SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
VILDABET MET 50 mg/850 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substances:
Each film tablet contains 50 mg of vildagliptin and 850 mg of metformin hydrochloride.

Excipient(s):
See 6.1 for excipients.

3. PHARMACEUTICAL FORM
Film-coated tablet.
Yellow, oblong, biconvex, unscored film-coated tablet.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
VILDABET MET is indicated for the treatment of Type 2 diabetes (T2DM).

VILDABET MET is indicated as an adjunct to diet and exercise to improve glycemic control in patients whose diabetes is not adequately controlled with metformin hydrochloride or vildagliptin alone, or in patients who have been previously treated with the combination of vildagliptin and metformin hydrochloride as separate tablets.

VILDABET MET is indicated in combination with a SU (triple combination therapy) in addition to diet and exercise in patients who are not adequately controlled with metformin and a sulfonylurea (SU).

VILDABET MET is indicated as an adjunct to insulin, in addition to diet and exercise, to improve glycemic control in patients for whom a stable dose of insulin and metformin alone do not provide adequate glycemic control.

VILDABET MET is also indicated as initial therapy in patients with T2DM whose diabetes is not adequately controlled by diet and exercise alone.

4.2. Posology and route of administration
Posology / frequency and duration of administration:
Adults with normal renal function (GFR ≥90 mL/min):
Based on the patient's current dose of metformin, administration of VILDABET MET 50 mg/850 mg or 50 mg/850 mg twice daily, one tablet in the morning and one in the evening may be initiated.

Doses above the maximum daily dose of 100 mg of vildagliptin are not recommended.

- In patients with inadequate glycemic control despite the maximum tolerated dose of metformin monotherapy: The dose of VILDABET MET should be given as vildagliptin 50 mg twice daily (total daily dose 100 mg) in addition to the dose of metformin already being taken.

Patients taking vildagliptin and metformin as separate tablets can be switched to VILDABET MET tablets containing the same dose of each ingredient.

- In patients not adequately controlled by the dual combination with metformin and a sulfonylurea: The dose of VILDABET MET should be 50 mg of vildagliptin (total daily dose of 100 mg) twice daily and a similar dose to the dose of metformin currently being taken. When VILDABET MET is used in combination with a sulfonylurea, a lower sulfonylurea dose may be considered to reduce the risk of hypoglycaemia.
- In patients not adequately controlled with dual combination therapy with insulin and the maximum tolerated dose of metformin: The dose of VILDABET MET should be 50 mg of vildagliptin (total daily dose of 100 mg) twice daily and a similar dose to the dose of metformin currently being taken.

Route of administration:
Intended for oral administration.

Taking VILDABET MET with or immediately after meals may reduce metformin-related gastrointestinal symptoms (see section 4.4). Section 5.2).

If a dose of VILDABET MET is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

General target population:
Adults 18 years and older.

Additional information for special populations:
Renal failure:
GFR should be evaluated before initiating treatment with metformin-containing products and at least annually thereafter. Renal function in patients at risk of further progression of renal impairment and in the elderly, such as every 3-6 months; should be evaluated more frequently.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. When it is planned to start metformin in patients with a GFR <60 mL/min, factors that may increase the risk of lactic acidosis in the patient (see section 4.4). Section 4.4) should be examined.

If the expected dosing strength is not achieved with VILDABET MET, individual monocomponents should be used instead of the fixed dose combination.

GFR mL/min	Metformin	Vildagliptin
60-89	The maximum daily dose is 3000 mg. Appropriate dose reduction may be considered in the event of decreased renal function.	No dose adjustment is required.
45-59	The maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	The maximum daily dose is 50 mg.
30-44	The maximum daily dose is 850 mg. The starting dose is at most half of the maximum dose.	
<30	Metformin is contraindicated.	

Liver insufficiency:
VILDABET MET should not be used in patients with hepatic impairment with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >2.5 times the upper limit of normal (ULN). Section 4.3, 4.4 and 4.8).

Pediatric population :
VILDABET MET is not recommended for use in children and adolescents (<18 years of age) due to the lack of safety and efficacy data.

Elderly:
Since metformin is excreted by the kidneys and elderly patients aged 65 years and older tend to have decreased renal function, renal function should be monitored regularly in elderly patients receiving VILDABET MET (see Section 4.4 and 5.2)

4.3. Contrendications
VILDABET MET is contraindicated in the following situations:

- Hypersensitivity to the active substances or any of the excipients (see Section 6.1).
- Presence of any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis),
- Diabetic pre-coma,
- Severe renal impairment (GFR <30 mL/min) (See Section 4.4).
- Acute conditions with the potential to alter kidney function, such as:
  - Dehydration
  - Severe infection
  - Shock
  - Intravenous administration of iodinated contrast material (See. Section 4.4)
- Acute or chronic disease that can cause tissue hypoxia, such as:
  - Cardiac or respiratory failure
  - Recent myocardial infarction
  - Shock
- Liver failure (see Section 4.2, 4.4 and 4.8).
- Acute alcohol intoxication, alcoholism,
- Breastfeeding (See. Section 4.6).

4.4. Special use warnings and precautions

General

VILDABET MET is not a substitute for insulin in patients requiring insulin and should not be used in patients with type 1 diabetes.

Lactic acidosis.

Lactic acidosis, a very rare but serious metabolic complication, often occurs in acute worsening of renal function or cardio-respiratory disease or sepsis. During acute worsening of renal function, accumulation of metformin occurs, increasing the risk of lactic acidosis.

