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

Prescribing Information

1. Generic Name

Vildagliptin Tablets 50 mg.
(Brand Name: BLUGLIP Tablets)

2. Qualitative and Quantitative Composition

Each uncoated tablet contains:
Vildagliptin…… 50 mg.
Excipients ……. q.s.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Vildagliptin 50 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

Vildagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:

- As monotherapy in patients for whom metformin is inappropriate due to contraindications or intolerance.
- As dual oral therapy in combination with metformin or sulphonylurea or thiazolidinedione (when monotherapy with either of these medicines provide inadequate glycaemic control).
- As triple oral therapy in combination with sulphonylurea plus metformin (when this dual therapy 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.

4.2Posology and Method of Administration

Oral: Adults: Recommended dose of vildagliptin is 50 mg to be administered twice daily. Doses higher than 100 mg per day are not recommended.
BLUGLIP Tablets can be administered with or without a meal.
Or, as prescribed by the physician.

4.3Contraindications

BLUGLIP Tablets are contraindicated in patients with known hypersensitivity to vildagliptin or to any of the excipients of the formulation.

4.4Special Warnings and Precautions for Use

General: Vildagliptin is not a substitute for insulin in insulin-requiring patients. Vildagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Renal impairment: There is limited experience in patients with end-stage renal disease (ESRD) on haemodialysis. Therefore vildagliptin should be used with caution in these patients.

Hepatic impairment: Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels more than 3 times (3x) of upper limit of normal (ULN).

Liver enzyme monitoring: Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function test results returned to normal after discontinuation of treatment. Liver function tests should be performed prior to the initiation of treatment with vildagliptin in order to know the patient's baseline value. Liver function should be monitored during treatment with vildagliptin at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the 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 liver function test (LFT) normalization, treatment with vildagliptin should not be reinitiated.

Cardiac failure: There is no experience of vildagliptin use in patients with cardiac failure therefore, vildagliptin is not recommended in these patients.

Skin disorders: Skin lesions, including blistering and ulceration have been reported in non-clinical toxicology studies. Furthermore, there have been post-marketing reports of bullous and exfoliative skin lesions. Therefore, in diabetic patients, 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 such as gliclazide, glipizide, or glimepiride 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.

4.5Drug Interactions

Vildagliptin has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P 450 (CYP) 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.

There may be an increased risk of angioedema in patients concomitantly taking angiotensin converting enzyme (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.

4.6Use in Special Populations

Pregnant Women

There are no adequate data from the use of vildagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Due to lack of human data, vildagliptin should not be used during pregnancy.

Lactating Women

It is unknown whether vildagliptin is excreted in human milk. Animal studies have shown excretion of vildagliptin in milk. Thus, vildagliptin should not be used during breast-feeding.

Paediatric Patients

As safety and efficacy of vildagliptin in children and adolescents have not been established, it is not recommended for use in paediatric patients.

Geriatric Patients

Elderly people can take the same dosage as like young adults. Dose adjustments are usually not necessary for elderly patients.

Renal Impairment Patients

No dose adjustment is required in patients with mild renal impairment (creatinine clearance $\geq$ 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 Patients

Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x of ULN.

4.7Effect on Ability to Drive and Use Machines

No data available on the effects on ability to drive and use machines. Patients who experience dizziness as an adverse reaction should avoid driving vehicles or using machines.

4.8Undesirable Effects

The majority of adverse reactions reported with vildagliptin 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. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials of up to 24 weeks in duration, the incidence of ALT or AST elevations ≥3x ULN was 0.2%, 0.3% and 0.2% for vildagliptin 50 mg once daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

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 ACE-inhibitor. The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

In comparative controlled monotherapy studies, hypoglycaemia was uncommon, reported in 0.4% (7 of 1,855) of patients treated with vildagliptin 100 mg 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.

Frequencies of adverse reactions 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).

Clinical Trials Experience

Adverse reactions reported in patients who received vildagliptin in double-blind clinical studies are listed below:

Infections and infestations: Very rare - Upper respiratory tract infection, nasopharyngitis.

Metabolism and nutrition disorders: Uncommon – Hypoglycaemia.

Nervous system disorders: Common – Dizziness; Uncommon – Headache.

Vascular disorders: Uncommon - Peripheral edema.

Gastrointestinal disorders: Uncommon – Constipation.

Musculoskeletal and connective tissue disorders: Uncommon – Arthralgia.

Post-Marketing Experience

Adverse reactions reported with vildagliptin in post-marketing surveillance studies include:

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.

4.9Overdose

There is limited information available on overdosage with vildagliptin.
Symptoms: Overdose symptoms reported with vildagliptin 400 mg dosage were muscle pain, individual cases of mild and transient paraesthesia, fever, edema, transient increase in lipase levels. Symptoms reported with 600 mg dosage were edema of the feet and hand, increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C-reactive protein (CRP) and myoglobin levels. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the drug.
Treatment: In the event of an overdose, supportive management is recommended. Vildagliptin cannot be removed by haemodialysis. However, the major hydrolysis metabolite can be removed by haemodialysis.

5. Pharmacological Properties

5.1 Mechanism of Action

Vildagliptin is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor. 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).

5.2Pharmacodynamic Properties

By increasing the endogenous levels of incretin hormones (GLP-1 and GIP), vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with vildagliptin 50 to 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.
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.

5.3Pharmacokinetic Properties

Absorption: Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.7 hours. The C_{max} and the area under the plasma concentrations versus time curves (AUC) of vildagliptin increases in a dose proportional manner over the therapeutic dose range. The absolute bioavailability is 85%.

