Professional Information

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

[PRODUCT NAME] 50/850 (film coated tablets)

[PRODUCT NAME] 50/1000 (film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[PRODUCT NAME] 50/850

Each film coated tablet contains:

Vildagliptin 50 mg and metformin hydrochloride 850 mg.

Sugar Free

[PRODUCT NAME] 50/1000

Each film coated tablet contains:

Vildagliptin 50 mg and metformin hydrochloride 1000 mg.

Sugar Free

For full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Film coated tablets

[PRODUCT NAME] 50/850

White to off white, film coated, oval shaped tablets debossed with 'VM2' on one side and plain on the other side.

[PRODUCT NAME] 50/1000

White to off white, film coated, oval shaped tablets debossed with 'VM1' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For patients with Type 2 diabetes mellitus (T2DM):

- **[PRODUCT NAME]** is indicated as an adjunct to diet and exercise in patients who are already stabilised with the combination of vildagliptin and metformin hydrochloride at the same dosages, as separate tablets.
- **[PRODUCT NAME]** is indicated as add-on to insulin as an adjunct to diet and exercise in patients on a stable dose of insulin plus vildagliptin and metformin hydrochloride.
- **[PRODUCT NAME]** is indicated as an add-on to insulin at the same dosages as the separate tablets of vildagliptin and metformin hydrochloride.
- **[PRODUCT NAME]** is indicated in combination with sulphonylurea (SU) (i.e. triple combination therapy) as an adjunct to diet and exercise in patients stabilised on vildagliptin, metformin hydrochloride and a sulphonylurea.
- **[PRODUCT NAME]** can be used to replace the vildagliptin and metformin hydrochloride at the same dosages as the separate tablets.

4.2 Posology and Method of Administration

In using **[PRODUCT NAME]** do not exceed the maximum daily dose of vildagliptin (100 mg).

The recommended starting dose of **[PRODUCT NAME]** should be based on the patient's current regimen of vildagliptin and/or metformin hydrochloride. **[PRODUCT NAME]** should be given with meals to reduce the gastrointestinal side effects associated with metformin hydrochloride.

Use in combination with sulphonylurea or with insulin:

The dose of **[PRODUCT NAME]** 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.

Patients with renal impairment:

A GFR should be assessed before initiation of treatment with metformin-containing products (such as **[PRODUCT NAME]**) and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3 to 6 months. The maximum daily dose of metformin should preferably be divided into 2 to 3 daily doses.

Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin-containing products (such as **[PRODUCT NAME]**) in patients with GFR < 60 ml/min. GALVUS MET is contraindicated in patients with GFR < 30 ml/min because of its metformin component (see section 4.3).

The following dosing recommendations apply to metformin and vildagliptin, used separately or in combination, in patients with renal impairment. If no adequate strength of **[PRODUCT NAME]** is available,individual components should be used instead of the fixed dose combination.

Dose adjustments in patients with renal impairment

GFR ml/min	**Metformin**	**Vildagliptin**
60 - 89	Maximum daily dose is 3000 mg*. Dose reduction may be considered if renal function declines.	Maximal daily dose is 100 mg.
45 - 59	Starting dose should not be more than 1000 mg with a maximum daily dose of 2000 mg*.	Maximal daily dose is 50 mg.
30 - 44	Starting dose should not be more than 500 mg with a maximum daily dose of 1000 mg	
< 30	Metformin is contraindicated.	

*If metformin doses higher than those achievable with **[PRODUCT NAME]** alone are considered necessary.

[PRODUCT NAME] should not be used in patients with renal failure or renal dysfunction, e.g. serum creatinine levels ≥ 1,5 mg/dl (> 135 µmol/l) in males and ≥ 1,4 mg/dl (> 110 µmol/l) in females (see **Sections 4.3 and 4.4**).

Patients with hepatic impairment:

[PRODUCT NAME] is not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment alanine aminotransferase (ALT) or AST > 2,5 X the upper limit of normal (see **Section 4.4**).

Elderly:

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking **[PRODUCT NAME]** should have their renal function monitored regularly.

The dosage of **[PRODUCT NAME]** for elderly patients should be adjusted based on renal function. (see **Section 4.3 "Renal disease" and 4.4 "Monitoring of renal function"**).

Paediatric patients:

Safely and efficacy of the combination of vildagliptin and metformin in paediatric patients have not been established. Therefore, **[PRODUCT NAME]** is not recommended for use in children below 18 years of age.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity:

[PRODUCT NAME] is contraindicated in patients with known hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients. (see section 6.1).