In case of dehydration (severe diarrhea or vomiting, fever or decreased fluid intake), metformin should be temporarily discontinued and physician consultation is recommended.

Caution should be exercised when initiating drugs (such as antihypertensives, diuretics, and NSAIDs) that are likely to severely impair renal function in patients treated with metformin. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, uncontrolled diabetes, ketosis, prolonged fasting, and all conditions associated with hypoxia, as well as the concomitant use of medicinal products that may cause lactic acidosis (see Section 4.3 and 4.5)

Patients and/or their caregivers should be informed of the risk of lactic acidosis. Lactic acidosis is characterized by acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. If suspicious symptoms are observed, the patient should stop using metformin and seek immediate medical attention. Diagnostic laboratory findings; decreased blood pH (<7.35), increased plasma lactate levels (>5 mmol/L), and increased anion gap and lactate/pyruvate ratio.

Administration of iodine-containing contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Therefore, metformin should be discontinued before or at the time of the imaging procedure and should not be restarted until at least 48 hours after renal function has been reassessed and found to be stable. Section 4.2 and 4.5)

Renal function

GFR should be evaluated before initiating treatment and at regular intervals thereafter (See Section 4.2) Metformin is contraindicated in patients with a GFR <30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function (See Section 4.3)

Liver failure

Patients with hepatic impairment with pre-treatment ALT or AST >2.5 times the upper limit of normal (ULN) should not be treated with VILDABET MET (see Section 4.2, 4.3 and 4.8).

Monitoring of liver enzymes

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, patients were generally asymptomatic with no clinical sequelae and liver function tests (KFTs) returned to normal levels after treatment was discontinued. KFT should be performed before starting treatment with VILDABET-MET in order to know the patient's baseline values. During treatment with VILDABET MET, liver function should be monitored every three months for the first year and periodically thereafter. Patients with elevated transaminase levels should have a second liver function evaluation to confirm this finding and then be followed up with frequent CFTs until the abnormality(s) return to normal. If an increase in AST or ALT of 3 times the upper limit of normal (ULN) or greater persists, discontinuation of VILDABET MET is recommended. Treatment with VILDABET MET should be discontinued in patients with jaundice or other signs of hepatic dysfunction.

After discontinuation of VILDABET MET therapy and normalization of KFT, VILDABET MET should not be restarted.

Heart Failure

A clinical study of vildagliptin in patients with New York Heart Association (NYHA) functional class I-III showed that treatment with vildagliptin was not associated with changes in left ventricular function or worsening of existing congestive heart failure (CHF) compared to placebo. Experience in NYHA functional class III patients treated with vildagliptin is still limited and findings preclude any definitive conclusions (see Section 5.1)

There is no experience with the use of vildagliptin in patients with NYHA functional class IV. Therefore, the use of vildagliptin is not recommended in these patients.

Metformin is contraindicated in patients with heart failure, therefore VILDABET MET is contraindicated in this patient population (See Section 4.3)

Skin diseases:

Skin lesions such as blisters and ulceration have been reported with the use of vildagliptin on the extremities of monkeys in nonclinical toxicology studies (see section 5.3). Although an increased incidence of skin lesions was not observed in clinical studies, experience in patients with diabetic skin complications is limited. Therefore, follow-up of skin diseases such as blisters or ulceration is recommended in accordance with the routine care of the diabetic patient.

Pancreatitis

Spontaneous side effects of acute pancreatitis have been reported in post-marketing experience. Patients should be informed about the characteristic symptoms of acute pancreatitis: Persistent, severe abdominal pain. After the vildagliptin treatment was discontinued, resolution of the pancreatitis was observed. If pancreatitis is suspected, treatment with vildagliptin and other potentially suspected drugs should be discontinued.

Hypoglycemia

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

Arthralgia

Post-marketing cases of severe and disabling arthralgia have been reported in patients receiving dipeptidyl-peptidase-4 (DPP-4) inhibitors. From the start of treatment, the time of onset of symptoms ranged from one day to years. It has been observed that the symptoms also disappeared when the drug was discontinued, and the symptoms recurred when the same drug or a different DPP-4 inhibitor was re-administered to the patients. DPP-4 inhibitors should be considered as a possible cause of severe joint pain and the drug should be discontinued if appropriate.

Bullous pemphigoid:

In the post-marketing period; Cases of bullous pemphigoid requiring hospital admission have been reported in patients receiving DPP-4 inhibitors. In most cases, patients improved when the drug was discontinued and systemic/topical immunosuppressive therapy was administered. Patients should be informed about the reporting of blisters and erosions that may occur on the skin while using VILDABET MET. If the risk of bullous pemphigoid is suspected, VILDABET MET should be discontinued immediately and the patient should be referred to a dermatologist for appropriate diagnosis and treatment.

Surgery

Metformin should be discontinued during operations to be performed under general, spinal or epidural anaesthesia. Treatment; should not be restarted until at least 48 hours after surgery or until oral feeding has been resumed and renal function has been reassessed and stable.

4.5. Interaction with other medicinal products and other forms of interaction

There is no official interaction study with VILDABET MET. The following sections reflect the available information for each active substance.

Vildagliptin

Vildagliptin has a low potential for interaction 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 unlikely to interact with active substances that are substrates, inhibitors or inducers of these enzymes.

Results of clinical studies with the oral antidiabetic pioglitazone, metformin and glyburide in combination with vildagliptin showed 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 showed no clinically relevant pharmacokinetic interactions after co-administration with vildagliptin.

Drug-drug interaction studies in healthy subjects were performed with amlodipine, ramipril, valsartan and simvastatin. No clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin in these studies. However, this has not been confirmed in the target population.