Food slightly delays the time to peak plasma concentration to 2.5 hours, but does not alter the overall exposure (AUC). Thus, vildagliptin can be given with or without food.

Distribution: The plasma protein binding of vildagliptin is low (9.3%) and vildagliptin distributes equally between plasma and red blood cells (RBCs). Vildagliptin is distributed mainly in the extravascular compartment.

Metabolism: About 69% of the orally administered dose of vildagliptin is metabolized. The major metabolite i.e., 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). Kidney is one of the major organs contributing to the hydrolysis of vildagliptin to its major inactive metabolite, LAY151. DPP-4 enzymes contribute partially to the hydrolysis of vildagliptin.

Vildagliptin is not metabolized by CYP 450 enzymes to any quantifiable extent. Further, vildagliptin does not inhibit or induce CYP 450 enzymes. Therefore, vildagliptin is not likely to affect metabolic clearance of medicines commonly co-prescribed with it.

Excretion: Following oral administration of vildagliptin, approximately 85% of the dose is excreted into the urine and 15% of the dose is excreted via biliary route. About 23% of the oral dose of vildagliptin excretes unchanged via renal route. The elimination half-life after oral administration is approximately 3 hours.

6. Nonclinical Properties

6.1 Animal Toxicology

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.

Vildagliptin was not mutagenic in conventional *in vitro* and *in vivo* tests for genotoxicity.

A fertility and early embryonic development study in rats revealed no evidence of impaired fertility, reproductive performance or early embryonic development due to vildagliptin. Embryo-foetal toxicity was evaluated in rats and rabbits. An increased incidence of wavy ribs was observed in rats in association with reduced maternal body weight parameters, with a no-effect dose of 75

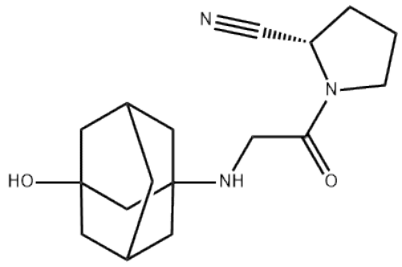
mg/kg (10-fold human exposure). In rabbits, decreased foetal weight and skeletal variations indicative of developmental delays were noted only in the presence of severe maternal toxicity, with a no-effect dose of 50 mg/kg (9-fold human exposure). A pre- and postnatal development study was performed in rats. Findings were only observed in association with maternal toxicity at ≥ 150 mg/kg and included a transient decrease in body weight and reduced motor activity in the F1 generation.
A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times human exposure at the maximum recommended dose). No increases in tumour incidence attributable to vildagliptin were observed. Another two-year carcinogenicity study was conducted in mice at oral doses up to 1,000 mg/kg. An increased incidence of mammary adenocarcinomas and haemangiosarcomas was observed with a no-effect dose of 500 mg/kg (59-fold human exposure) and 100 mg/kg (16-fold human exposure), respectively. The increased incidence of these tumours in mice is considered not to represent a significant risk to humans based on the lack of genotoxicity of vildagliptin and its principal metabolite, the occurrence of tumours only in one species and the high systemic exposure ratios at which tumours were observed.

7. Description

BLUGLIP Tablets are white to off white, round, flat uncoated tablet scored on one side and plain on the other.

Each tablet of BLUGLIP contains 50 mg of vildagliptin for oral administration.

Vildagliptin is a cyanopyrrolidine-based oral anti-hyperglycemic agent. Vildagliptin is a potent and selective inhibitor of dipeptidyl peptidase 4 (DPP-4) enzymes.
Vildagliptin is a white solid compound.
Molecular Weight: 303.4 g/mol.
Molecular Formula: C17H25N3O2.
Chemical Name: (2S)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl]pyrrolidine-2-carbonitrile.
Structural Formula:



Inactive ingredients (excipients) of BLUGLIP Tablet contain Lactose, Microcrystalline Cellulose, Sodium Starch Glycolate, and Magnesium stearate.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 months.

8.3Packaging Information

15 Tablets packed in Alu – Alu Blister.

8.4Storage and Handling Instructions

Store protected from light and moisture at a temperature not exceeding 25°C.
Keep out of reach of children

9. Patient Counseling Information

- Instruct patients to take this medicine exactly as prescribed by your doctor. Do not change the dose or stop therapy without consulting your doctor.
- Instruct patients not to take this medicine during pregnancy and lactation unless advised by healthcare professionals.
- Instruct patients not to take this medicine if they have liver impairment/dysfunction.
- Patients are advised not to take this medicine for type 1 diabetes or for the treatment of diabetic ketoacidosis.
- Patients should be advised to take this medicine as an additional therapy to diet and exercise to improve blood sugar levels. Drug therapy is not an alternative or substitute for diet and exercises thus, patients should continue to follow a good lifestyle.

10.Details of Manufacturer

Pure & Cure Healthcare Pvt. Ltd.
(A subsidiary of Akums Drugs & Pharmaceutical Ltd.)
Plot No. 26A, 27-30, Sector -8A, I.I.E., SIDCUL, Ranipur,
Haridwar – 249 403, Uttarakhand, India.

11.Details of Permission or License Number with Date

DCG(I) approval date: 18/01/2008.
Manufacturing License No: 31/UA/2013.
Date of Product Permission: 20/11/2019.

12. Date of Revision

February 2021.

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