- Renal disease:

[PRODUCT NAME] is contraindicated in patients with severe renal impairment (GFR<30 ml/min(see **Section 4.2 and 4.4)**

- Patients with hepatic impairment:

[PRODUCT NAME] is contraindicated in patients with hepatic impairment, including patients with a pre-treatment ALT or AST > 2,5 X the upper limit of normal (see section 4.4).

- Congestive heart failure:

[PRODUCT NAME] is contraindicated in patients with congestive heart failure requiring pharmacological treatment (see **Section 4.4**).

- Metabolic acidosis

[PRODUCT NAME] is contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis or lactic acidosis with or without coma. Diabetic ketoacidosis should be treated with insulin.

4.4 Special warnings and precautions for use

Combination of vildagliptin and metformin hydrochloride

[PRODUCT NAME] is not a substitute for insulin in insulin requiring patients and should not be used in patients with Type I diabetes or for the treatment of diabetic ketoacidosis.

If metabolic acidosis is suspected, treatment with **[PRODUCT NAME]** should be discontinued and the patient hospitalised immediately (see **Section 4.9**).

[PRODUCT NAME] should be discontinued if evidence of renal impairment is present.

Alcohol is known to potentiate the effect of metformin hydrochloride on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving **[PRODUCT NAME]**. Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Administration of intravascular iodinated contrast materials:

[PRODUCT NAME] should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function and increase the risk of lactic acidosis. In patients undergoing such studies, **[PRODUCT NAME]** should be temporarily discontinued at the time of or prior to the procedure, withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Vildagliptin:

Hepatic impairment:

Vildagliptin is not recommended in patients with hepatic impairment, including patients with a pre-treatment AL Tor AST > 2,5 X the upper limit of normal (see **section 4.3**).

Liver enzyme monitoring:

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 **[PRODUCT NAME]**. **[PRODUCT NAME]** is not recommended in patients with a pre-treatment ALT or AST > 2,5 X the upper limit of normal. LFTs should be monitored during **[PRODUCT NAME]** treatment at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality (ies) return to normal.

Should an increase in AST or ALT of 3 X upper limit of normal or greater persist, withdrawal of therapy with **[PRODUCT NAME]** is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue **[PRODUCT NAME]** and contact their physician immediately. Following withdrawal of treatment with **[PRODUCT NAME]** and LFT normalisation, **[PRODUCT NAME]** should not be reinitiated.

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 a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive.

There is no reported experience of vildagliptin use in clinical trials in patients with NYHA functional class IV and therefore use is not recommended in these patients.

Vildagliptin as contained in **[PRODUCT NAME]** may cause arthralgia that can be severe.

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.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven- Johnson syndrome, erythema multiforme, acute generalised exanthematous pustulosis, erythroderma (generalised exfoliative dermatitis) and pemphigoid have been reported in patients treated with DPP-4 inhibitors including GALVUS MET. SCARs are regarded as a class effect of DPP-4 inhibitors such as GALVUS MET. If a patient develops SCAR, treatment with DPP-4 inhibitors such as GALVUS MET must immediately be discontinued and appropriate treatment instituted. Patients should continue with an alternative class of anti-diabetic medicines

Rhabdomyolysis

Rhabdomyolysis has been reported during use of DPP-4 inhibitor containing products such as **[PRODUCT NAME**]. However, causality could not be assessed due to confounding factors such as concomitant use of medicines (statins, colchicine, etc.) or co-morbid conditions (Renal failure, hypovolemia, etc.), known to cause or predispose to development of rhabdomyolysis. Close monitoring of patients using DPP-4 inhibitor containing products in presence of predisposing risk factors is recommended.

Metformin hydrochloride:

Lactic Acidosis:

Lactic acidosis is a serious metabolic complication that can occur due to metformin accumulation. Medicines that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors, such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia (see **sections 4.3 and 4.5**). 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.

Diagnosis of lactic acidosis:

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH (<7,35), plasma lactate levels above 5 mmol/l and an increased anion gap and lactate/pyruvate ratio.

If metabolic acidosis is suspected, treatment with metformin containing products, such as **[PRODUCT NAME**] should be discontinued and the patient should be immediately hospitalised.