Combination with angiotensin Converting Enzyme (ACE) inhibitors Patients taking VILDABET MET with concomitant ACE inhibitors may be at increased risk of angioedema (see Section 4.8).
As with other oral antidiabetic medicinal products, the hypoglycemic effect of vildagliptin may be reduced by certain active substances such as thiazides, corticosteroids, thyroid products and sympathomimetics.

Metformin
Non-recommended combinations:
Alcohol: Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in states of fasting, malnutrition or hepatic impairment.

Contrast agents containing iodine: Metformin should be discontinued before or at the time of the imaging procedure and should not be restarted until at least 48 hours after renal function has been reassessed and found stable (see Section 4.2 and 4.5)

Cationic active ingredients: Cationic active substances (e.g. cimetidine) that are eliminated by renal tubular secretion may interact with metformin by competition for common renal tubular transport systems, thereby delaying metformin elimination and increasing the risk of lactic acidosis. A study in healthy volunteers showed that cimetidine 400 mg twice daily increased the systemic exposure (AUC) of metformin by 50%. Therefore, close monitoring of glycemic control, dose adjustment within the recommended posology, and changes in diabetic therapy should be considered when co-administered with cationic medicinal products that are eliminated by renal tubular secretion (See Section 4.4).

Combinations to be careful in use
Certain drugs, such as NSAIDs, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics, including selective cyclo-oxygenase (COX) II inhibitors, may adversely affect renal function and increase the risk of lactic acidosis. Close monitoring of renal function is essential when such products are started or used in combination with metformin.

Glucocorticoids, beta-2-agonists and diuretics have intrinsic hyperglycemic activity. The patient should be informed and more frequent blood glucose monitoring should be performed, especially at the beginning of the treatment. Dosage of VILDABET MET may need to be

adjusted, if necessary, during or when concomitant therapy is discontinued.

ACE inhibitors can lower blood glucose levels. The dosage of the antihyperglycemic medicinal product should be adjusted, if necessary, during treatment with the other medicinal product and when it is discontinued.

Additional information for special populations:
Clinical interaction studies for specific populations were not conducted.

Pediatric population :
No interaction studies have been conducted in the pediatric population.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: C

Women of childbearing potential / Birth control (Contraception)

Women of childbearing potential should be advised to use an effective method of contraception during treatment with VILDABET MET.

Pregnancy period

There are insufficient data on the use of VILDABET MET in pregnant women.

Studies of vildagliptin in animals have shown reproductive toxicity at high doses. No reproductive toxicity was detected in metformin studies in animals. Animal studies of vildagliptin and metformin showed no signs of teratogenicity, but fetotoxic effects were observed at maternotoxic doses (see Section 5.3).

Animal studies are inconclusive regarding effects on pregnancy and/or embryonal/foetal development and/or parturition/postnatal development (See Section 5.3). The potential risk for humans is unknown.

VILDABET MET should not be used during pregnancy as there is insufficient data on its use in humans.

Lactation period

Animal studies indicate that both vildagliptin and metformin are excreted in milk. It is not known whether vildagliptin is excreted in human milk, but metformin is excreted in human milk in small amounts. VILDABET MET should not be used during lactation because of the possible risk of neonatal hypoglycaemia due to metformin and the lack of human data with vildagliptin.

Reproductive capacity / Fertility

Fertility studies in rats using doses up to 200 times the human dose yielded no evidence of impaired fertility or early embryonic development due to vildagliptin. The effects of Vildagliptin/Metformin on human fertility have not been studied.

4.7. Effects on vehicle and machine use

No studies have been conducted on the effects on the ability to drive and use machines. Therefore, patients who feel dizzy as an undesirable effect should avoid driving or using machines.

4.8. Adverse effects

There are no therapeutic clinical studies with VILDABET MET. However, VILDABET MET has been shown to be bioequivalent to co-administered vildagliptin and metformin (see section 5.2). The data presented here relate to co-administration of vildagliptin and metformin with vildagliptin added to metformin. There are no studies in which metformin was added to vildagliptin.

The data presented here relate to the administration of vildagliptin and metformin as free or fixed dose combinations.

The majority of adverse reactions were mild and transient that did not require discontinuation of therapy. No relationship was found between adverse reactions and age, ethnicity, exposure time, and daily dose.

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, patients were generally asymptomatic, with no clinical sequelae, and liver function tests returned to normal after treatment was discontinued. In data from controlled monotherapy and add-on therapy studies that can last up to 24 weeks, incidence of elevation of ALT or AST $\geq$3 times the upper limit of normal (ULN) (classified as present at at least 2 consecutive measurements or at the last treatment visit) was 0.2%, 0.3% and 0.2%, respectively for vildagliptin 50 mg once daily, vildagliptin 50 mg twice daily, and for all comparator drugs. These elevations in transaminases are usually asymptomatic, non-progressive, and unrelated to cholestasis or jaundice.

Rare cases of angioedema have been reported with vildagliptin at a rate similar to controls. The majority of cases have been reported when vildagliptin was administered in combination with an ACE inhibitor. The majority of cases were of mild severity and resolved during continued vildagliptin treatment.

Adverse reactions reported in patients receiving vildagliptin as adjunct to metformin and as monotherapy in double-blind studies are listed below by MedDRA system organ class and absolute frequency.

Within each system organ class, adverse drug reactions are ranked according to their frequency, with the most frequent reactions listed first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing severity. Also, the frequency category corresponding to each adverse drug reaction is based on the following system:

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)

Adverse reactions reported in patients given vildagliptin 100 mg daily as add-on to metformin compared to placebo plus metformin in double-blind studies (N=208).

