For the use of Registered Medical Practitioner
or a Hospital or a Laboratory only.

Vildagliptin and Metformin Hydrochloride Tablets

VILDAMET®

50/500, 50/850, 50/1000

Oral Use

Composition :
Each film-coated tablet contains :
Vildagliptin ..... 50 mg
Metformin hydrochloride BP ... 500 mg
Excipients ..... q.s.
Colour: Approved colour used
Composition :
Each film-coated tablet contains :
Vildagliptin ..... 50 mg
Metformin hydrochloride BP ... 850 mg
Excipients ..... q.s.
Colour: Approved colour used
Composition :
Each film-coated tablet contains :
Vildagliptin ..... 50 mg
Metformin hydrochloride BP ... 1000 mg
Excipients ..... q.s.
Colour: Approved colour used

PHARMACEUTICAL FORM : Film-coated tablet

THERAPEUTIC INDICATIONS:
VILDAMET is indicated in the treatment of type 2 diabetes mellitus:
- VILDAMET is 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.
- VILDAMET is 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.
- VILDAMET is 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.

POSOLOGY AND METHOD OF ADMINISTRATION:
Posology
Adults
The dose of antihyperglycaemic therapy with VILDAMET 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.
Based on the patient's current dose of metformin, VILDAMET may be initiated at either the 50 mg/500 mg or 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening. The recommended daily dose is 100 mg vildagliptin plus 2000 mg metformin hydrochloride.
- Patients receiving vildagliptin and metformin from separate tablets may be switched to VILDAMET containing the same doses of each component.
- For patients inadequately controlled on dual combination with metformin and a sulphonylurea:
- The doses of VILDAMET 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 VILDAMET 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 VILDAMET 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.
Doses higher than 100 mg of vildagliptin are not recommended.
The maximum recommended daily dose is 3000 mg for metformin.
Hepatic impairment
VILDAMET 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).
Elderly (≥ 65 years)
As metformin is excreted via the kidneys, and elderly patients tend to exhibit decreased renal function, elderly patients taking VILDAMET should have their renal function monitored regularly. The dosage of VILDAMET for elderly patients should be adjusted based on renal function.
Metformin treatment should not be initiated in patients ≥80 years of age.
Metformin should be used with caution in patients <80 years of age.
Paediatric population (< 18 years)
VILDAMET is not recommended for use in children and adolescents. The safety and efficacy of VILDAMET in children and adolescents (< 18 years) have not been established.
Method of administration
Oral use.
Taking VILDAMET with or just after food may reduce gastrointestinal symptoms associated with metformin.

CONTRAINDICATIONS:
- Hypersensitivity to the active substances or to any of the excipients
- Diabetic ketoacidosis or diabetic pre-coma
- Severe renal failure or renal dysfunction, eGFR < 30 ml/min/1.73m2
- 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
- Lactation
- Metformin are contraindicated in patients with: serum creatinine levels =1.5 mg/dL [males], =1.4 mg/dL [females]

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
General
VILDAMET 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 VILDAMET .
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 VILDAMET in order to know the patient's baseline value. Liver function should be monitored during treatment with VILDAMET 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 VILDAMET therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue VILDAMET.
Following withdrawal of treatment with VILDAMET and LFT normalisation, treatment with VILDAMET should not be re-initiated.
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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
There have been no formal interaction studies for VILDAMET. 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 VILDAMET 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.

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
No studies on the effects on the ability to drive and use machines have been performed. Patients who may experience dizziness as an adverse reaction should avoid driving vehicles or using machines.

UNDESIRABLE EFFECTS:
Like all medicines, this medicine can cause side effects, although not everybody gets them. You should stop taking VILDAMET and see your doctor immediately if you experience the following side effects:
Lactic acidosis (very rare: may affect up to 1 user in 10,000): VILDAMET may cause a very rare, but very serious side effect called lactic acidosis. If this happens you must stop taking VILDAMET and contact a doctor or the nearest hospital immediately, as lactic acidosis may lead to coma.
Angioedema (rare: may affect up to 1 in 1,000 people): Symptoms include swollen face, tongue or throat, difficulty swallowing, difficulty breathing, sudden onset of rash or hives, which may indicate a reaction called "angioedema".
Liver disease (hepatitis) (rare): Symptoms include yellow skin and eyes, nausea, loss of appetite or dark-coloured urine, which may indicate liver disease (hepatitis).
Inflammation of the pancreas (pancreatitis) (frequency not known): Symptoms include severe and persistent pain in the abdomen (stomach area), which might reach through to your back, as well as nausea and vomiting.

