORMATION

Blister Pack of 15 Tablets.

8.4 STORAGE AND HANDLING INSTRUCTIONS:

Store protected from moisture, at a temperature not exceeding 25°C.

9. Patient Counselling Information

Vildagliptin & Metformin Hydrochloride Film coated tablet

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Vildagliptin/Metformin is and what it is used for
2. What you need to know before you take Vildagliptin/Metformin
3. How to take Vildagliptin/Metformin
4. Possible side effects
5. How to store Vildagliptin/Metformin

1. What is the Vildagliptin/Metformin and what it is used for

The active substances of Vildagliptin/Metformin, vildagliptin and metformin, belong to a group of medicines called "oral antidiabetics".
Vildagliptin/Metformin is used to treat adult patients with type 2 diabetes. This type of diabetes is also known as non- insulin-dependent diabetes mellitus. Vildagliptin/Metformin is used when diabetes cannot be controlled by diet and exercise alone and/or with other medicines used to treat diabetes (insulin or sulphonylureas).
Type 2 diabetes develops if the body does not make enough insulin or if the insulin that the body makes does not work as well as it should. It can also develop if the body produces too much glucagon.
Both insulin and glucagon are made in the pancreas. Insulin helps to lower the level of sugar in the blood, especially after meals. Glucagon triggers the liver to make sugar, causing the blood sugar level to rise.

How Vildagliptin/Metformin works

Both active substances, vildagliptin and metformin, help to control the level of sugar in the blood. The substance vildagliptin works by making the pancreas produce more insulin and less glucagon. The substance metformin works by helping the body to make better use of insulin. This medicine has been shown to reduce blood sugar, which may help to prevent complications from your diabetes.

2. What you need to know before you take Vildagliptin/Metformin

Do not take Vildagliptin/Metformin

- If you are allergic to vildagliptin, metformin or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic to any of these, talk to your doctor before taking Vildagliptin/Metformin.
- If you have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see "Risk of lactic acidosis" below) or ketoacidosis. Ketoacidosis is a condition in which substances called ketone bodies accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.
- If you have recently had a heart attack or if you have heart failure or serious problems with your blood circulation or difficulties in breathing which could be a sign of heart problems. if you have severely reduced kidney function.
- If you have a severe infection or are seriously dehydrated (have lost a lot of water from your body).
- If you are going to have a contrast x-ray (a specific type of x-ray involving an injectable dye).

Please also see information about this in section "Warnings and precautions"

- If you have liver problems. -
- If you drink alcohol excessively (whether every day or only from time to time).
- If you are breast-feeding (see also "Pregnancy and breast-feeding").

Warnings and precautions

Risk of lactic acidosis

Vildagliptin/Metformin may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease).

Talk to your doctor promptly for further instructions if:

- You are known to suffer form genetically inherited diseases affecting mitochondria (the energy producing components within cells) such as MELAS syndrome (Mitochondrial Encephalopathy, myopathy, Lactic acidosis and Stroke-like episodes) or Maternal inherited diabetes and deafness (MIDD).
- You have any of these symptoms after starting metformin: seizure, declined cognitive abilities, difficulty with body movements, symptoms indicating nerve damage (e.g. pain or numbness), migraine and deafness. If any of the above apply to you, talk to your doctor for further instructions.

Stop taking Vildagliptin/Metformin for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.
Stop taking Vildagliptin/Metformin and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.
Symptoms of lactic acidosis include:-

- Stomach ache (abdominal pain)
- Muscle cramps
- A general feeling of not being well with severe tiredness
- Difficulty in breathing
- Reduced body temperature and heartbeat.

Lactic acidosis is a medical emergency and must be treated in a hospital. Vildagliptin/Metformin is not a substitute for insulin. Therefore, you should not receive Vildagliptin/ Metformin for the treatment of type 1 diabetes. Talk to your doctor, pharmacist or nurse before taking Vildagliptin/Metformin if you have or have had a disease of the pancreas. Talk to your doctor, pharmacist or nurse before taking Vildagliptin/Metformin if you are taking an anti-diabetic medicine known as a sulphonylurea. Your doctor may want to reduce your dose of the sulphonylurea when you take it together with Vildagliptin/Metformin in order to avoid low blood glucose (hypoglycaemia). If you have previously taken vildagliptin but had to stop taking it because of liver disease, you should not take this medicine. Diabetic skin lesions are a common complication of diabetes. You are advised to follow the recommendations for skin and foot care that you are given by your doctor or nurse. You are also advised to pay particular attention to new onset of blisters or ulcers while taking Vildagliptin/Metformin. Should these occur, you should promptly consult your doctor. If you need to have major surgery you must stop taking Vildagliptin/Metformin during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Vildagliptin/Metformin. A test to determine your liver function will be performed before the start of Vildagliptin/Metformin treatment, at three-month intervals for the first year and periodically thereafter. This is so that signs of increased liver enzymes can be detected as early as possible. During treatment with Vildagliptin/Metformin, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or have worsening renal function. Your doctor will test your blood and urine for sugar regularly.

Children and adolescents

The use of Vildagliptin/Metformin in children and adolescents up to 18 years of age is not recommended.

Other medicines and Vildagliptin/Metformin

If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking Vildagliptin/Metformin before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Vildagliptin/Metformin. Tell your doctor if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of Vildagliptin/Metformin. It is especially important to mention the following:

- Glucocorticoids are generally used to treat inflammation
- Beta-2 agonists generally used to treat respiratory disorders
- Other medicines used to treat diabetes medicines which increase urine production (diuretics)
- Medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib)
- Certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists)
- Certain medicines affecting the thyroid, certain medicines affecting the nervous system, certain medicines used to treat angina (e.g. ranolazine).
- Certain medicines used to treat HIV infection (e.g. dolutegravir)
- Certain medicines used to treat a specific type of thyroid cancer (medullary thyroid cancer) (e.g. vandetanib)
- Certain medicines used to treat heartburn and peptic ulcers (e.g cimetidine).