Metabolism and nutrition disorders
Common: Hypoglycemia

Nervous system disorders
Common: Tremor, headache, dizziness
Uncommon: Fatigue

Gastrointestinal disorders
Common: Nausea

In controlled clinical studies with the combination of vildagliptin 100 mg daily and metformin, there were no patients who discontinued due to adverse reactions in the combination vildagliptin 100 mg daily and metformin combination or the placebo and metformin combination group.

In clinical studies, the incidence of hypoglycaemia was reported as common (1%) in patients receiving vildagliptin 100 mg daily in combination with metformin, and uncommon (0.4%) in patients receiving placebo + metformin. Severe hypoglycemic events were not reported in the vildagliptin arms.

When vildagliptin 100 mg/day was added to metformin therapy in clinical studies, there was no change from baseline in body weight (+0.2 kg and -1.0 for vildagliptin and placebo, respectively).

In clinical studies lasting more than 2 years, no additional safety signals or unanticipated risks were observed when vildagliptin was added to metformin therapy.

No additional safety signals or unanticipated risks were observed when vildagliptin was studied as initial combination therapy with metformin.

Combination with metformin and sulfonylurea (SU):
While there were no patients in the vildagliptin + metformin + glimepiride treatment group who dropped out of the study due to adverse reactions; this rate was 0.6% in the placebo + metformin + glimepiride treatment group.

The incidence of hypoglycemia was common in both treatment groups (5.1% for the vildagliptin + metformin + glimepiride versus 1.9% for the placebo + metformin + glimepiride group). 1 severe hypoglycemic event was reported in the vildagliptin group.

At the end of the study, the effect on mean body weight appeared to be neutral (+0.6 kg in the vildagliptin group and -0.1 kg in the placebo group).

Adverse reactions reported in patients receiving vildagliptin 50 mg twice daily in combination with metformin and a sulphonylurea (N=157):

Metabolism and nutrition disorders
Common: Hypoglycemia

Nervous system disorders
Common: Drowsiness, tremor

Cutaneous and subcutaneous tissue disorders
Common: Hyperhidrosis

General disorders and administration site conditions
Common: Asthenia

Combination with insulin
In controlled clinical trials using vildagliptin 50 mg twice daily in combination with concomitant insulin with or without metformin, the overall incidence of discontinuation due to adverse events was 0.3% in the vildagliptin treatment group compared to no patients in the placebo group.

The incidence of hypoglycemia was similar in the two treatment groups (14.0% in the vildagliptin group versus 16.4% in the placebo group). 2 patients in the vildagliptin group and 6 patients in the placebo group reported severe hypoglycemic events.

At the end of the study, the effect on mean body weight was determined to be neutral. (change from baseline was + 0.6 kg in the vildagliptin group versus no change in the placebo group).

Adverse reactions reported in patients receiving vildagliptin 100 mg daily in combination with insulin (with or without metformin) in double-blind studies (N=371):

Metabolism and nutrition disorders
Common: Decrease in blood glucose

Nervous system disorders
Common: Headache, feeling cold

Gastrointestinal disorders
Common: Nausea, gastroesophageal reflux disease
Uncommon: Diarrhea, flatulence

Additional information on the drug substances of the fixed combination:
Vildagliptin:
Adverse reactions reported in patients given vildagliptin 100 mg daily as monotherapy in double-blind studies (N=1855).

Infection and infestations
Very rare: Upper respiratory tract infection, nasopharyngitis

Metabolism and nutrition disorders
Uncommon: Hypoglycemia

Nervous system disorders
Common: Stupor
Uncommon: Headache

Vascular disorders
Uncommon: Peripheral edema

Gastrointestinal disorders
Uncommon: Constipation

Musculoskeletal disorders, connective tissue and bone diseases
Uncommon: Arthralgia

In controlled monotherapy studies, the overall incidence of discontinuation due to adverse reactions was not higher in patients treated with vildagliptin 100 mg daily (0.3%) compared with those treated with placebo (0.6%) or comparators (0.5%).
In comparative controlled monotherapy studies, hypoglycemia was uncommon and occurred in 0.4% (7 out of 1855) of patients treated with vildagliptin 100 mg daily, while this occurred in 0.2% of patients in the active comparator or placebo-treated groups (2 out of 1082) and there were no reports of serious or severe events.

In clinical studies, when vildagliptin 100 mg/day was given as monotherapy, body weight did not change from baseline (-0.3 kg and -1.3 kg for vildagliptin and placebo, respectively).
In clinical studies lasting more than 2 years, no safety signals or unanticipated risks were observed with vildagliptin monotherapy.

<u>Metformin :</u>
Known adverse reactions for the metformin component

Metabolism and nutrition disorders
Very rare: Decreased absorption of vitamin B_{12}* and lactic acidosis

Nervous system disorders
Common: Metallic taste

Gastrointestinal disorders
Very common: Nausea, vomiting, diarrhea, abdominal pain and loss of appetite

Hepatobiliary disorders
Very rare: Liver function test abnormalities or hepatitis**

Cutaneous and subcutaneous tissue disorders
Very rare: Skin reactions such as erythema, pruritus, urticaria

* A decrease in the absorption and serum levels of vitamin B12, which is generally of no clinical significance, has been observed very rarely in patients treated with long-term metformin. Evaluation of such an etiology is recommended when a patient presents with megaloblastic anemia.
** Isolated cases of liver function test abnormality or hepatitis that improved upon metformin discontinuation have been reported.

