BIOVILDA™-M

Each uncoated tablet contains

Vildagliptin – 50 mg
Metformin HCl IP – 500 mg

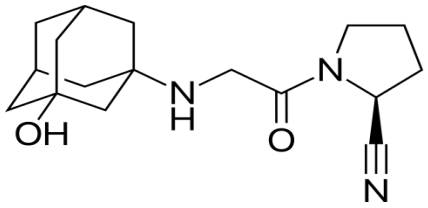
DESCRIPTION

BIOVILDA-M combines two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: vildagliptin, a member of the DPP-4 (dipeptidyl-peptidase-4) inhibitor class and metformin hydrochloride, a member of the biguanide class.

PHARMACEUTICAL DESCRIPTION

VILDAGLIPTIN:

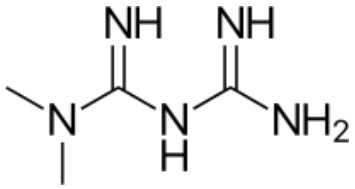
Generic name: Vildagliptin
Chemical name: (2*S*)-1-{2-[(3-hydroxy-1-adamantyl)amino]acetyl}pyrrolidine-2-carbonitrile
Molecular mass: 303.399 g/mol
Structural formula:



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

METFORMIN:

Generic name: Metformin HCl
Chemical name: N, N-Dimethyl imidodi carbonimidic diamide
Molecular mass: 129.16364 g/mol
Structural formula:



Empirical formula - $C_4H_{11}N_5$

PHARMACODYNAMIC PROPERTIES & MECHANISM OF ACTION

The efficacy and safety of the separate components have been previously established and the co-administration of the separate components has been evaluated for efficacy and safety in clinical studies. These clinical studies established an added benefit of

vildagliptin in patients with inadequately controlled type 2 diabetes while on metformin hydrochloride therapy.

Vildagliptin

Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor that improves glycemic control. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

The administration of vildagliptin results in rapid and complete inhibition of DPP-4 activity. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. 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 50 to 100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function. The degree of improvement in beta-cell function is dependent on the initial degree of impairment; in non-diabetic (normal glycemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion. The reduction in inappropriate glucagon during meals in turn attenuates insulin resistance. The enhanced increase in the insulin/glucagon ratio during hyperglycemia due to increased incretin hormone levels, it results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycemia.

The known effect of increased GLP-1 levels to delay gastric emptying is not observed with vildagliptin treatment. In addition, a reduction in postprandial lipemia that is not associated with vildagliptin's incretin- mediated effect to improve islet function has been observed.

Metformin

Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase and increase the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Unlike sulfonylureas, metformin hydrochloride does not cause hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances), and does not cause hyperinsulinemia. With metformin hydrochloride therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

In humans, metformin hydrochloride has favourable effects on lipid metabolism, independent of its action on glycemia. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride

reduces total cholesterol, low-density lipoprotein cholesterol (LDLc) and triglyceride levels.

PHARMACOKINETIC PROPERTIES

Absorption

In the bioequivalence studies of BIOVILDA M at two dose strengths (50 mg/500 mg ,and 50 mg/1,000 mg), versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses, the area under the curve (AUC) and maximum concentration (C_{max}) of both the vildagliptin component and the metformin hydrochloride component of the BIO-VILDA™-M 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 BIO-VILDA™-M. The C_{max} and AUC of the metformin hydrochloride component from BIO-VILDA™-M were decreased by 26% and 7%, respectively when given with food. The absorption of metformin hydrochloride was also delayed as reflected by the T_{max} (2.0 to 4.0 hours) when given with food. These changes in C_{max} and AUC are consistent but lower than those observed when metformin hydrochloride was given alone under fed conditions. The effects of food on the pharmacokinetics of both the vildagliptin component and metformin hydrochloride component of BIOVILDA M were similar to the pharmacokinetics of vildagliptin and metformin hydrochloride when given alone with food.

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. A peak plasma concentration 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

The absolute bioavailability of a 500mg metformin hydrochloride tablet given under fasting conditions is approximately 50 to 60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 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.

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 (V_{SS}) is 71 liters, suggesting extravascular distribution.