Other side effects
Some patients have experienced the following side effects while taking VILDAMET:
Very common (may affect more than 1 in 10 people): nausea, vomiting, diarrhoea, pain in and around the stomach (abdominal pain), loss of appetite.
Common (may affect up to 1 in 10 people): dizziness, headache, trembling that cannot be controlled, metallic taste, low blood glucose.
Uncommon (may affect up to 1 in 100 people): joint pain, tiredness, constipation, swollen hands, ankle or feet (oedema).
Very rare (may affect up to 1 in 10,000 people): sore throat, runny nose, fever; signs of a high level of lactic acid in the blood (known as lactic acidosis) such as drowsiness or dizziness, severe nausea or vomiting, abdominal pain, irregular heart beat or deep, rapid breathing; redness of the skin, itching; decreased vitamin B12 levels (paleness, tiredness, mental symptoms such as confusion or memory disturbances).
Some patients have experienced the following side effects while taking VILDAMET and a sulphonylurea:
Common: dizziness, tremor, weakness, low blood glucose, excessive sweating.
Some patients have had the following side effects while taking VILDAMET and insulin:
Common: headache, chills, nausea (feeling sick), low blood glucose, heartburn.
Uncommon: diarrhoea, flatulence.

OVERDOSE
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 phoshokinase (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
Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD08
Mechanism of action
VILDAMET 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.
Pharmacodynamic effects
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-ß (Homeostasis Model Assessmentß), 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).

PHARMACOKINETIC PROPERTIES
VILDAMET
Absorption
Bioequivalence has been demonstrated between VILDAMET 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 VILDAMET. The rate and extent of absorption of metformin from VILDAMET 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 VILDAMET.
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 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 (V_d) 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.

STORAGE:
Store below 30°C.
Protect from light and moisture.
Keep out of reach of children.

LAST REVISION DATE: 11/2023

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16/0797

Pour l'usage des médecins, hôpitaux et laboratoires seulement

Vildagliptine et Chlorhydrate de metformine Comprimés

VILDAMET®

50/500, 50/850, 50/1000

Voie orale

Composition :
Chaque comprimé pelliculé contient :
Vildagliptine ..... 50 mg
Chlorhydrate de metformine BP ... 500 mg
Excipients ..... q.s.
Colorant: Colorant utilisé approuvé
Composition :
Chaque comprimé pelliculé contient :
Vildagliptine ..... 50 mg
Chlorhydrate de metformine BP ... 850 mg
Excipients ..... q.s.
Colorant: Colorant utilisé approuvé
Composition :
Chaque comprimé pelliculé contient :
Vildagliptine ..... 50 mg
Chlorhydrate de metformine BP ... 1000 mg
Excipients ..... q.s.
Colorant: Colorant utilisé approuvé

FORME PHARMACEUTIQUE : Comprimé enrobé

INDICATIONS THÉRAPEUTIQUES :
VILDAMET est indiqué dans le traitement du diabète de type 2:
- VILDAMET est indiqué dans le traitement des patients adultes qui ne parviennent pas à maîtriser suffisamment la glycémie à la dose maximale tolérée de metformine orale seule ou qui sont déjà traités par l'association de vildagliptine et de metformine sous forme de comprimés distincts.
- VILDAMET est indiqué en association avec une sulfonylurée (c.-à-d. une trithérapie) comme complément au régime alimentaire et à l'exercice chez les patients adultes dont l'état est mal maîtrisé par la metformine et une sulfonylurée.
- VILDAMET est indiqué en trithérapie avec l'insuline comme complément au régime alimentaire et à l'exercice pour améliorer l'équilibre glycémique chez les patients adultes lorsque l'insuline à dose stable et la metformine seule ne permettent pas d'obtenir un équilibre glycémique adéquat.