Gastrointestinal undesirable effects are most common at the beginning of treatment and resolve spontaneously in most cases. To prevent these, it is recommended to take metformin in 2 daily doses with or after a meal. A slow increase in dose may also improve gastrointestinal tolerability.
Adverse drug reactions reported from spontaneous reports and literature cases

Post-marketing experience (frequency not known):
The following undesirable effects have been collected through spontaneous case reports and literature cases from post-marketing experience with combined Vildagliptin/Metformin. Because these effects are reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency. For this reason, it was categorized as "unknown frequency".

Gastrointestinal disorders
Unknown: Pancreatitis

Hepatobiliary disorders
Unknown: Hepatitis (returning on drug withdrawal), abnormal liver function tests (returning on drug discontinuation)

Cutaneous and subcutaneous tissue disorders
Unknown: Urticaria, blisters or exfoliative skin lesion, bullous pemphigoid (see Precautions). Section 4.4)

Musculoskeletal disorders, connective tissue and bone diseases
Unknown: Myalgia

4.9. Overdose and treatment

There are no data on overdose for VILDABET MET.

Vildagliptin:
Data on overdose with vildagliptin are limited.

Information on possible symptoms of overdose with vildagliptin was obtained from an incremental dose tolerability study in healthy subjects given vildagliptin for 10 days. At a dose of 400 mg, three patients had muscle pain and one patient had mild and temporary paresthesia, fever, edema, and a temporary increase in lipase levels. Edema in the hands and feet, increased levels of creatine phosphokinase (CPK), AST, C-reactive protein (CRP) and myoglobin were observed in one patient at a dose of 600 mg. In three different cases, edema of the feet and paresthesia were also observed in two of them. After discontinuation of the study medicinal product, all symptoms and laboratory abnormalities resolved without treatment.

Metformin :
A large metformin overdose (or the accompanying risk of lactic acidosis) can cause lactic acidosis, which is a medical emergency and must be treated in hospital.

Treatment:
The most effective way to remove metformin is hemodialysis. However, although vildagliptin cannot be removed by hemodialysis, the major hydrolysis metabolite (LAY 151) can. Supportive treatment is recommended.

5. PHARMACOLOGICAL PARTICULARS

5.1. Pharmacodynamic particulars

Pharmacotherapeutical group: Oral blood sugar lowering drug combinations
ATC Code: A10BD08

Mechanism of action:
VILDABET MET is a combination of two antihyperglycemic agents with adjunctive mechanisms of action in improving glycemic control in patients with type 2 diabetes: vildagliptin, a member of the islet stimulant class, and metformin hydrochloride, a member of the biguanide class.

Vildagliptin, a member of the islet-stimulatory class, is a potent and selective inhibitor of dipeptidyl-peptidase-4 (DPP-4). Metformin acts mainly by reducing endogenous hepatic glucose production.

Pharmacodynamic effects:

Vildagliptin:

Vildagliptin acts mainly by inhibiting DPP-4, the enzyme responsible for the breakdown of the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide).

Vildagliptin administration causes rapid and complete inhibition of DPP-4 activity, resulting in increased levels of fasting and postprandial endogenous GLP-1 and GIP incretin hormones.

Vildagliptin increases the sensitivity of beta cells to glucose by increasing the endogenous levels of these incretin hormones, resulting in an increase in glucose-dependent insulin secretion. In patients with type 2 diabetes, treatment with vildagliptin 50-100 mg/day resulted in significant improvement in markers of beta cell function, such as HOMAβ (Homeostasis Model Assessment-β), proinsulin/insulin ratio, and measures of beta cell sensitivity from frequent meal tolerance testing. In non-diabetic (normal glycemic) persons, vildagliptin does not stimulate insulin secretion or decrease glucose levels.

Vildagliptin also increases the sensitivity of alpha cells to glucose by raising endogenous GLP-1 levels; this causes glucagon release that is more appropriate for the blood glucose level.

The increase in the insulin/glucagon ratio due to the increase in incretin hormone levels during hyperglycemia leads to a decrease in fasting and postprandial hepatic glucose production and thus a decrease in glycemia.

Increasing GLP-1 levels are known to delay gastric emptying; on the other hand, this effect is not observed with vildagliptin treatment.

In a 52-week, multicenter, randomized, double-blind study in patients with type 2 diabetes and CHF (NYHA class I-III); the effect of vildagliptin 50 mg twice daily (N=128) on left ventricular ejection fraction (LVEF) was evaluated in comparison with placebo (N=126). Vildagliptin was not associated with changes in left ventricular function or worsening of existing CHF. Cardiovascular (CV) events were judged to be generally balanced. Cardiac events in NYHA class III heart failure patients treated with vildagliptin were slightly greater than with placebo. However, imbalances in CV risk in favor of placebo at the outset and low number of events prevent firm conclusions from being drawn. Compared with placebo, vildagliptin significantly reduced HbA1c from the mean baseline value of 7.8% (0.6% difference). The incidence of hypoglycemia in the general population was 4.7% and 5.6% in the vildagliptin and placebo groups, respectively.

Metformin :

Metformin is a biguanide that has antihyperglycemic effects and reduces basal and postprandial plasma glucose levels. It does not stimulate insulin release and therefore does not cause hypoglycemia or an increase in weight gain.

