To be sold by retail on the prescription of a Registered Medical Practitioner only.

VILDAGLIPTIN AND METFORMIN HYDROCHLORIDE TABLETS IP 50MG/500MG, 50MG/850MG AND 50MG/1000MG

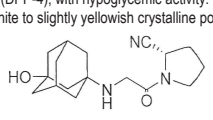
Vilumet 50/500, 50/850 & 50/1000

COMPOSITION

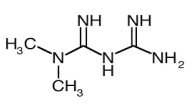
Vildagliptin 50 mg and Metformin Hydrochloride 500 mg Tablets IP
Each Film Coated Tablet Contains
Vildagliptin IP .... 50 mg
Metformin Hydrochloride IP ....500 mg
Colours: Titanium Dioxide IP Ferric Oxide Yellow USP NF Ferric Oxide Red USP NF
Vildagliptin 50 mg and Metformin Hydrochloride 850 mg Tablets IP
Each Film Coated Tablet Contains
Vildagliptin IP .... 50 mg
Metformin Hydrochloride IP ....850 mg
Colours: Titanium Dioxide IP Ferric Oxide Yellow USP NF
Vildagliptin 50 mg and Metformin Hydrochloride 1000 mg Tablets IP
Each Film Coated Tablet Contains
Vildagliptin IP .... 50 mg
Metformin Hydrochloride IP ....1000 mg
Colours: Titanium Dioxide IP Ferric Oxide Yellow USP NF

DRUG DESCRIPTION

Vildagliptin is a cyanopyrrolidine-based, orally bioavailable inhibitor of dipeptidyl peptidase 4 (DPP-4), with hypoglycemic activity. It is (2S)-1-[2-[(3-hydroxy1-adamantyl) amino]acetyl]pyrrolidine-2-carbonitrile. The empirical formula of vildagliptin is $C_{17}H_{25}N_3O_2$. Its molecular weight is 303.40 g/mol. It is available as white to slightly yellowish crystalline powder which is soluble in water, sparingly soluble in tetrahydrofuran and in soluble in cyclohexane. Its chemical structure:



Metformin Hydrochloride is the hydrochloride salt of the biguanide metformin with **antihyperglycemic** activity. It is 3-(diaminomethylidene)-1,1-dimethylguanidine;hydrochloride. The empirical formula of metformin hydrochloride is C4H11N5. HCl Its molecular weight is 165.6 g/mol. Its chemical structure:



DOSAGE FORMS AND STRENGTHS

Film coated tablets; 50/500mg, 50/850 and 50/1000 mg

INDICATIONS

Vildagliptin and Metformin hydrochloride tablets are indicated in the treatment of type 2 diabetes mellitus:

- Vildagliptin and Metformin hydrochloride tablets are indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets.
- Vildagliptin and Metformin hydrochloride tablets are indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulphonylurea.
- Vildagliptin and Metformin hydrochloride tablets are indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control.

DOSE AND METHOD OF ADMINISTRATION

Adults with normal renal function (GFR ≥ 90 ml/min)

The dose of antihyperglycaemic therapy with Vildagliptin/Metformin hydrochloride tablets should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Vildagliptin/Metformin hydrochloride may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening.

-For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy:

The starting dose of Vildagliptin/Metformin hydrochloride tablets should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken.

- For patients switching from co-administration of vildagliptin and metformin as separate tablets:

Vildagliptin/Metformin hydrochloride should be initiated at the dose of vildagliptin and metformin already being taken.

- For patients inadequately controlled on dual combination with metformin and a sulphonylurea

The doses of Vildagliptin/Metformin hydrochloride tablets should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Vildagliptin/Metformin hydrochloride tablet is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.

- For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin:

The dose of Vildagliptin/Metformin hydrochloride tablets should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established.

Method of administration

Oral use.

Taking Vildagliptin/Metformin hydrochloride tablets with or just after food may reduce gastrointestinal symptoms associated with metformin.