POSOLOGIE ET MODE D'ADMINISTRATION:
Posologie
Adultes
La dose du traitement par VILDAMET doit être individualisée en fonction du schéma thérapeutique actuel du patient, de son efficacité et de sa tolérabilité, sans dépasser la dose quotidienne maximale recommandée de 100 mg de vildagliptine.
Selon la dose actuelle de metformine administrée au patient, le traitement avec VILDAMET peut être commencé à la concentration de 50 mg/500 mg ou de 50 mg/850 mg ou de 50 mg/1000 mg en comprimés deux fois par jour, un comprimé le matin et l'autre le soir. La dose quotidienne recommandée est de 100 mg de vildagliptine plus 2000 mg de chlorhydrate de metformine.
- Les patients qui reçoivent de la vildagliptine et de la metformine en comprimés distincts peuvent passer à VILDAMET contenant les mêmes doses de chaque composant.
- Pour les patients dont l'état n'est pas bien maîtrisé par une double association de metformine et d'une sulfonylurée :
- Les doses de VILDAMET doivent fournir de la vildagliptine à raison de 50 mg deux fois par jour (dose quotidienne totale de 100 mg) et une dose de metformine semblable à la dose déjà prise. Lorsque VILDAMET est utilisé en association avec une sulfonylurée, on peut envisager d'administrer une dose plus faible de la sulfonylurée pour réduire le risque d'hypoglycémie.
- Pour les patients dont l'état n'est pas bien maîtrisé par la bithérapie avec l'insuline et la dose maximale tolérée de metformine :
La dose de VILDAMET doit permettre l'administration de vildagliptine à raison de 50 mg deux fois par jour (dose quotidienne totale de 100 mg) et d'une dose de metformine semblable à la dose déjà prise.
Les doses supérieures à 100 mg de vildagliptine ne sont pas recommandées.
La dose quotidienne maximale recommandée est de 3000 mg pour la metformine
Insuffisance hépatique
VILDAMET ne doit pas être utilisé chez les patients présentant une insuffisance hépatique, y compris ceux dont l'alanine aminotransférase (ALAT) ou l'aspartate aminotransférase (ASAT) avant le traitement est > 3 fois la limite supérieure de la normale (LSN).
Personnes âgées (? 65 ans)
Comme la metformine est excrétée par les reins et que les personnes âgées ont tendance à présenter une diminution de leur fonction rénale, il faut surveiller régulièrement la fonction rénale des patients âgés qui prennent VILDAMET. La posologie de VILDAMET chez les patients âgés doit être ajustée en fonction de la fonction rénale.
Le traitement par metformine ne doit pas être instauré chez les patients âgés de 80 ans.
La metformine doit être utilisée avec prudence chez les patients de moins de 80 ans.
Population pédiatrique (<18 ans)
VILDAMET n'est pas recommandé pour les enfants et les adolescents. L'innocuité et l'efficacité de VILDAMET chez les enfants et les adolescents (< 18 ans) n'ont pas été établies.
Mode d'administration
Voie orale.
La prise de VILDAMET avec ou juste après des aliments peut réduire les symptômes gastro-intestinaux associés à la metformine.

CONTRE-INDICATIONS:
- Hypersensibilité aux substances actives ou à l'un des excipients
- Acidocétose diabétique ou pré-coma diabétique
- Insuffisance rénale sévère ou dysfonctionnement rénal, Cl < 30 ml/min/1,73m2
- Pathologies aiguës pouvant altérer la fonction rénale, telles que : déshydratation, infection grave, choc, administration intravasculaire d'agents de contraste iodés
- Maladie aiguë ou chronique pouvant causer une hypoxie tissulaire, telle que : insuffisance cardiaque ou respiratoire, infarctus du myocarde récent, choc.
- Insuffisance hépatique
- Intoxication alcoolique aiguë, alcoolisme
- Allaitement
- La metformine est contre-indiquée chez les patients présentant: des taux de créatinine sérique 1,5 mg/dl [hommes], 1,4 mg/dl [femmes]