Metformin exerts its glucose-lowering effects through three mechanisms:

- Reduction in hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis;
- Increasing peripheral glucose uptake and utilization by slightly increasing insulin sensitivity in muscle;

- Delaying glucose absorption from the gut.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase and increases the carrying capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

In humans, metformin has positive effects on lipid metabolism, independent of its effect on glycemia. This has been demonstrated at therapeutic doses in controlled, mid-term or long-term clinical studies: Metformin lowers serum levels of total cholesterol, LDL cholesterol and triglycerides.

The prospective randomized UKPDS (UK Prospective Diabetes Study) study demonstrated the benefit of long-term intensive blood glucose control in type 2 diabetes. Analysis of these results in overweight patients treated with metformin following inadequate diet alone showed:

- A significant reduction in the absolute risk of all diabetes-related complications in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and the combined sulfonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034;
- A significant reduction in the absolute risk of diabetes-related mortality: metformin 7.5 events/850 patient-years, diet alone 12.7 events/850 patient-years, p=0.017;
- A significant reduction in the absolute risk of overall mortality: Metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years (p=0.011), and the combined sulfonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021);
- A significant reduction in the absolute risk of myocardial infarction: Metformin 11 events/850 patient-years, diet alone 18 events/850 patient-years (p=0.01).

Clinical efficacy and safety:

Vildagliptin added to treatment in patients with poor glycemic control despite treatment with metformin monotherapy, resulted in additional statistically significant reductions in mean HbA1c after 6 months of treatment compared to placebo (between groups differences of -0.7% vs -1.1% for vildagliptin 50 and 100 mg, respectively). The proportion of patients who achieved a ≥0.7% reduction from baseline in HbA1c was statistically significantly higher in the vildagliptin plus metformin groups (46% and 60%, respectively) compared to the metformin plus placebo group (20%).

In a 24-week study, metformin (mean daily dose: 2020 mg), vildagliptin (50 mg twice daily) was compared with pioglitazone (30 mg once daily). Mean reductions from baseline HbA1c of 8.4% were -0.9% with vildagliptin added to metformin and -1.0% with pioglitazone added to metformin. The mean weight gain in patients receiving pioglitazone added to metformin was +1.9 kg, compared to +0.3 kg in patients receiving vildagliptin supplemented with metformin.

In a clinical trial lasting 2 years, metformin (mean daily dose: 1894 mg) was compared to vildagliptin (50 mg twice daily) glimepiride (up to 6 mg/kg –mean dose at 2 years): 4.6 mg). After 1 year, mean reductions from mean baseline HbA1c of 7.3% were -0.4% with

vildagliptin added to metformin and -0.5% with glimepiride added to metformin. Body weight change with vildagliptin was -0.2 kg, while with glimepiride it was +1.6 kg. The incidence of hypoglycemia was significantly lower in the vildagliptin group (1.7%) compared to the glimepiride (16.2%) group. At the study endpoint (2 years), HbA1c levels were similar to baseline in both treatment groups, and differences in body weight and hypoglycemia were maintained.

In a 52-week study, vildagliptin (50 mg twice daily) was compared with gliclazide (average daily dose: 229,5 mg) in patients inadequately controlled with metformin (initial metformin dose 1928 mg/day). After 1 year, the mean reductions in HbA1c were -0.81% with vildagliptin added to metformin (mean baseline HbA1c 8.4%) and -0.85% with gliclazide added to metformin (mean baseline HbA1c 8.5%) ; statistically non inferiority was obtained (95% Confidence interval (CI) -0.11–0.20). The body weight change with vildagliptin was +0.1 kg, while the body weight change with gliclazide was +1.4 kg.

A 24-week study evaluated the use of a fixed-dose combination of vildagliptin and metformin (50 mg/500 mg twice daily or gradually titrated to 50 mg/850 mg twice daily) as initial therapy in previously untreated patients. Mean HbA1c reductions were found to be significantly higher with vildagliptin plus metformin combination therapy compared to monotherapy of both treatments. A greater reduction in HbA1c was observed in patients with baseline HbA1c $\geq$10.0%.

A 24-week, randomized, double-blind, placebo-controlled study was conducted with 318 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with metformin (1500 mg/day) and glimepiride (4 mg/day). Compared to placebo, vildagliptin in combination with metformin and glimepiride significantly reduced HbA1c. The mean reduction in mean baseline HbA1c (8.8%), corrected for placebo, was -0.76%.

A 24-week, randomized, double-blind, placebo-controlled study was conducted with 449 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice a day) in combination with a stable dose of basal or premixed insulin (average daily dose: 41 units, with or without concomitant metformin (N = 276) or not (N = 173). Compared with placebo, vildagliptin in combination with insulin significantly reduced HbA1c. The mean reduction in HbA1c from 8.8% at baseline in the entire population was -0.72%, corrected for placebo. The mean placebo-adjusted HbA1c reduction in the subgroups treated with insulin with or without concomitant metformin was -0.63% and -0.84%, respectively. The incidence of hypoglycemia in the general population was 8.4% and 7.2% in the vildagliptin and placebo groups, respectively. While there was no weight gain in patients receiving vildagliptin (+0.2 kg), weight reduction was observed in those receiving placebo (-0.7 kg).

In another 24-week study of patients with more advanced type 2 diabetes uncontrolled with insulin (short- and long-acting, mean insulin dose 80 IU/day), when vildagliptin (50 mg twice daily) was added to insulin, the mean reduction in HbA1c was statistically significantly greater (0.5% vs. 0.2%) compared with placebo plus insulin. The incidence of hypoglycemia was lower in the vildagliptin group than in the placebo group (29.6% vs. 22.9%).