Monitoring of renal function:

GFR should be assessed before treatment initiation and regularly thereafter (see section 4.2). Metformin-containing products, such as [PN] are contraindicated in patients with GFR < 30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function (see section 4.3).

Metformin hydrochloride is substantially excreted by the kidney, and the risk of metformin hydrochloride accumulation and lactic acidosis increases with the degree of renal function impairment. Since advancing age is associated with reduced renal function, **[PRODUCT NAME]** should be carefully titrated in the elderly to establish the minimum dose for adequate glycaemic effect, and renal function should be monitored regularly. Also, special caution should be exercised where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID. Renal function should be assessed and verified as normal before the initiation of **[PRODUCT NAME]**, then at least once a year in patients with normal renal function and at least two to four times a year in patients with serum creatinine levels at the upper limit of normal. Additionally, patients in whom renal dysfunction is anticipated, should have their renal function assessed more frequently.

Concomitant medications that may affect renal function or metformin hydrochloride disposition:

Concomitant medications that may affect renal function, result in significant haemodynamic change or interfere with the disposition of metformin hydrochloride, such as cationic medicines that are eliminated by renal tubular secretion should be used with caution (see **section 4.5**).

Hypoxic states:

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxaemia have been reported to be associated with lactic acidosis and may also cause pre renal uraemia. If such events occur in patients receiving **[PRODUCT NAME]** therapy, the medication should be promptly discontinued.

Surgical procedures:

Use of **[PRODUCT NAME]** should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Impaired hepatic function:

Since impaired hepatic function has been associated with some cases of lactic acidosis, a risk associated with metformin hydrochloride, **[PRODUCT NAME]** should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels:

The metformin component of **[PRODUCT NAME]** has been reported to be associated with a decrease in serum Vitamin B_{12} levels without clinical manifestations, in approximately 7 % of patients. Such decrease, is very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride and/or vitamin B_{12} supplementation. Measurement of haematological parameters on at least an annual basis is advised for patients receiving **[PRODUCT NAME]** and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (e.g. those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In

these patients, routine serum vitamin B_{12} measurements at minimally two-to-three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes:
A patient with type 2 diabetes previously well-controlled on **[PRODUCT NAME]** who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should promptly be evaluated for ketoacidosis and/or lactic acidosis. If acidosis of either form occurs, **[PRODUCT NAME]** must be stopped immediately and appropriate measures initiated.

Hypoglycaemia:
Hypoglycaemia does not usually occur in patients receiving **[PRODUCT NAME]** alone, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or ethanol use. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking medicines. Hypoglycaemia may occur when **[PRODUCT NAME]** is used as add-on therapy to other anti-diabetic medicines.

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.

Loss of control of blood glucose:
When a patient stabilised on any diabetic regimen is exposed to stress such as fever, trauma, infection, surgery, etc., a temporary loss of glycaemic control may occur. At such times, it may be necessary to withhold **[PRODUCT NAME]** and temporarily administer insulin. **[PRODUCT NAME]** may be reinstituted after the acute episode is resolved.

4.5 Interaction with other medicines and other forms of interaction

Combination of vildagliptin and metformin

No clinically relevant pharmacokinetic interaction has been reported when vildagliptin (100 mg once daily) was co-administered with metformin hydrochloride (1000 mg once daily). Medicine interactions for each component of the combination of vildagliptin and metformin have been extensively studied. However, the concomitant use of the active substances in patients in reported clinical studies and in widespread clinical use has not resulted in any unexpected interactions.

The following statements reflect the information reported on the individual active substances (vildagliptin and metformin).

Vildagliptin:

Vildagliptin has a low potential for medicine interactions. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit nor induces CYP 450 enzymes, it is not likely to interact with co- medications that are substrates, inhibitors or inducers of these enzymes.

Furthermore, vildagliptin does not affect metabolic clearance of co-medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2CI9, CYP 2D6, CYP 2E1, and CYP 3A4/5. Interaction studies were conducted with commonly co-prescribed medications for patients with type 2 diabetes or medications with a narrow therapeutic window. As a result of these reported studies, no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, and metformin hydrochloride), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.

Combination with ACE inhibitors

There may be an increased risk of angioedema in patients concomitantly taking ACE inhibitors (see **section 4.8**). The hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

Metformin hydrochloride:

The following is known for metformin component:

Furosemide: Furosemide increased Cmax and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreased Cmax blood AUC of furosemide, with no change in renal clearance of furosemide.