USE IN SPECIAL POPULATIONS

Pregnancy

There are no adequate data from the use of Vildagliptin/Metformin in pregnant women. For vildagliptin studies in animals have shown reproductive toxicity at high doses. For metformin, studies in animals have not shown reproductive toxicity. Studies in animals performed with vildagliptin and metformin have not shown evidence of teratogenicity, but foetotoxic effects at maternotoxic doses. The potential risk for humans is unknown. Vildagliptin/ Metformin should not be used during pregnancy.

Breast-feeding

Studies in animals have shown excretion of both metformin and vildagliptin in milk. It is unknown whether vildagliptin is excreted in human milk, but metformin is excreted in human milk in low amounts. Due to both the potential risk of neonate hypoglycaemia related to metformin and the lack of human data with vildagliptin, Vildagliptin/Metformin should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted for Vildagliptin/Metformin.

Elderly (≥ 65 years)

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking Vildagliptin/Metformin hydrochloride tablets should have their renal function monitored regularly.

Renal impairment

A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR<60 ml/min.

If no adequate strength of Vildagliptin/Metformin hydrochloride tablets is available, individual monocomponents should be used instead of the fixed dose combination.

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

Hepatic impairment

Vildagliptin/Metformin hydrochloride tablets should not be used in patients with hepatic impairment, including those with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN).

Pediatric population

Vildagliptin/Metformin hydrochloride tablets are not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Vildagliptin/Metformin tablets in children and adolescents (< 18 years) have not been established. No data are available.

CONTRAINDICATIONS

Hypersensitivity to the active substances or to any of the excipients listed in
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (GFR < 30 ml/min)
- Acute conditions with the potential to alter renal function, such as:
  - dehydration,
  - severe infection,
  - shock,
  - intravascular administration of iodinated contrast agents
- Acute or chronic disease which may cause tissue hypoxia, such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock
- Hepatic impairment
- Acute alcohol intoxication, alcoholism
- Breast-feeding

WARNINGS AND PRECAUTIONS

General

Vildagliptin/Metformin hydrochloride is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes.

Lactic acidosis

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

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

Administration of iodinated contrast agents

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

Renal function

GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR < 30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function.

Hepatic impairment

Patients with hepatic impairment, including those with pre-treatment ALT or AST > 3x ULN, should not be treated with Vildagliptin/Metformin hydrochloride.

Liver enzyme monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with Vildagliptin/Metformin hydrochloride in order to know the patient's baseline value. Liver function should be monitored during treatment with Vildagliptin/Metformin hydrochloride at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent LFTs until the abnormality(ies) return(s) to normal. Should an increase in AST or in ALT of 3x ULN or greater persist, withdrawal of Vildagliptin/Metformin hydrochloride therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Vildagliptin/Metformin hydrochloride.
Following withdrawal of treatment with Vildagliptin/Metformin hydrochloride and LFT normalisation, treatment with Vildagliptin/Metformin hydrochloride should not be re-initiated.

Skin disorders

Skin lesions, including blistering and ulceration have been reported with vildagliptin in extremities of monkeys in nonclinical 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 postmarketing 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.

Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

DRUG INTERACTIONS

There have been no formal interaction studies for Vildagliptin/Metformin tablets. The following statements reflect the information available on the individual active substances.

Vildagliptin

Vildagliptin has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate and does not inhibit or induce CYP 450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes.

Results from clinical trials conducted with the oral antidiabetics pioglitazone, metformin and glyburide in combination with vildagliptin have shown no clinically relevant pharmacokinetic interactions in the target population.

Drug-drug interaction studies with digoxin (P-glycoprotein substrate) and warfarin (CYP2C9 substrate) in healthy subjects have shown no clinically relevant pharmacokinetic interactions after co-administration with vildagliptin.

Drug-drug interaction studies in healthy subjects were conducted with amlodipine, ramipril, valsartan and simvastatin. In these studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin.

However, this has not been established in the target population.

Combination with ACE inhibitors

There may be an increased risk of angioedema in patients concomitantly taking ACE inhibitors.
As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

Metformin

Combinations not recommended

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents

Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable

Cationic active substances

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

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.
Glucocorticoids, beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment. If necessary, the dosage of Vildagliptin/Metformin tablets may need to be adjusted during concomitant therapy and on its discontinuation.