Cardiovascular risk:

A meta-analysis of independent and prospectively agreed cardiovascular events was performed from 25 phase III clinical trials, the longest of which lasted more than two years. This meta-analysis included 8956 patients with type 2 diabetes treated with vildagliptin, and the analysis showed that vildagliptin therapy was not associated with an increased cardiovascular risk. The combined endpoint of agreed cardio-cerebrovascular (CSV) events [acute coronary syndrome (ACS), stroke, or CSV death] was similar for vildagliptin compared with the combined active and placebo comparators. The Mantel–Haenszel hazard ratio [0.84 (95% confidence interval 0.63–1.12)] supports the cardiovascular safety of vildagliptin. In total, 99 of 8956 patients in the vildagliptin group and 91 of 6061 patients in the comparison group reported an event.

5.2. Pharmacokinetc properties General properties

VILDABET MET is a combination of two antihyperglycemic agents with adjunctive mechanisms of action in improving glycemic control in patients with type 2 diabetes: vildagliptin, a member of the islet-stimulating class of DPP-4 (dipeptidyl-peptidase-4) inhibitors, and metformin hydrochloride, a member of the biguanide class.

Absorption:

Bioequivalence of free combinations of vildagliptin and metformin hydrochloride tablets at the respective doses has been demonstrated against VILDABET MET (50 mg/850 mg and 50 mg/850 mg).

The rate and rate of absorption of vildagliptin in VILDABET MET tablets are not affected by food. The rate and rate of absorption of the metformin hydrochloride component of VILDABET MET 50 mg/850 mg film-coated tablet are decreased when taken with food. This reduction was demonstrated by a 26% decrease in C_{max}, a 7% decrease in AUC, and a delay in T_{max} (2 to 4 h).

The following information reflects the pharmacokinetic properties of each active ingredient of VILDABET MET.

Vildagliptin:

Absorption:

Vildagliptin taken orally on an empty stomach is rapidly absorbed, reaching peak plasma concentrations in 1.7 hours. Taking it with food delays the peak plasma concentration level to 2.5 hours; on the other hand, the total exposure value AUC (area under the curve) does not change. Co-administration of vildagliptin with food reduced the C_{max} (19%) compared to the fasted dose. However, since the magnitude of change is not clinically significant, vildagliptin may be given with or without food. Absolute bioavailability is 85%.

Distribution:

Plasma protein binding of vildagliptin is low (9.3%), and vildagliptin is evenly distributed between plasma and erythrocytes. The mean volume of distribution (Vss) of vildagliptin at steady state following intravenous administration is 71 liters, suggesting extravascular distribution.

Biotransformation:

Metabolism is the major route of elimination of vildagliptin in humans and comprises 69% of the dose. The major metabolite (LAY 151) is pharmacologically inactive and is the product of hydrolysis of the cyano moiety, comprising 57% of the dose followed by the amide hydrolysis product (4% of the dose). According to an in vivo study in DPP-4-deficient rats, DPP-4 partially contributes to the hydrolysis of vildagliptin. Vildagliptin is hardly metabolized by CYP 450 enzymes and accordingly the metabolic clearance of vildagliptin is not expected to be affected by drugs that are inhibitors and/or inducers of CYP 450. In vitro studies have shown that vildagliptin does not inhibit/induce CYP 450 enzymes. Therefore, vildagliptin is unlikely to affect the metabolic clearance of drugs metabolized by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

Elimination

Following oral administration of [14C]vildagliptin, approximately 85% of the dose is excreted in the urine and 15% of the dose is found in the faeces. After oral administration, 23% of the dose is excreted via the kidneys as unchanged vildagliptin. Following intravenous administration in 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-linear State:

Vildagliptin is rapidly absorbed with an absolute oral bioavailability of 85%.

Peak plasma concentrations and area under the plasma concentrations-time curve (AUC) of vildagliptin increased approximately dose proportionally over the therapeutic dose range.

Characteristics of patients

Renal failure:

In patients with mild, moderate, and severe renal impairment, the AUC of vildagliptin increased on average 1.4, 1.7, and 2-fold, respectively, compared to normal healthy volunteers. Compared with healthy volunteers, the AUC of the metabolite LAY151 was 1.6, 3.2, and 7.3-fold, and the AUC of BQS867 was 1.4, 2.7, and 7.3-fold, respectively, in patients with mild, moderate, and severe renal impairment. times increased. Limited data in patients with end-stage renal disease (ESRD) indicate that exposure to vildagliptin is similar to patients with severe renal impairment. In ESRD patients, LAY151 concentrations were approximately 2-3 times higher than in patients with severe renal impairment.

Vildagliptin was removed in limited amounts by hemodialysis (3% in a 3-4 hour hemodialysis session initiated 4 hours post-dose).

Liver insufficiency

There was no clinically significant change in exposure to vildagliptin (~30% maximum) in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh AC).

Pediatric patients:

There are no pharmacokinetic data for these patients.

Elderly:
Overall exposure of vildagliptin (100 mg once daily) was increased by 32% in healthy elderly volunteers (≥70 years) and there was an 18% increase in peak plasma concentration compared to young healthy subjects (18-40 years). However, these changes are also not clinically significant. DPP-4 inhibition by vildagliptin was not affected by age.

Gender:
No clinically significant differences in the pharmacokinetics of vildagliptin were observed between healthy male and female volunteers over a wide range of age and body mass index (BMI). Inhibition of DPP-4 by vildagliptin is not affected by gender.

Race:
Based on the limited data available, racial differences do not have a significant impact on the pharmacokinetics of vildagliptin.

