Vildiab® M

Vildagliptin / Metformin Hydrochloride

FORMS AND PRESENTATION
Vildiab® M 50/850: Film Coated Tablet; Box of 60.
Vildiab® M 50/1000: Film Coated Tablet; Box of 60.

COMPOSITION
Vildiab® M 50/850: Each film coated tablet contains Vildagliptin 50 mg and Metformin Hydrochloride 850 mg.
Vildiab® M 50/1000: Each film coated tablet contains Vildagliptin 50 mg and Metformin Hydrochloride 1000 mg.
Excipients: hydroxypropylcellulose, microcrystalline cellulose, crospovidone, magnesium stearate, titanium dioxide, macrogol, talc, iron oxide yellow.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group:
Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD08.
Mechanism of action
~~Vildiab® M combine~~s 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.
Pharmacodynamic effects:
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 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 favourable 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.
Pharmacokinetic properties
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 Cmax (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 (Vss) 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 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 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.
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 litres.
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.

INDICATIONS
Vildiab® M is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus:
- in patients who are inadequately controlled with metformin hydrochloride alone.
- in patients who are already being treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets.
- in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control.

CONTRAINDICATIONS
– Hypersensitivity to the active substances or to any of the excipients.
– 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.

PRECAUTIONS
Vildiab® M is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes.
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. Concomitant medicinal products that may affect renal function, result in significant haemodynamic change, or inhibit renal transport and increase metformin systemic exposure, should be used with caution.
Hepatic impairment: Patients with hepatic impairment, including those with pre-treatment ALT or AST > 3x ULN, should not be treated with Vildiab® M.
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 Vildiab® M in order to know the patient's baseline value. Liver function should be monitored during treatment with Vildiab® M 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 Vildiab® M therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Vildiab® M.
Skin disorders: Skin lesions, including blistering and ulceration have been reported with vildagliptin in extremities of monkeys in non-clinical 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 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.
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.
Effects on ability to drive and use machines
Patients who may experience dizziness as an adverse reaction should avoid driving vehicles or using machines.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy: There are no adequate data from the use of Vildiab® M 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. Vildiab® M 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, Vildiab® M should not be used during breast-feeding.
Fertility: No studies on the effect on human fertility have been conducted for Vildiab® M.

DRUG INTERACTIONS
There have been no formal interaction studies for Vildiab® M. 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.
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* intoxication: increases~~ the 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.
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 Vildiab® M 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.
Concomitant use of medicinal products that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g. organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir and cimetidine) could increase systemic exposure to metformin.

ADVERSE EFFECTS
Adverse reactions 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).
Infections and infestations: upper respiratory tract infection, nasopharyngitis (common).
Metabolism and nutrition disorders: hypoglycaemia, loss of appetite (uncommon).
Nervous system disorders: dizziness, headache, tremor (common); metallic taste (uncommon).
Gastrointestinal disorders: vomiting, diarrhea, nausea, gastro-oesophageal reflux disease, flatulence, constipation, abdominal pain including upper (common); pancreatitis (uncommon).
Hepatobiliary disorders: hepatitis (uncommon).
Skin and subcutaneous tissue disorders: hyperhidrosis, pruritis, rash, dermatitis (common); erythema, urticaria (uncommon); exfoliative and bullous skin lesions including bullous pemphigoid (not known).
Musculoskeletal and connective tissue disorders: arthalgia (common); myalgia (uncommon).
General disorders and administration site conditions: asthenia (common); fatigue, chills, oedema peripheral (uncommon).
Investigations: abnormal liver function tests (uncommon).

DOSAGE AND ADMINISTRATION
Posology
Adults with normal renal function (GFR > 90 ml/min)
The dose of antihyperglycaemic therapy with Vildiab® M 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. Vildiab® M 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 Vildiab® M 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:
Vildiab® M 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 Vildiab® M 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 Vildiab® M 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 Vildiab® M 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.
Special populations
Elderly (≥ 65 years)
As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking Vildiab® M should have their renal function monitored regularly.
Renal impairment: 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 Vildiab® M 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
Vildiab® M 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).
Paediatric population
Vildiab® M is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Vildiab® M in children and adolescents (< 18 years) have not been established. No data are available.
Method of administration
For oral use.
Taking Vildiab® M with or just after food may reduce gastrointestinal symptoms associated with metformin.

OVERDOSAGE
No data are available with regard to overdose of Vildiab® M.
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 400mg, 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 600mg, 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.

STORAGE CONDITIONS
Store below 30°C.
Keep in original pack in intact conditions.

Date of revision: August 2023.

Marketing Authorization Holder and Manufacturer:
Benta S.A.L.
Dbayeh-Lebanon