Nifedipine: Nifedipine increased absorption, Cmax and AUC of metformin, and increased excretion of metformin in urine. Metformin had minimal effects on nifedipine.

Glyburide: Glyburide produced no changes in metformin PK/PD parameters. Decreases in Cmax blood AUC of glyburide were observed, but were highly variable. Therefore the clinical significance of this finding was unclear.

Cationic medicines: Cationic medicines (e.g. amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Thus, with cimetidine increases in metformin plasma/blood concentration and AUC were observed to be 60% and 40% respectively. Metformin had no effect on cimetidine PK. Although such interactions remain theoretical (except for cimetidine), careful monitoring of patients and doses of metformin and such medications are recommended.

Other: Certain medicines tend to produce hyperglycaemia and may lead to loss of glycaemic control. These medicines include the thiazides and other diuretics, corticosteroids,

phenothiazines, thyroid products, oestrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking medicines, and isoniazid. Close monitoring of glycaemic control and metformin dose adjustments are recommended when such medicines are administered or withdrawn for these patients.

Combinations not recommended

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment. Avoid consumption of alcohol and medicines containing alcohol (see **section 4.4**).

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 (see **sections 4.2 and 4.4**).

Combinations requiring precautions for use

Some medicines 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 the combination of vildagliptin and metformin 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 medicine should be adjusted during therapy with the other medicine and on its discontinuation.

Concomitant use of medicine that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g. organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir and cimetidine) could increase systemic exposure to metformin.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety in pregnancy has not been established. Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, thus insulin- monotherapy should be used during pregnancy to maintain blood glucose levels as close to normal as possible.

For vildagliptin, reported studies in animals have shown reproductive toxicity at high doses. For metformin, reported studies in animals have not shown reproductive toxicity. Reported 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. The combination of vildagliptin and metformin hydrochloride should not be used during pregnancy.

Breastfeeding:

Safety in lactation has not been established. Reported 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 **[PRODUCT NAME]** should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted for **[PRODUCT NAME].**

4.7 Effects on ability to drive and use machines

[PRODUCT NAME] can cause drowsiness. Patients who ~~may~~ experience dizziness should avoid driving vehicles or using machines.

4.8 Undesirable effects

The data reported here refers to the administration of vildagliptin and metformin as a free or fixed combination.

Cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

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 alter discontinuation of treatment

Adverse Reactions

System Organ Class	**Frequent**	**Less frequent**
Infections and infestations	-	Upper respiratory tract infection, Nasopharyngitis

Metabolism and nutrition disorders	Hypoglycaemia	Decrease of vitamin B_{12} absorption*, lactic acidosis
Nervous system disorders	Tremor, dizziness, headache, chills and metallic taste	Fatigue
Gastrointestinal disorders	Nausea, gastroesophageal reflux disease, vomiting, diarrhoea, abdominal pain, loss of appetite	flatulence constipation
Hepato-biliary disorders	-	Liver function test abnormalities, hepatitis**,
Skin and subcutaneous tissue disorders	Hyperhidrosis	Skin reactions such as erythema, pruritus, urticaria
Musculoskeletal and connective tissue disorders	-	Arthralgia
General disorders and administration site conditions	Asthenia	Oedema peripheral

*****A decrease of vitamin B_{12} absorption with decrease of serum levels has been very rarely observed in patients treated long-term with metformin and appears generally to be without clinical significance. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

**Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.

**Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.

Gastrointestinal undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 daily doses during or after meals. A slow increase in the dose may also improve gastrointestinal tolerability.

Reported post-marketing experience

Table: Reported post-marketing adverse reactions

System Organ Class	**Not known**
Gastrointestinal disorders	Pancreatitis
Hepato-biliary disorders	Hepatitis (reversible upon discontinuation of the medicine) Abnormal liver function tests (reversible upon discontinuation of the medicine)
Skin and subcutaneous tissue disorders	Urticaria Bullous or exfoliative skin lesions
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “Adverse drug reaction and quality problem reporting form”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/documents/adverse-drug -reactions-and-quality-problem-reporting-form/

4.9 Overdose

No data have been reported with regard to overdose of the combination of vildagliptin and metformin hydrochloride.

Signs and symptoms

Vildagliptin

Information regarding overdose with vildagliptin is limited.

Likely symptoms of overdose with vildagliptin are muscle pain, mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels, increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C -reactive protein (CRP) and myoglobin levels..