MISES EN GARDE ET PRÉCAUTIONS PARTICULIÈRES D'UTILISATION:
Général
VILDAMET ne remplace pas l'insuline chez les patients ayant besoin d'insuline et ne doit pas être utilisé chez les patients atteints de diabète de type 1.
Acidose lactique
L'acidose lactique, une complication métabolique très rare mais grave, survient le plus souvent lors d'une aggravation aiguë de la fonction rénale, ou d'une maladie cardiorespiratoire ou d'une septicémie. L'accumulation de metformine se produit lors d'une aggravation aiguë de la fonction rénale et augmente le risque d'acidose lactique.
En cas de déshydratation (diarrhée ou vomissements graves, fièvre ou réduction de l'apport liquidien), il faut interrompre temporairement l'administration de la metformine et il est recommandé de consulter un professionnel de la santé.
Les médicaments qui peuvent altérer de façon aiguë la fonction rénale (tels que les antihypertenseurs, les diurétiques et les AINS) doivent être administrés avec prudence aux patients traités par la metformine. Les autres facteurs de risque d'acidose lactique sont la consommation excessive d'alcool, l'insuffisance hépatique, le diabète mal contrôlé, la cétose, le jeûne prolongé et toute condition associée à l'hypoxie, ainsi que l'utilisation concomitante de médicaments pouvant provoquer une acidose lactique.
Les patients et/ou les soignants doivent être informés du risque d'acidose lactique. L'acidose lactique est caractérisée par une dyspnée acidotique, des douleurs abdominales, des crampes musculaires, une asthénie et une hypothermie suivies d'un coma. En cas de symptômes suspects, le patient doit cesser de prendre la metformine et consulter immédiatement un médecin. Les résultats des analyses diagnostiques sont une diminution du pH sanguin (< 7,35), une augmentation des taux de lactate plasmatique (> 5 mmol/l) et une augmentation de l'écart anionique et du rapport lactate/pyruvate.
Administration d'agents de contraste iodés
L'administration intravasculaire d'agents de contraste iodés peut entraîner une néphropathie induite par contraste, ce qui entraîne une accumulation de metformine et un risque accru d'acidose lactique. L'administration de metformine doit être interrompue avant ou au moment de la procédure d'imagerie et ne doit être reprise qu'au moins 48 heures après, à condition que la fonction rénale ait été réévaluée et qu'elle soit stable .
Fonction rénale
Le DFG doit être évalué avant le début du traitement et régulièrement par la suite. La metformine est contre-indiquée chez les patients présentant un DFG < 30 ml/min et doit être temporairement arrêtée en présence de conditions qui altèrent la fonction rénale.
Insuffisance hépatique
Les patients atteints d'insuffisance hépatique, y compris ceux qui présentent une ALAT ou une ASAT > 3x a la normale avant le traitement, ne doivent pas être traités avec VILDAMET.
Surveillance des enzymes hépatiques
De rares cas de dysfonctionnement hépatique (y compris d'hépatite) ont été signalés avec la vildagliptine. Dans ces cas, les patients étaient généralement asymptomatiques, sans séquelles cliniques, et les résultats des tests de la fonction hépatique (TFH) sont revenus à la normale après l'arrêt du traitement. On doit effectuer des TFH avant d'amorcer le traitement par VILDAMET afin de connaître la valeur de base du patient. La fonction hépatique doit être surveillée pendant le traitement par VILDAMET à des intervalles de trois mois au cours de la première année et périodiquement par la suite. Les patients qui présentent des taux accrus de transaminases doivent faire l'objet d'une deuxième évaluation de la fonction hépatique pour confirmer la constatation et être suivis par la suite au moyen de fréquents TFH jusqu'à ce que la ou les anomalies reviennent à la normale. Si une augmentation de l'ASAT ou de l'ALAT de 3 fois la LSN ou plus persiste, il est recommandé d'interrompre le traitement par VILDAMET. Les patients qui présentent un ictère ou d'autres signes évocateurs d'une dysfonction hépatique doivent interrompre le traitement par VILDAMET.
Après l'arrêt du traitement par VILDAMET et la normalisation du TFH, le traitement par VILDAMET ne doit pas être recommencé.
Problèmes dermatologiques
Des lésions cutanées, y compris des cloques et des ulcérations, ont été signalées avec la vildagliptine dans les extrémités de singes lors d'études toxicologiques non cliniques. Bien que les lésions cutanées n'aient pas été observées à une fréquence accrue dans les essais cliniques, l'expérience a été limitée chez les patients souffrant de complications cutanées diabétiques. De plus, des lésions cutanées bulleuses et exfoliatrices ont été signalées après la commercialisation du produit. Par conséquent, dans le cadre des soins habituels du patient diabétique, il est recommandé de surveiller les troubles cutanés, comme la formation d'ampoules ou d'ulcérations.
Pancréatite aiguë
L'utilisation de la vildagliptine a été associée à un risque de développer une pancréatite aiguë. Les patients doivent être informés du symptôme caractéristique de la pancréatite aiguë.
Si l'on soupçonne une pancréatite, il faut cesser l'administration de la vildagliptine; si la pancréatite aiguë est confirmée, il ne faut pas recommencer l'administration de la vildagliptine. Il faut faire preuve de prudence chez les patients ayant des antécédents de pancréatite aiguë.
Hypoglycémie
Les sulfonylurées sont connues pour provoquer une hypoglycémie. Les patients qui reçoivent de la vildagliptine en association avec une sulfonylurée peuvent être à risque d'hypoglycémie. Par conséquent, on peut envisager d'administrer une dose plus faible de sulfonylurée pour réduire le risque d'hypoglycémie.
Chirurgie
On doit cesser l'administration de la metformine au moment de l'intervention chirurgicale sous anesthésie générale, rachidienne ou épidurale. Le traitement peut être repris au plus tôt 48 heures après l'intervention chirurgicale ou la reprise de l'alimentation par voie orale, à condition que la fonction rénale ait été réévaluée et qu'elle soit stable.

