Vilu® विलु

Vildagliptin Tablets IP 50 mg

Not to be sold by retail without the prescription of a Registered Medical Practitioner.

PRESCRIBING INFORMATION

1. GENERIC NAME

Vildagliptin Tablets IP 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vildagliptin Tablets IP 50 mg

Each uncoated tablet contains:

Vildagliptin IP……50 mg

3. DOSAGE FORM AND STRENGTH

Vildagliptin is available as 50 mg tablets.

4. CLINICAL PARTICULARS

4.1. Indications

Vildagliptin is indicated in the treatment of type 2 diabetes mellitus in adults:

As monotherapy

-in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

As dual oral therapy in combination with

-metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,

- a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance,

- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate,

As triple oral therapy in combination with

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.

4.2. Posology and Method of Administration

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.

Method of administration

Vildagliptin can be administered with or without a meal.

4.3. Contraindications

Patients may develop hypersensitivity to the active substance or to any of the excipients.

4.4. Special Warnings and Precautions for Use

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

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

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 abnormality(ies) return(s) 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

There is no experience of vildagliptin use in patients with NYHA functional class IV and therefore use is not recommended in these patients.

Skin disorders

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.

Excipients

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5. Drug Interactions

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

No clinically relevant pharmacokinetic interactions have been observed.

Digoxin (Pgp substrate), warfarin (CYP2C9 substrate)

No clinically relevant pharmacokinetic interactions have been observed.

Combination with amlodipine, ramipril, valsartan or simvastatin

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 hypoglycemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

4.6. Use in Special Populations (such as pregnant women, **lactating women, paediatric patients, geriatric patients etc.)**

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. Vildagliptin should not be used during pregnancy.

Nursing Mothers

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.

Elderly (≥ 65 years)

No dose adjustments are necessary in elderly patients.

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.

4.7. Effects on Ability to Drive and Use Machines

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

4.8. Undesirable Effects

Rare cases of hepatic dysfunction (including hepatitis) have been reported. 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 was mild in severity and resolved with ongoing vildagliptin treatment.

Tabulated list of adverse reactions

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.

Combination with metformin

Table 1:

Metabolism and nutrition disorders	
Common	Hypoglycaemia
Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness
Uncommon	Fatigue
Gastrointestinal disorders	
Common	Nausea

Combination with a sulphonylurea

Table 2:

Infections and infestations	
Very rare	Nasopharyngitis
Metabolism and nutrition disorders	
Common	Hypoglycaemia
Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness
Common	Asthenia
Gastrointestinal disorders	
Uncommon	Constipation

Combination with a thiazolidinedione

Table 3:

Metabolism and nutrition disorders	
Common	Weight increase
Uncommon	Hypoglycaemia
Nervous system disorders	
Uncommon	Headache
Uncommon	Asthenia
Vascular disorders	
Common	Oedema peripheral

Monotherapy

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

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

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

Post-marketing experience

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.

4.9. Overdose

Information regarding overdose with vildagliptin is limited. Symptoms of overdose included mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels, oedema of the feet and hands, and increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C-reactive protein (CRP) and myoglobin levels.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

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).

5.2 Pharmacokinetic Properties

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%). Vildagliptin can be given with or without food. The absolute bioavailability is 85%.

Distribution

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

Biotransformation

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite (LAY 151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the glucuronide (BQS867) and the amide hydrolysis products (4% of dose). Vildagliptin is not metabolised 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. 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 is recovered in the faeces. Renal excretion of the unchanged vildagliptin accounted for 23% of the dose after oral administration. 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 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 exposure to vildagliptin in patients with mild and moderate hepatic impairment was decreased (20% and 8%, respectively), while the exposure to vildagliptin for patients with severe impairment were 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

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.

6. NONCLINICAL PROPERTIES

6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 noeffect dose of 500 mg/kg (59-fold human exposure) and 100 mg/kg (16-fold human exposure), respectively. The increased incidence of these tumours in mice is considered not to represent a significant risk to humans based on the lack of genotoxicity of vildagliptin and its principal metabolite, the occurrence of tumours only in one species and the high systemic exposure ratios at which tumours were observed.

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at doses ≥ 5 mg/kg/day. These were consistently located on the extremities (hands, feet, ears and tail). At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), only blisters were observed. They were reversible despite continued treatment and were not associated with histopathological abnormalities. Flaking skin, peeling skin, scabs and tail sores with correlating histopathological changes were noted at doses ≥ 20 mg/kg/day (approximately 3 times human AUC exposure at the 100 mg dose). Necrotic lesions of the tail were observed at ≥ 80 mg/kg/day. Skin lesions were not reversible in the monkeys treated at 160 mg/kg/day during a 4-week recovery period *[Reference: Vildagliptin EU SmPC, dated Feb 2019]*.

7. DESCRIPTION

Vildagliptin is a cyanopyrrolidine-based, orally bioavailable inhibitor of dipeptidyl peptidase 4 (DPP-4), with hypoglycemic activity. Chemically it is 1-[2-[(3-hydroxy-1-adamantyl) amino] acetyl] pyrrolidine-2-carbonitrile. The molecular formula is C17H25N3O2 and the molecular weight is 303.4 g/mol.

The chemical structure of vildagliptin is:

Vildagliptin mesylate is a white to slightly yellowish crystalline powder. It is soluble in water, sparingly soluble in tetrahydrofuran and is insoluble in cyclohexane.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None

8.2 Packing Information

10's Alu-Alu Blister Pack

8.3 Storage and Handling Instructions

Store protected at a temperature not exceeding 30°C.

9. PATIENT COUNSELING INFORMATION

Advise the patient to read prescribing information.

Advice the patient not to take Vildagliptin

- If the patient is allergic to vildagliptin or any of the other ingredients of this medicine.

Advice the patient to talk to doctor, pharmacist or nurse before taking Vildagliptin

- if patient has type 1 diabetes (i.e. your body does not produce insulin) or if the patient has a condition called diabetic ketoacidosis
- if patient is taking an anti-diabetic medicine known as sulphonylurea (doctor may want to reduce the dose of the sulphonylurea when taken it together with Vildagliptin in order to avoid low blood glucose [hypoglycaemia])
- if patient has moderate or severe kidney disease
- if patient is on dialysis
- if patient has liver disease
- if patient is suffering from heart failure
- if patient has or had a disease of the pancreas

Liver disease

Advice the patient not to take vildagliptin, if the patient had previously stopped taking it because of liver disease.

Diabetic skin lesions

Diabetic skin lesions are a common complication of diabetes. Advised the patient to follow the recommendations for skin and foot care. The patient is also advised to pay particular attention to new onset of blisters or ulcers while taking Vildagliptin.

Children and adolescents

The use of this medicinal product in children and adolescents up to 18 years of age is not recommended.

Pregnancy and breast-feeding

If the patient is pregnant or breast-feeding, or planning to have a baby, ask doctor or pharmacist for advice before taking this medicine. Vildagliptin should not be used during pregnancy.

10. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited
(Formulations Division),
Plot No. 42, Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325, Telangana, India.

11. DETAILS OF MANUFACTURING LICENCE NUMBER

38/MD/AP/2007/F/CC

12. DATE OF REVISION

September-2021

® Registered Trade Mark

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