Metformin Hydrochloride

Hypoglycaemia may develop and should be monitored for. Lactic acidosis has been reported in approximately 32 % of metformin hydrochloride overdose cases. Metformin hydrochloride is dialyzable with a clearance of up to 170 ml/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated medicine from patients in whom metformin hydrochloride overdosage is suspected.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.2. Oral hypoglycaemics

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD08

[PRODUCT NAME]:

[PRODUCT NAME] combines two antihyperglycaemic medicines with different mechanisms of action to improve glycaemic control in patients with type 2 diabetes: vildagliptin, a member of the DPP-4 (dipeptidylpeptidase-4) inhibitor class and metformin hydrochloride, a member of the biguanide class.

Vildagliptin

Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor that improves glycaemic control.

The administration of vildagliptin results in inhibition of DPP-4 activity. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon- like peptide -1) and GIP (glucose-dependent insulinotropic polypeptide).

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 50 to 100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function. The degree of improvement in beta-cell function is dependent on the initial

degree of impairment; in non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP- 1Ievels, vildagliptin enhances the sensitivity of alpha cells to glucose, resulting in more glucoseappropriate glucagon secretion. The reduction in inappropriate glucagon during meals in turn attenuates insulin resistance. 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 to delay gastric emptying is not observed with vildagliptin treatment. In addition, a reduction in postprandial lipaemia that is not associated with vildagliptin's incretin mediated effect to improve islet function, has been observed.

Metformin hydrochloride:

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. With metformin hydrochloride therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase and increase the transport capacity of specific types of membrane glucose transporters (GLUT-I and GLUT-4).

In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been reported at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDL cholesterol and triglyceride levels.

5.2 Pharmacokinetic properties

[PRODUCT NAME]

Absorption

Food does not affect the extent and rate of absorption of vildagliptin from the **[PRODUCT NAME]**. The C_{max} and AUC metformin hydrochloride from **[PRODUCT NAME]** were reported to be decreased by 26 % and 7 % respectively when given with food. The absorption of metformin hydrochloride was also delayed as reflected by the T_{max} (2,0 to 4,0 hours) when given with food. These changes in C_{max} and AUC are consistent but lower than those observed when metformin hydrochloride when given alone under fed conditions. The effects of food on the pharmacokinetics of both the vildagliptin component and metformin hydrochloride component of the combination of vildagliptin and metformin were similar to the pharmacokinetics of vildagliptin and metformin hydrochloride when given alone with food.

The following statements reflect the pharmacokinetic properties of the individual active substances of the combination of vildagliptin and metformin hydrochloride.

Absorption

Vildagliptin:

Following oral administration in the fasting state, vildagliptin is well absorbed with peak plasma concentrations reported at 1,75 hours. The absolute oral bioavailability is reported as 85 %. Co-administration with food slightly decreases the rate of absorption of vildagliptin, as characterised

by a 19% decrease in peak concentrations, and a delay in the time to peak plasma concentration to 2,5 hours. There is no change in the extent of absorption, and food does not alter the overall exposure (AUC).

Linearity:

Peak plasma concentrations for vildagliptin and the area under the plasma concentration versus time curve (AUC) increased in an approximately dose-proportional manner over the therapeutic dose range.

Metformin hydrochloride:

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is reported as approximately 50 to 60 %. Reported studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin hydrochloride, as shown by approximately a 40 % lower mean peak plasma concentration (C_{max}), a 25 % lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin hydrochloride with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

<u>Distribution</u>:

Vildagliptin

The plasma protein binding of vildagliptin is reported to be 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 reported as 71 litres, suggesting extravascular distribution.

Metformin hydrochloride:

The apparent volume of distribution (V/F) of metformin hydrochloride following single oral doses of 850 mg averaged 654 ± 358 litres. Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90 % protein bound. Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride, steady state plasma concentrations of metformin hydrochloride are reached within 24 to 48 hours and are generally < 1 µgram/ml. During reported clinical trials of metformin hydrochloride, maximum metformin hydrochloride plasma levels did not exceed 5 µgram/ml, even at maximum doses.

Biotransformation:

Vildagliptin:

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69 % of the dose. The major metabolite, LAY151, 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 the dose). DPP-4 contributes partially to the hydrolysis of vildagliptin as shown in an in-vivo study using DPP-4 deficient rats. Vildagliptin is not metabolised by cytochrome P450 enzymes to any quantifiable extent. Reported i*n-vitro* studies demonstrated that vildagliptin does not inhibit or induce cytochrome P450 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.