Vildagliptin/Metformin with alcohol

Avoid excessive alcohol intake while taking Vildagliptin/Metformin since this may increase the risk of lactic acidosis (please see section "Warnings and precautions").
Pregnancy and breast-feeding-

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will discuss with you the potential risk of taking Vildagliptin/Metformin during pregnancy.
- Do not use Vildagliptin/Metformin if you are pregnant or breast-feeding (see also "Do not take Vildagliptin/Metformin").
- Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

If you feel dizzy while taking Vildagliptin/Metformin, do not drive or use any tools or machines.

3. How to take Vildagliptin/Metformin

The amount of Vildagliptin/Metformin that people have to take varies depending on their condition. Your doctor will tell you exactly the dose of Vildagliptin/Metformin to take. Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose is one film-coated tablet of either 50 mg/850 mg or 50 mg/1000 mg taken twice a day. If you have reduced kidney function, your doctor may prescribe a lower dose. Also if you are taking an anti-diabetic medicine known as a sulphonylurea your doctor may prescribe a lower dose. Your doctor may prescribe this medicine alone or with certain other medicines that lower the level of sugar in your blood.

When and how to take Vildagliptin/Metformin

- Swallow the tablets whole with a glass of water, Take one tablet in the morning and the other in the evening with or just after food. Taking the tablet just after food will lower the risk of an upset stomach.
- Continue to follow any advice about diet that your doctor has given you. In particular, if you are following a diabetic weight control diet, continue with this while you are taking Vildagliptin/Metformin.

If you take more Vildagliptin/Metformin than you should

If you take too many Vildagliptin/Metformin tablets, or if someone else takes your tablets, talk to a doctor or pharmacist immediately. Medical attention may be necessary. If you have to go to a doctor or hospital, take the pack and this leaflet with you.

If you forget to take Vildagliptin/Metformin

If you forget to take a tablet, take it with your next meal unless you are due to take one then anyway. Do not take a double dose (two tablets at once) to make up for a forgotten tablet.

If you stop taking Vildagliptin/Metformin

Continue to take this medicine as long as your doctor prescribes it so that it can continue to control your blood sugar. Do not stop taking Vildagliptin/Metformin unless your doctor tells you to. If you have any questions about how long to take this medicine, talk to your doctor. If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. You should stop taking Vildagliptin/Metformin and see your doctor immediately if you experience the following side effects:

- Lactic acidosis (very rare: may affect up to 1 user in 10,000): Vildagliptin/Metformin may cause a very rare, but very serious side effect called lactic acidosis. If this happens you must stop taking Vildagliptin/Metformin and contact a doctor or the nearest hospital immediately, as lactic acidosis may lead to coma.
- Angioedema (rare: may affect up to 1 in 1,000 people): Symptoms include swollen face, tongue or throat, difficulty swallowing, difficulty breathing, sudden onset of rash or hives, which may indicate a reaction called "angioedema"
- Liver disease (hepatitis) (uncommon: may affect up to 1 in 100 people): Symptoms include yellow skin and eyes, nausea, loss of appetite or dark-coloured urine, which may indicate liver disease (hepatitis).
- Inflammation of the pancreas (pancreatitis) (uncommon: may affect up to 1 in 100 people): Symptoms include severe and persistent pain in the abdomen (stomach area), which might reach through to your back, as well as nausea and vomiting.

Other side effects

Some patients have experienced the following side effects while taking Vildagliptin/Metformin:

- Common (may affect up to 1 in 10 people): sore throat, runny nose, fever, itchy rash, excessive sweating, joint pain, dizziness, headache, trembling that cannot be controlled, constipation, nausea (feeling sick), vomiting, diarrhoea, flatulence, heartburn, pain in and around the stomach (abdominal pain).
- Uncommon (may affect up to 1 in 100 people): tiredness, weakness, metallic taste, low blood glucose, loss of appetite, swollen hands, ankles or feet (oedema), chills, inflammation of the pancreas, muscle pain.
- Very rare (may affect up to 1 in 10 000 people): signs of a high level of lactic acid in the blood (known as lactic acidosis) such as drowsiness or dizziness, severe nausea or vomiting, abdominal pain, irregular heart beat or deep, rapid breathing; redness of the skin, itching; decreased vitamin B12 levels (paleness, tiredness, mental symptoms such as confusion or memory disturbances).

Since this product has been marketed, the following side effects have also been reported:
Frequency not known (cannot be estimated from the available data): localised peeling of skin or blisters, blood vessel inflammation (vasculitis) which may result in skin rash or pointed, flat, red, round spots under the skin's surface or bruising.

5. How to store Vildagliptin/Metformin

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the blister and carton after "EXP". The expiry date refers to the last day of that month.
- Store protected from moisture, at a temperature not exceeding 25°C.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

License No.: 34/UA/2013 **Dated:** 10/10/2022

12. DATE OF REVISION: NA

Marketed by:

AMERICAN REMEDIES ©
Care & Cure with Research
American Remedies Healthcare Pvt. Ltd.
(An ISO 9001-2015 Certified Company)
Gala No. 105 to 111, 1st Flr., Bldg. No. E-15/A,
Harihar Complex, Bhiwandi, Mumbai - 421302
E-mail: info@americanremedies.in
ICO: American Remedies LLC, DE, USA

© Copyright

Scan for Batch Certificate

SIZE : 420X330 MM FOLD SIZE : 105X82.5MM / 54 GSM MAPLITHO PAPER