Angiotensin converting enzyme (ACE) inhibitors may decrease the blood glucose levels. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

UNDESIRABLE EFFECTS

The data presented here relate to the co-administration of vildagliptin and metformin, where vildagliptin has been added to metformin. There have been no studies of metformin added to vildagliptin.

Summary of the safety profile

The majority of adverse reactions were mild and transient, not requiring treatment discontinuations. No association was found between adverse reactions and age, ethnicity, duration of exposure or daily dose.
Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function returned to normal after discontinuation of treatment. The elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.
Rare cases of angioedema have been reported on vildagliptin. A greater proportion of cases were reported when vildagliptin was administered in combination with an ACE inhibitor. The majorities of events were mild in severity and resolved with ongoing vildagliptin treatment.

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 by system organ class and absolute frequency. Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reactions reported in patients who received vildagliptin 100 mg daily as add-on therapy to Metformin.

Metabolism and nutrition disorders	
Common	Hypoglycaemia
Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness
Un common	Fatigue

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Artwork Information		Specification for Printed Leaflet	
		Test	Specification
Brand Name	Vilumet 50/500, 50/850 & 50/1000	Substrate	Bible Paper
Generic Name	Vildagliptin and Metformin Hydrochloride Tablets IP 50 mg/500 mg	GSM	40 ± 10%
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Version	00	Reviewed by	Avinash
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Customer	MSN Labs Peru S.A.C.		
Folding Type	Booklet with glue		

*Pharma code position is not fixed, so it may vary based on the printer's requirement.

Gastrointestinal disorders	
Common	Nausea

Combination with a sulphonylurea

Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with metformin and a sulphonylurea

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

Combination with insulin

Adverse reactions reported in patients who received vildagliptin 100 mg daily in combination with insulin (with or without metformin)

Metabolism and nutrition disorders	
Common	Decreased blood glucose
Nervous system disorders	
Common	Headache, chills
Gastrointestinal disorders	
Common	Nausea, gastro-oesophageal reflux disease
Uncommon	Diarrhoea, flatulence

Additional information on the individual active substances of the fixed combination Vildagliptin

Adverse reactions reported in patients who received vildagliptin

Infections and infestations	
Very rare	Upper respiratory tract infection
Very rare	Nasopharyngitis
Metabolism and nutrition disorders	
Uncommon	Hypoglycaemia
Nervous system disorders	
Common	Dizziness
Uncommon	Headache
Vascular disorders	
Uncommon	Oedema peripheral
Gastrointestinal disorders	
Uncommon	Constipation
Musculoskeletal and connective tissue disorders	
Uncommon	Arthralgia

Metformin

Adverse reactions for metformin component

Metabolism and nutrition disorders	
Very rare	Decrease of vitamin B12 absorption and lactic acidosis*
Nervous system disorders	
Common	Metallic taste
Gastrointestinal disorders	
Very common	Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite
Hepatobiliary disorders	
Very rare	Liver function test abnormalities or hepatitis**
Skin and subcutaneous tissue disorders	
Very rare	Skin reactions such as erythema, pruritus and urticaria

*A decrease in vitamin B12 absorption with decrease in serum levels has been very rarely observed in patients treated long-term with metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.
**Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.

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

Post-marketing experience

Post-marketing adverse reactions

Gastrointestinal disorders	
Not known	Pancreatitis
Hepatobiliary disorders	
Not known	Hepatitis (reversible upon discontinuation of the medicinal product) Abnormal liver function tests (reversible upon discontinuation of the medicinal product)
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Skin and subcutaneous tissue disorders	
Not known	Urticaria Exfoliative and bullous skin lesions, including bullous pemphigoid

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

OVERDOSE

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

Vildagliptin

Information regarding overdose with vildagliptin is limited.

Symptoms

Information on the likely symptoms of overdose with vildagliptin was taken from a rising dose tolerability study in healthy subjects given vildagliptin for 10 days. At 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), AST, C-reactive protein (CRP) and myoglobin levels. Three other subjects experienced oedema of the feet, with paraesthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product.