Metformin

Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride, steady state plasma concentrations of metformin hydrochloride are reached within 24 to 48 hours and are generally <1 microgram/mL. During controlled clinical studies of metformin hydrochloride, maximum metformin hydrochloride plasma levels did not exceed 5 micrograms/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 of 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 rates. 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

Metformin 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 unchanged vildagliptin accounts for 23% of the dose after oral administration. After 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

Intravenous single-dose studies in normal subjects demonstrate that metformin hydrochloride 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.

INDICATION

Type 2 diabetes mellitus

For patients of age 18 years and above with Type 2 diabetes mellitus (T2DM):

BIOVILDA M is indicated as an adjunct to diet and exercise to improve glycemic control in patients whose diabetes is not adequately controlled on metformin hydrochloride or vildagliptin alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets.

BIO-VILDA™-M 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 and a sulfonylurea.

BIO-VILDA™-M 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 alone do not provide adequate glycemic control.

BIO-VILDA™-M is also indicated for the treatment of type 2 diabetes mellitus having HbA1c > 8% where diabetes is not adequately controlled by diet and exercise alone.

CONTRAINDICATIONS

Hypersensitivity

BIO-VILDA™-M is contraindicated in patients with known hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients.

Patients with Renal Impairment

BIO-VILDA™-M is contraindicated in patients with severe renal impairment (GFR <30 ml/min).

Congestive Heart Failure

BIO-VILDA™-M is contraindicated in patients with congestive heart failure requiring pharmacological treatment.

Metabolic Acidosis

BIO-VILDA™-M 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.

DOSAGE ANDADMINISTRATION

General

The use of antihyperglycemic therapy in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability. When using BIO-VILDA™-M do not exceed the maximum daily dose of vildagliptin (100 mg). The recommended starting dose of BIO-VILDA™-M should be based on the patient's condition and/or current regimen of vildagliptin and/or metformin hydrochloride.

Starting Dose for Patients Inadequately Controlled on Vildagliptin Monotherapy

Based on the usual starting doses of metformin hydrochloride (500 mg twice daily), BIO-VILDA™-M 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 Hydrochloride Monotherapy

Based on the patient's current dose of metformin hydrochloride, BIO-VILDA™-M may be initiated at either the 50 mg/500 mg, or 50 mg/1,000 mg tablet strength twice daily.

Starting Dose for Patients Switching from Combination Therapy of Vildagliptin plus Metformin Hydrochloride as Separate Tablets

BIO-VILDA™-M may be initiated with either the 50 mg/500 mg, mg or 50 mg/1,000 mg tablet strength based on the dose of vildagliptin or metformin already being taken.

Starting Dose for Treatment Naïve Patients

In treatment naïve patients, BIO-VILDA™-M may be initiated at 50 mg/500 mg once daily and gradually titrated to a maximum dose of 50mg/1000 mg twice

Renal Impairment

A GFR should be assessed before initiation of treatment with metformin-containing products (such as BIO-VILDA™-M) 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 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-containing products (such as BIO-VILDA™-M) in patients with GFR<60 ml/min. BIO-VILDA™-M is contraindicated in patients with GFR <30 ml/min because of its metformin component.

The following dosing recommendations apply to metformin and vildagliptin, used separately or in combination, in patients with renal impairment. If no adequate strength of BIO-VILDA™-M 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	Vildagliptin
60 – 89	Maximum daily dose is 3000 mg*. Dose reduction may be considered if renal functiondeclines.	Maximum daily dose is 100 mg.
45 – 59	Starting dose should not be more than 1000mg with a maximum daily dose of 2000 mg*.	Maximum daily dose is 50 mg.

30 – 44	Starting dose should not be more than 500mg with a maximum daily dose of 1000 mg.
<30	Metformin is contraindicated.

*If metformin doses higher than those achievable with BIO-VILDA™-M alone are considered necessary.

Hepatic Impairment

BIO-VILDA™-M is not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment ALT or AST >2.5x the ULN (upper limit of normal).

Pediatric

The safety and effectiveness of BIO-VILDA™-M in pediatric patients have not been established. Therefore, BIO-VILDA™-M is not recommended for use in children below 18 years of age.