INTERACTION AVEC D'AUTRES MÉDICAMENTS ET AUTRES FORMES D'INTERACTION:
Aucune étude officielle d'interaction n'a été menée pour VILDAMET. Les déclarations suivantes reflètent les informations disponibles sur les différentes substances actives.
Vildagliptine
La vildagliptine présente un faible potentiel d'interactions avec les médicaments co-administrés. Puisque la vildagliptine n'est pas un substrat de l'enzyme cytochrome P (CYP) 450 et qu'elle n'inhibe ni n'induit les enzymes CYP 450, elle n'est pas susceptible d'interagir avec des substances actives qui sont des substrats, des inhibiteurs ou des inducteurs de ces enzymes.
Les résultats des essais cliniques menés avec les antidiabétiques oraux pioglitazone, metformine et glyburide en association avec la vildagliptine n'ont révélé aucune interaction pharmacocinétique cliniquement pertinente dans la population cible.
Les études sur les interactions médicamenteuses avec la digoxine (substrat de la glycoprotéine P) et la warfarine (substrat du CYP2C9) chez des sujets sains n'ont révélé aucune interaction pharmacocinétique cliniquement pertinente après l'administration concomitante de vildagliptine.
Des études sur les interactions médicamenteuses ont été menées chez des sujets en bonne santé avec l'amlodipine, le ramipril, le valsartan et la simvastatine. Dans ces études, aucune interaction pharmacocinétique cliniquement pertinente n'a été observée après l'administration concomitante de vildagliptine. Toutefois, cela n'a pas été établi dans la population cible.
Combinaison avec des inhibiteurs de l'ECA
Il peut y avoir un risque accru d'angio-œdème chez les patients prenant des inhibiteurs de l'ECA en concomitance.
Comme pour les autres antidiabétiques oraux, l'effet hypoglycémiant de la vildagliptine peut être réduit par certaines substances actives, notamment les thiazides, les corticostéroïdes, les produits thyroïdiens et les sympathomimétiques.
Metformine
Combinaisons non recommandées
Alcool
L'intoxication alcoolique est associée à un risque accru d'acidose lactique, notamment en cas de jeûne, de malnutrition ou d'insuffisance hépatique.
Agents de contraste iodés
La metformine doit être interrompue avant ou au moment de la procédure d'imagerie et ne doit pas être recommencée avant au moins 48 heures après, à condition que la fonction rénale ait été réévaluée et qu'elle soit stable.
Substances actives cationiques
Les substances actives cationiques qui sont éliminées par la sécrétion tubulaire rénale (p. ex. la cimétidine) peuvent interagir avec la metformine en entrant en compétition pour les systèmes de transport tubulaire rénal courants et ainsi retarder l'élimination de la metformine, ce qui peut augmenter le risque d'acidose lactique. Une étude menée chez des volontaires sains a montré que la cimétidine, administrée à raison de 400 mg deux fois par jour, augmentait de 50 % l'exposition systémique (ASC) à la metformine. Par conséquent, il faut envisager une surveillance étroite de l'équilibre glycémique, un ajustement de la dose selon la posologie recomm