Metformin hydrochloride:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Excretion and elimination:

Vildagliptin:

Following oral administration of [^{14}C]-vildagliptin, approximately 85 % of the dose is reported to be excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of the unchanged vildagliptin accounts for 23% of the dose after oral administration. After an intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 l/hour and 13 l/hour, respectively.

The mean elimination half-life after intravenous administration is reported as approximately 2 hours. The elimination half-life after oral administration is reported as approximately 3 hours and is independent of dose.

Metformin hydrochloride:

Reported intravenous single-dose studies in normal subjects demonstrate that metformin hydrochloride is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is reported as approximately 3,5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of elimination. Following oral administration, approximately 90% of the absorbed medicine is reported to be eliminated via the renal route within the first 24 hours, with a plasma elimination half- life of approximately 6,2 hours. In blood, the elimination half-life is approximately 17,6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special populations: Obesity:

Vildagliptin:

BMI does not show any impact on the pharmacokinetic parameters of vildagliptin. DPP-4 inhibition by vildagliptin was unaffected by BMI.

Hepatic impairment:

***Vildagliptin*:**

The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in subjects with mild, moderate, and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison to subjects with normal hepatic function. The exposure to vildagliptin (100 mg) after a single dose in subjects with mild and moderate hepatic impairment was decreased (20% and 8%, respectively), while the exposure to vildagliptin for subjects with severe impairment was increased by 22%. The maximum change (increase or decrease) in the exposure to vildagliptin is approximately 30%, which is not considered to be clinically relevant. There was no correlation between the severity of hepatic function impairment and changes in exposure to vildagliptin.

The use of vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST > 2,5 X the upper limit of normal.

Metformin Hydrochloride:

No pharmacokinetic studies of metformin hydrochloride have been conducted in subjects with hepatic insufficiency.

Renal impairment:

Vildagliptin:

Vildagliptin AUC increased on average 1.4, 1.7 and 2 -fold in patients with mild, moderate and severe renal impairment, respectively, compared to normal healthy subjects. AUC of the metabolites LAY151increased 1.6, 3.2 and 7.3 -fold and that of BQS867 increased 1.4, 2.7 and 7.3 -fold in patients with mild,moderate and severe renal impairment, respectively, compared to healthy volunteers. Limited data from patients with end stage renal disease (ESRD) indicate that vildagliptin exposure is similar to that in patients with severe renal impairment. LAY151 concentrations in ESRD patients were approximately 2- 3-fold higher than in patients with severe renal impairment.

Vildagliptin was removed by haemodialysis to a limited extent (3 % over a 3 - 4 hour haemodialysis session starting 4 hours post dose).

Metformin hydrochloride:

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin hydrochloride is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Elderly:

Vildagliptin:

In otherwise healthy elderly subjects (≥ 70 years), the overall exposure to vildagliptin (100 mg once daily) was reported to be increased by 32 % with an 18 % increase in peak plasma concentration compared to younger healthy subjects (18 to 40 years). These changes are not considered to be clinically relevant. DPP-4 inhibition by vildagliptin is not affected by age in the age groups studied.

Metformin hydrochloride:

Limited data from reported pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin hydrochloride is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function.

The combination of vildagliptin and metformin treatment should not be initiated in patients 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Ethnic group

Limited data report that race does not have any major influence on vildagliptin pharmacokinetics.

Paediatric:

No pharmacokinetic data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hyroxypropylcellulose, Magnesium Stearate (vegetable origin) and Purified Water.

Film coating

Opadry® White (YS-1-7040) and Purified Water.\

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 ºC in the original pack. Keep the blister/strips in the outer carton in order to protect from moisture.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

Strip Pack

Hard tempered, heat sealable aluminium foil coated with HSL and of printable quality. Each strip will contain 10 tablets. Stips are packed in cartons of 30 or 60 tablets.

Cold Form Blister

Cold form laminate composed of aluminium foil one side bright, soft tampered, plain, dull side lacquer-laminated to oriented polyamide film bright side lacquer-laminated to PVC film. Each blister will contain 10 tablets. Blisters are packed in a carton in cartons of 30 or 60 tablets.

6.6 Special precautions for disposal <and other handling>

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext.1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER(S)

VILEPTIN CO 50/850: 57/21.2/0060

VILEPTIN CO 50/1000: 57/21.2/0061

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

September 2024

10. DATE OF REVISON OF THE TEXT

September 2024