Geriatric

As metformin is excreted via the kidneys, and elderly patients tend to exhibit decreased renal function, elderly patients taking metformin-containing products (such as BIO-VILDA™-M) should have their renal function monitored regularly. The dosage of BIO-VILDA™-M for elderly patients should be adjusted based on renal function.

METHOD OF ADMINISTRATION

For oral use, BIO-VILDA™-M should be given with meals to reduce the gastrointestinal side effects associated with metformin hydrochloride. If a dose of BIO-VILDA™-M is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

UNDESIRABLE EFFECTS

The data presented here relate to the administration of vildagliptin and metformin as a free or fixed dose combination. Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an ACE inhibitor. The majority of events was mild in severity and resolved with ongoing vildagliptin treatment.

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. In data from controlled monotherapy and add-on therapy studies lasting up to 24 weeks, 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.
In clinical studies with the combination of vildagliptin + metformin, 0.4% of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily + metformin treatment group, and no withdrawal due to adverse reactions was reported in either the vildagliptin 50 mg twice daily + metformin or the placebo + metformin treatment groups.
In clinical studies, the incidence of hypoglycemia was uncommon in patients receiving vildagliptin 50 mg once daily in combination with metformin (0.9%), patients receiving vildagliptin 50 mg twice daily in combination with metformin (0.5%) and in patients receiving placebo and metformin (0.4%). No severe hypoglycemic events were reported in the vildagliptin arms.
Vildagliptin is weight neutral when administered in combination with metformin.
Gastrointestinal adverse reactions including diarrhea and nausea, are known to occur very commonly during the introduction of metformin hydrochloride. In the vildagliptin monotherapy clinical program (n =2,264) where vildagliptin was administered 50 mg once daily, 50 mg twice daily, or 100 mg once daily, the rate of diarrhea was 1.2%, 3.5% and 0.8 %, respectively, and the rate of nausea was 1.7%, 3.7% and 1.7%, respectively, as compared to 2.9% for both in the placebo group (n = 347) and 26.2% and 10.3%, respectively, in the metformin hydrochloride group (n = 252).
Overall, gastrointestinal symptoms were reported in 13.2% (50 mg once daily or twice daily) of patients treated with the combination of vildagliptin and metformin hydrochloride compared to 18.1% of patients treated with metformin hydrochloride alone.

Summary of Adverse Drug Reactions from Clinical Studies

Adverse reactions reported in patients who received vildagliptin in double-blind studies as an add-on to metformin and as monotherapy 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).

Table 2: Other adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=233) or 50 mg twice daily (n=183) as add-on therapy to metformin compared to placebo plus metformin in double-blind studies

Nervous system disorders		
	Common	Tremor, dizziness, headache

Long-term clinical studies of up to more than 2 years in duration, did not show any additional safety signals or unforeseen risks when vildagliptin was added on to metformin.

When vildagliptin was studied as an initial combination therapy with metformin, no additional safety signals or unforeseen risks were observed.

Combination with Insulin

In controlled clinical studies using vildagliptin 50 mg twice daily in combination with insulin, with or without concomitant metformin, the overall incidence of withdrawals 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 vs 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).

Table 3: Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with insulin (with or without metformin (n= 371))

Nervous system disorders		
	Common	Headache
Gastrointestinal disorders		
	Common	Nausea, gastroesophageal reflux disease
	Uncommon	Diarrhea, flatulence
General disorders and administration site conditions		
	Common	Chills
Investigations		
	Common	Blood glucose decreased

Combination with SU

There were no cases of withdrawal reported due to adverse reactions in the vildagliptin + metformin + glimepiride treatment group versus 0.6% in the placebo + metformin + glimepiride treatment group.

The incidence of hypoglycemia was common in both treatment groups (5.1% for the vildagliptin + metformin + glimepiride vs. 1.9 % for the placebo + metformin + 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).

Table 4: Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with metformin and SU (n=157)

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

Vildagliptin

Adverse reactions for vildagliptin component from monotherapy double blind studies are presented in Table 5.

