Vildiab®

Vildagliptin

FORMS AND PRESENTATION

Vildiab®: Tablets: Box of 30.

COMPOSITION

Vildiab®: Each tablet contains Vildagliptin 50mg.

Excipients: microcrystalline cellulose, lactose, maize starch partially pregelatinized, magnesium stearate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH02

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).

Pharmacodynamic effects

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 glycemic) 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 hyperglycemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycemia.

The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptin treatment.

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 Cmax (19%). However, the magnitude of change is not clinically significant, so that vildagliptin can be given with or without food. The absolute bioavailability is 85%.

Distribution

The plasma protein binding of vildagliptin is low (9.3%) and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady state after intravenous administration (Vss) is 71 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 the dose). In vitro data in human kidney microsomes suggest that the kidney may be one of the major organs contributing to the hydrolysis of vildagliptin to its major inactive metabolite, LAY151. DPP-4 contributes partially to the hydrolysis of vildagliptin based on an in vivo study using DPP-4 deficient rats. Vildagliptin is not metabolized by CYP 450 enzymes to any quantifiable extent. Accordingly, the metabolic clearance of vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. In vitro studies demonstrated that vildagliptin does not inhibit/induce CYP 450 enzymes. Therefore, vildagliptin is not likely to affect metabolic clearance of co-medications metabolized by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

Elimination

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

Linearity/non-linearity

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

Characteristics in specific groups of patients

Elderly

DPP-4 inhibition by vildagliptin is not affected by age.

Hepatic impairment

There was no correlation between the severity of hepatic disease and changes in 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.

INDICATIONS

Vildiab® 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 glycemic control despite maximal tolerated dose of monotherapy with metformin.

• a sulphonylurea, in patients with insufficient glycemic 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 glycemic 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 glycemic 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 glycemic control.

CONTRAINDICATIONS

Hypersensitivity to vildagliptin or to any of the excipients listed.

PRECAUTIONS

General

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

Renal impairment

There is limited experience in patients with ESRD on hemodialysis. 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 transaminase (ALT) or aspartate transaminase (AST) > 3x the 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 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 the withdrawal of treatment with vildagliptin and liver function tests normalization, treatment with vildagliptin should not be reinitiated.

Cardiac failure

There is no experience of vildagliptin use in clinical trials in patients with New York Heart Association (NYHA) functional class IV and therefore use is not recommended in these patients.

Skin disorders

In keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.

Acute pancreatitis

The 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.

Hypoglycemia

Sulphonylureas are known to cause hypoglycemia. Patients receiving vildagliptin in combination with sulphonylurea may be at risk for hypoglycemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycemia.

Excipients

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines

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

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PREGNANCY AND LACTATION

Pregnancy

There are no adequate data on the use of vildagliptin in pregnant women. Due to a lack of human data, vildagliptin should not be used during pregnancy.

Breast-feeding

It is unknown whether vildagliptin is excreted in human milk. Animal studies have shown the excretion of vildagliptin in milk. Vildagliptin should not be used during breastfeeding.

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

Results from studies conducted with these oral antidiabetics have shown no clinically relevant pharmacokinetic interactions.

Digoxin (Pgp substrate), warfarin (CYP2C9 substrate)

Clinical studies performed with healthy subjects have shown no clinically relevant pharmacokinetic interactions. However, this has not been established in the target population.

Combination with amlodipine, ramipril, valsartan or simvastatin

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

Combination with ACE-inhibitors

There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors.

As with other oral antidiabetic medicinal products the hypoglycemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

ADVERSE EFFECTS

Adverse reactions are listed below for each indication by system organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 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.

Monotherapy

Infections and infestations: upper respiratory tract infection, nasopharyngitis (very rare).
Metabolism and nutrition disorders: hypoglycemia (uncommon).
Nervous system disorders: dizziness (common); headache (uncommon).
Vascular disorders: peripheral oedema (uncommon).
Gastrointestinal disorders: constipation (uncommon).
Musculoskeletal and connective tissue disorders: arthralgia (uncommon).

Combination with metformin

Metabolism and nutrition disorders: hypoglycemia (common)
Nervous system disorders: tremor, headache, dizziness (common); fatigue (uncommon).
Gastrointestinal disorders: nausea (common).

Combination with a sulphonylurea

Infections and infestations: nasopharyngitis (very rare).
Metabolism and nutrition disorders: hypoglycemia (common).
Nervous system disorders: tremor, headache, dizziness, asthenia (common).
Gastrointestinal disorders: constipation (uncommon).

Combination with a thiazolidinedione

Metabolism and nutrition disorders: weight increase (common); hypoglycemia (uncommon).
Nervous system disorders: headache, asthenia (uncommon).
Vascular disorders: peripheral oedema (common).

Combination with metformin and a sulphonylurea

Metabolism and nutritional disorders: hypoglycemia (common).
Nervous system disorders: dizziness, tremor (common).
Skin and subcutaneous tissue disorders: hyperhidrosis (common).
General disorders: asthenia (common).

Combination with insulin

Metabolism and nutrition disorders: decreased blood glucose (common).
Nervous system disorders: headache, chills (common).
Gastrointestinal disorders: nausea, gastro-oesophageal reflux disease (common); diarrhea, flatulence (uncommon).

Post-marketing experience

Gastrointestinal disorders: pancreatitis (not known).
Hepatobiliary disorders: hepatitis reversible upon discontinuation of the medicinal product, abnormal liver function tests reversible upon discontinuation of the medicinal product (not known).
Musculoskeletal and connective tissue disorders: myalgia (not known).
Skin and subcutaneous tissue disorders: urticaria, exfoliative and bullous skin lesions including bullous pemphigoid (not known).

DOSAGE AND ADMINISTRATION

Posology

Adults

When used as monotherapy, in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea, or in combination with insulin (with or without metformin), the recommended daily dose of Vildiab® 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 sulphonylurea, the recommended dose of Vildiab® 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 sulphonylurea, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycemia.

Doses higher than 100 mg are not recommended.

If a dose of Vildiab® 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 Vildiab® as triple oral therapy in combination with metformin and thiazolidinedione have not been established.

Special Populations

Elderly (≥ 65 years)

No dose adjustments are necessary for 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 ESRD, the recommended dose of Vildiab® is 50 mg once daily.

Hepatic impairment

Vildiab® should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3x (ULN).

Pediatric population

Vildiab® is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Vildiab® in children and adolescents (< 18 years) have not been established.

Method of administration

Oral use. Vildiab® can be administered with or without a meal.

OVERDOSAGE

Symptoms

Information on the likely symptoms of overdose was taken from a rising dose tolerability study in healthy subjects given vildagliptin for 10 days. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paresthesia, fever, oedema, and a transient increase in lipase levels. At 600 mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C-reactive protein (CRP), and myoglobin levels. Three other subjects experienced oedema of the feet, with paresthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product.

Management

In the event of an overdose, supportive management is recommended. Vildagliptin cannot be removed by hemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by hemodialysis.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

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Marketing Authorization Holder and Manufacturer

Benta S.A.L. – Lebanon

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