Metformin :
Absorption:
After an oral dose of metformin, the maximum plasma concentration (C_{max}) is reached approximately 2.5 hours later. The absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. The fraction found in unabsorbed stool after an oral dose is 20-30%. After oral administration, metformin absorption is saturable and incomplete. Intake with meals slightly delays metformin absorption and reduces its absorption rate. Following administration of a dose of 850 mg, the plasma peak concentration was 40% lower, the AUC decreased by 25%, and the time to peak plasma concentration was prolonged by 35 minutes. The clinical significance of this decrease is unknown.

Distribution:
Its binding to plasma proteins is negligible. Metformin is cleaved in erythrocytes. The mean volume of distribution (Vd) ranges from 63-276 liters.

Biotransformation:
Metformin is excreted unchanged in the urine. There are no metabolites detected in humans.

Elimination
Metformin is eliminated via the kidney. The renal clearance of metformin is >400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. The apparent terminal elimination half-life following an oral dose is approximately 6.5 hours. When renal function is impaired, renal clearance decreases proportionally to creatinine, thereby prolonging the elimination half-life, leading to increased plasma metformin levels.

Linearity/Non-linear State:
The pharmacokinetics of metformin absorption are assumed to be nonlinear. At the usual metformin doses and dosing schedules, steady-state plasma concentrations are reached within 24-48 hours and are usually below 1 µg/mL. Maximum metformin plasma levels (C_{max}) did not exceed 4 µg/mL even at maximum doses in controlled clinical studies.

5.3. Preclinical safety data

13-week animal studies have been conducted with the combination agents in VILDABET MET. No new toxicity associated with the combination was detected. Below are findings from studies conducted with vildagliptin or metformin separately.

Vildagliptin:

Intracardiac impulse conduction delays were observed in dogs at the 15 mg/kg dose (7 times human exposure based on C_{max}) with no effects.

Accumulation of foamy alveolar macrophages in the lung was observed in rats and mice. The no-effect dose was determined to be 25 mg/kg (5 times the human exposure based on AUC) in rats and 750 mg/kg (142 times human exposure) in mice.

Gastrointestinal symptoms have been observed in dogs, particularly soft stools, mucoid stools, diarrhea, and high doses of bloody stools. The level at which no effect was observed was not detected.

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

In the fertility and early embryonic development study conducted in rats, impairment of fertility, reproductive performance or early embryonic development due to vildagliptin was not demonstrated. Embryofetal toxicity was evaluated in rats and rabbits. In rats, an increase in the incidence of wavy ribs due to decrease in maternal body weight parameters was detected at 75 mg/kg dose (10-fold human exposure) at no effect. Decreased fetal weight and skeletal variations, indicative of developmental delay in rabbits, were detected only at the 50 mg/kg dose (9 times the human exposure) at which no effects were observed in the presence of severe maternal toxicity. A pre- and postnatal developmental study was conducted in rats. Only findings associated with maternal toxicity were observed at doses $\geq$150 mg/kg and included a transient increase in body weight and a decrease in motor activity in the F1 generation.

A 2-year carcinogenicity study was conducted in rats; Oral doses up to 900 mg/kg (the highest recommended dose, approximately 200 times the human exposure) were administered to rats in this study. No increase in tumor incidence attributable to vildagliptin was observed. Another 2-year carcinogenicity study was performed in mice; oral doses up to 850 mg/kg were administered to rats in this study. At no-effect doses of 500 mg/kg (59 times the human exposure) and 100 mg/kg (16 times the human exposure), the incidence of breast adenocarcinoma and hemangiosarcoma were increased, respectively. Because vildagliptin and its principal metabolite lack genotoxicity, tumors occur in only one species, and tumors occur at high systemic exposure rates, the increased incidence of these tumors in mice is not considered to pose a significant risk to humans.

In a 13-week toxicology study in cynomolgus monkeys, doses $\geq$5 mg/kg/day caused skin lesions. These lesions were constantly observed in the extremities (hands, feet, ears and tail). Only papula were observed at a dose of 5 mg/kg/day (approximately equivalent to human AUC exposure at a 100 mg dose). These lesions disappeared despite continued treatment and were not associated with histopathological abnormalities. At doses $\geq$ 20 mg/kg/day

(equivalent to approximately 3 times the human AUC exposure at a 100 mg dose), skin scaling, peeling, crusting and tail sores consistent with histopathological changes were observed. Necrotic lesions on the tail were observed at doses ≥80 mg/kg/day. Skin lesions were not reversible in monkeys treated with 160 mg/kg/day over a 4-week recovery period.

Metformin :
Based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction, none of the non-clinical data of metformin reveal a special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hydroxypropyl Cellulose (HPC-LF)
Hydroxypropyl Cellulose (HPC-EXF)
Magnesium stearate
Titanium dioxide
Yellow iron oxide
Talc
Polyethylene Glycol,
Polyvinyl alcohol

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

Shelf life: 24 months

6.4. Special warnings for storage

Store at room temperature below 30ºC.

6.5. Nature and contents of packaging

It is offered to the market in aluminum/aluminum blister packs of 60 tablets.

6.6. Disposal of residues from medicinal products for human use and other special measures

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Waste Control Regulation".

7. AUTHORIZATION HOLDER

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8. AUTHORIZATON NO(s)

09164/10505/NMR/2023

9. FIRST AUTHORIZATON DATE / AUTHORIZATON RENEWAL DATE

Date of first authorization: Dec 7, 2023

Date of renewal of the authorization:

10. RENEWAL DATE OF THE SPC