Table 5: Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=409) or 50 mg twice daily (n=1,373) as monotherapy in double-blind studies

Nervous system disorders		
	Common	Dizziness
	Uncommon	Headache
Gastrointestinal disorders		
	Uncommon	Constipation
General disorders and administration site conditions		
	Uncommon	Edemaperipheral

None of the adverse reactions reported for the vildagliptin monotherapy were observed at clinically significantly higher rates when vildagliptin was administered concomitantly with metformin.

The overall incidence of withdrawal from monotherapy studies 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. Long term clinical studies of up to 2 years did not show any additional safety signals or unforeseen risks with vildagliptin monotherapy.

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 BIO-VILDA™-M 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.

Hepatitis, reversible upon drug discontinuation
Urticaria, bullous and exfoliative skin lesions, including bullous pemphigoid
Pancreatitis
Arthralgia, sometimes severe

Metformin

Known adverse reactions for the metformin component are summarized in Table 6.

Table 6: Known adverse reactions for metformin

Metabolism and Nutrition disorders		
	Very common	Decreased appetite
	Very Rare	Lactic acidosis
Nervous system disorders		
	Common	Dysgeusia
Gastrointestinal disorders		
	Very Common	Flatulence, nausea, vomiting, diarrhea, abdominal pain
Hepatobiliary disorders		
	Very Rare	Hepatitis**
Skin and subcutaneous tissue disorders		
	Very rare	Skin reactions such as erythema, pruritus, urticaria
Investigations		
	Very rare	Decrease of vitamin B12 absorption*, Liver function test

*A decrease of vitamin B12 absorption with decrease of serum levels has very rarely

been observed in patients treated long-term with metformin and appears to generally not be of clinical significance. Consideration of such etiology is recommended if a patient presents with megaloblastic anemia.

**Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported. Gastrointestinal adverse effects occur most frequently during initiation of therapy and resolve spontaneously in most cases.

If you experience any side-effects, talk to your doctor or pharmacist or write to info@bioslab.co.in
By reporting side-effects, you can help provide more information on the safety of this product.

OVERDOSAGE

Vildagliptin:

In healthy subjects (seven to fourteen subjects per treatment group), BIO-VILDA™-M 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 feet and hands, 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. BIO-VILDA™-M is not dialyzable; however the major hydrolysis metabolite (LAY151) can be removed by hemodialysis.

Metformin:

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 hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin hydrochloride overdose cases. Metformin hydrochloride 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 hydrochloride overdosage is suspected. In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

INCOMPATIBILITY: Notapplicable.

WARNINGS AND PRECAUTIONS

Drug Interactions

No clinically relevant pharmacokinetic interactions have been observed when

vildagliptin (100 mg once daily) was co- administered with metformin hydrochloride (1,000 mg once daily). Drug interactions for each component of BIO-VILDA™-M have 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 and metformin).

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, and metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.

Metformin:
Furosemide
Furosemide increased C_{max} and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreased C_{max}, blood AUC of furosemide, with no change in renal clearance of furosemide.
Nifedipine
Nifedipine increased absorption, C_{max} and AUC of metformin, and increased excretion of metformin in urine. Metformin had minimal effects on nifedipine.
Glyburide
Glyburide produced no changes in metformin PK/PD parameters. Decreases in C_{max}, blood AUC of glyburide were observed, but were highly variable. Therefore, the clinical significance of this finding was unclear.
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 by competing for common renal tubular transport systems. Thus, with cimetidine increases in metformin plasma/blood concentration and AUC were observed to be 60% and 40% respectively. Metformin had no effect on cimetidine PK. Although such interactions remain theoretical (except for cimetidine), careful monitoring of patients and doses of metformin-containing products (such as BIO-VILDA™-M) and such medications are recommended.

Administration of intravascular iodinated contrast materials

Metformin-containing products (such as BIO-VILDA™-M) 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- containing products (such as BIO-VILDA™-M), 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 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. Avoid consumption of alcohol and medicinal products containing alcohol.