Metformin

A large overdose of metformin (or co-existing risk of lactic acidosis) may lead to lactic acidosis, which is a medical emergency and must be treated in hospital.

Management

The most effective method of removing metformin is haemodialysis. However, vildagliptin cannot be removed by haemodialysis, although the major hydrolysis metabolite (LAY 151) can. Supportive management is recommended.

PHARMACODYNAMIC PROPERTIES

Mechanism of action

Vildagliptin/Metformin hydrochloride tablets combines two antihyperglycaemic agents with complimentary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: vildagliptin, a member of the islet enhancer class, and metformin hydrochloride, a member of the biguanide class. Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor. Metformin acts primarily by decreasing endogenous hepatic glucose production.

Pharmacodynamics

Vildagliptin

Vildagliptin acts primarily by inhibiting DPP-4, the enzyme responsible for the degradation of the incretin hormones GLP- 1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide). The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 and GIP.

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.

Metformin

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia or increased weight gain. Metformin may exert its glucose-lowering effect via three mechanisms:
- by reduction of hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis;
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation;
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase and increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4). In humans, independently of its action on glycaemia, metformin has favorable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces serum levels of total cholesterol, LDL cholesterol and triglycerides.

Cardiovascular risk

Vildagliptin treatment was not associated with an increase in cardiovascular risk versus comparators.

Paediatric population

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

PHARMACOKINETIC PROPERTIES

Vildagliptin/Metformin

Absorption

Bioequivalence has been demonstrated between Vildagliptin/Metformin hydrochloride at three dose strengths (50 mg/500 mg, 50 mg/850 mg and 50 mg/1000 mg) versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses. Food does not affect the extent and rate of absorption of vildagliptin from Vildagliptin/Metformin hydrochloride. The rate and extent of absorption of metformin from Vildagliptin/Metformin hydrochloride 50 mg/1000 mg were decreased when given with food as reflected by the decrease in C_{max} by 26%, AUC by 7% and delayed T_{max} (2.0 to 4.0 h). The following statements reflect the pharmacokinetic properties of the individual active substances of Vildagliptin/Metformin hydrochloride.

Vildagliptin

Absorption

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

Distribution

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

Biotransformation

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

Elimination

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

Linearity/non-linearity

The C_{max} 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 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.

Age: 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 not considered to be clinically relevant, however. DPP-4 inhibition by vildagliptin is not affected by age. Hepatic impairment: In subjects with mild, moderate or severe hepatic impairment (Child-Pugh A-C) there were no clinically significant changes (maximum ~30%) in exposure to vildagliptin.

Renal impairment: In subjects with mild, moderate, or severe renal impairment, systemic exposure to vildagliptin was increased (C_{max} 8-66%; AUC 32-134%) and total body clearance was reduced compared to subjects with normal renal function.
Ethnic group: Limited data suggest that race does not have any major influence on vildagliptin pharmacokinetics.

Metformin

Absorption

After an oral dose of metformin, the maximum plasma concentration (C_{max}) is achieved after about 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/ml, even at maximum doses. Food slightly delays and decreases the extent of the absorption of metformin. Following administration of a dose of 850 mg, the plasma peak concentration was 40% lower, AUC was decreased by 25% and time to peak plasma concentration was prolonged by 35 minutes. The clinical relevance of this decrease is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The mean volume of distribution (Vd) ranged between 63-276 liters.

Biotransformation

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

Elimination

Metformin is eliminated by renal excretion. Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

INCOMPATIBILITIES

Not applicable.

PACKING INFORMATION

10's & 15's Alu-Alu blister pack.

STORAGE AND HANDLING INFORMATION

Store below 25°C.
Protect from moisture.

Keep out of reach and sight of children

630020-00

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Manufactured by:
MSN Laboratories Private Limited,
Formulations Division, Unit-06,
Sy. No. (Parts of), 745,811-813,824 & 825,
Burgul Village, Farooqnagar Mandal,
Ranga Reddy District, Pincode 509202,
Telangana State, India.