Renal Impairment

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

Hepatic Impairment

Vildagliptin is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >2.5x the 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 BIO-VILDA™-M. LFTs should be monitored during BIO-VILDA™-M 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 BIO-VILDA™-M is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue BIO-VILDA™-M and contact their physician immediately. Following withdrawal of treatment with BIO-VILDA™-M and LFT normalization,
BIO-VILDA™-M should not be reinitiated.
BIO-VILDA™-M 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 hydrochloride, metformin-containing products (such as BIO-VILDA™-M) should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Pregnancy

There is insufficient experience with BIO-VILDA™-M in pregnant women. Embryo-fetal development (teratology) studies have been conducted in rats and rabbits with the combination of vildagliptin and metformin hydrochloride in a 1:10 ratio and produced no evidence of teratogenicity in either species. BIO-VILDA™-M 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.

Lactation

No studies have been conducted with the combined components of BIO-VILDA™-M. Metformin is excreted into human breast milk. It is not known whether vildagliptin is excreted in human milk or not. BIO-VILDA™-M should not be administered to breast-feeding women.

General

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

Heart Failure

A clinical study 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 studies in patients with NYHA functional class IV and therefore use is not recommended in these patients.

Lactic Acidosis

Lactic acidosis is a very rare but serious metabolic complication that most often occurs with acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs with acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (e.g. due to severe diarrhea or vomiting, fever or reduced fluid intake), the patient should stop taking metformin-containing products (such as BIO-VILDA™-M) 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-containing products (such as BIO-VILDA™-M). 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 -containing products (such as BIO-VILDA™-M) 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-containing products (such as BIO-VILDA™-M) 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-containing products (such as BIO-VILDA™-M), the medication should be promptly discontinued.

Surgical Procedures
Metformin-containing products (such as BIO-VILDA™-M) 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 hydrochloride on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving metformin-containing products (such as BIO-VILDA™-M). Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Vitamin B_{12} Levels
Metformin has been associated with a decrease in serum vitamin B_{12} levels without clinical manifestations, in approximately 7% of patients. Such a decrease is very rarely

associated with anemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride and/or vitamin B_{12} supplementation. Measurement of hematological parameters on at least an annual basis is advised for patients receiving metformin-containing products (such as BIO-VILDA™-M) and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (e.g. those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} 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 BIO-VILDA™-M 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, BIO-VILDA™-M must be stopped immediately and appropriate measures initiated.

Hypoglycemia

Hypoglycemia does not usually occur in patients receiving BIO-VILDA™-M 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 BIO-VILDA™-M and temporarily administer insulin. BIO-VILDA™-M may be reinstituted after the acute episode is resolved.

SPECIAL POPULATIONS:

Renal Impairment

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. The AUC of the metabolites LAY151 increased 1.6, 3.2 and 7.3-fold and that of BQS867 increased on average about 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 2-3-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).

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin hydrochloride is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

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 decreased (20% and 8%, respectively), while the exposure to vildagliptin for subjects with severe impairment 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 >2.5x the ULN. No pharmacokinetic studies of metformin hydrochloride have been conducted in subjects with hepatic impairment.

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.

Metformin hydrochloride pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin hydrochloride was comparable in males and females.

Obesity

BMI does not show any impact on the pharmacokinetic parameters of vildagliptin.

DPP-4 inhibition by vildagliptin was unaffected by BMI.

Geriatric

In otherwise healthy elderly subjects (≥70 years), the overall exposure to vildagliptin (100 mg once daily) 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.

Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin hydrochloride is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function.

BIO-VILDA™-M treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Pediatric

No pharmacokinetic data available.

Ethnicity

There was no evidence that ethnicity affects the pharmacokinetics of vildagliptin. No studies of metformin hydrochloride pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin hydrochloride in patients with type 2 diabetes, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51) and Hispanics (n=24).

STORAGE CONDITION:

- Protect from moisture.
- BIOVILDA M should not be used after the date marked "EXP" on the pack.
- BIOVILDA M must be kept out of reach and sight of children.

PRESENTATION: Vildagliptin 50 mg + Metformin HCl IP 500 mg Tablets

PACKING: 1*10 TAB

BiosLab® inspired by life

BIOS LAB PVT. LTD.

Gujarat-India
www.bioslab.co.in