APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

VIDAMACE 50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg vildagliptin.

VIDAMACE 50 mg contains sugar (lactose monohydrate 43,84 mg per tablet).

VIDAMACE 50 mg contains 3,00 mg sodium and is essentially sodium-free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets.

White to light yellowish, round, flat-faced bevelled edge tablets, debossed with “50” on one side with dimensions, diameter: 8,1 $\pm$ 0,1 mm and thickness: 3,2 $\pm$ 0,3 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VIDAMACE 50 mg is indicated for the treatment of type 2 diabetes mellitus in adults:

VIDAMACE 50 mg is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus, as add-on therapy, in combination with

metformin, a sulphonylurea (SU), or insulin (with or without metformin) when diet, exercise and a single antidiabetic medicine do not result in adequate glycaemic control.

VIDAMACE 50 mg is also indicated in triple combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicines do not provide adequate glycaemic control.

Management of diabetes should always include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient. This is important not only for the primary treatment of diabetes, but also as an adjunct to medicinal therapy.

4.2 Posology and method of administration

Posology

The management of antidiabetic therapy should be individualised.

The recommended daily dose is either one VIDAMACE 50 mg a day, or one VIDAMACE 50 mg taken twice daily, in combination with metformin or with insulin (with or without metformin).

When taken as triple combination with metformin and a sulphonylurea, the recommended dose is one VIDAMACE 50 mg twice a day.

When used in combination with a sulphonylurea, the recommended dose of VIDAMACE is 50 mg once daily, taken in the morning. In this patient population, VIDAMACE 100 mg daily (2 x 50 mg) was no more effective than 50 mg once daily.

Special populations

Renal impairment:

In patients with moderate or severe renal impairment or with end-stage renal disease (ESRD) on haemodialysis, the recommended dose of VIDAMACE 50 mg is 50 mg tablet once daily (see sections 4.4 and 5.2).

The maximum dose should be 50 mg in patients with mild renal impairment.

Elderly:

In patients treated with vildagliptin, as in VIDAMACE 50 mg, ≥ 65 years of age and ≥ 75 years of age no differences were observed in the overall safety, tolerability, or efficacy between this elderly population and younger patients.

No dose adjustments are necessary in elderly patients (≥ 65 years old) (see section 5.2).

Paediatric population

VIDAMACE 50 mg is not recommended for use in children and adolescents (< 18 years) as the safety and efficacy in this population group have not been established.

Method of administration

For oral use.

VIDAMACE 50 mg can be taken with or without food.

Missed dose:

Doctors should advise patients who forget to take VIDAMACE 50 mg to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- hypersensitivity to vildagliptin or to any of the ingredients of VIDAMACE 50 mg (see section 6.1)
- in patients with hepatic impairment, including patients with a pre-treatment ALT or AST > 2,5 x the upper limit of normal.

4.4 Special warnings and precautions for use

Hepatic impairment:

VIDAMACE 50 mg is contraindicated in patients with hepatic impairment, including patients with a pre-treatment elevated ALT or AST (see section 4.3).

Liver enzyme monitoring:

Cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patient's were generally asymptomatic and liver function tests (LFTs) returned to normal after discontinuation of treatment. Liver function tests should be performed prior to the initiation of treatment with VIDAMACE 50 mg to determine the patients baseline value.

Liver function test-monitoring is imperative and should be monitored during 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(s) to normal. Should an increase in AST or ALT of 3 x upper limit of normal or greater persist, VIDAMACE 50 mg should be discontinued.

Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue VIDAMACE 50 mg and contact their medical practitioner immediately. Following withdrawal of treatment with VIDAMACE 50 mg and LFT normalisation, VIDAMACE 50 mg treatment should not be reinitiated.

Cardiac failure:

Vildagliptin, as in VIDAMACE 50 mg, is not recommended in patients with New York Heart Association (NYHA) Class III. Rates of reported cardiac adverse events were higher in patients with NYHA functional class III treated with vildagliptin than with placebo.

There is no experience of vildagliptin, as in VIDAMACE 50 mg, use in clinical trials in patients with NYHA functional class IV and therefore use is not recommended in these patients.

Skin disorders:

Skin lesions, including blistering and ulceration have been reported in extremities of monkeys in nonclinical toxicology studies. Although skin lesions were not observed at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications. Furthermore, there have been post-marketing reports of bullous and exfoliative skin lesions.

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

Acute pancreatitis:

Use of vildagliptin, as in VIDAMACE 50 mg 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, VIDAMACE 50 mg should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.

Hypoglycaemia:

Sulphonylureas are known to cause hypoglycaemia. Patients receiving VIDAMACE 50 mg 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.

Arthralgia:

VIDAMACE 50 mg may cause arthralgia that can be severe.

General:

VIDAMACE 50 mg is not a substitute for insulin in insulin-requiring patients. VIDAMACE 50 mg should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Renal impairment:

There is limited experience in patients with ESRD on haemodialysis. Therefore, VIDAMACE 50 mg should be used with caution in these patients (see sections 4.2 and 5.2).

Excipients:

VIDAMACE 50 mg contains lactose. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take VIDAMACE 50 mg.

4.5 Interaction with other medicines and other forms of interaction

VIDAMACE 50 mg has a low potential for interactions. Since VIDAMACE 50 mg is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit nor induce CYP 450 enzymes, it is not likely to interact with co-medications that are substrates, inhibitors or inducers of these enzymes.

Furthermore, VIDAMACE 50 mg does not affect metabolic clearance of co-medications metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. Interaction studies were conducted with commonly co-prescribed medicines for patients with type 2 diabetes or medications with a narrow therapeutic window. As a result of these studies no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin, as in VIDAMACE 50 mg.

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, as in VIDAMACE 50 mg, may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

4.6 Fertility, pregnancy and lactation

Pregnancy

VIDAMACE 50 mg should not be used in pregnant and breastfeeding women, as safety in pregnancy and lactation has not been established.

Breastfeeding

It is unknown whether vildagliptin, as in VIDAMACE 50 mg, is excreted in human milk. Mothers on VIDAMACE 50 mg should not breastfeed their infants.

Fertility

No studies on the effect on human fertility have been conducted for VIDAMACE 50 mg.

4.7 Effects on ability to drive and use machines:

Dizziness has been reported in patients taking vildagliptin, as in VIDAMACE 50 mg. Patients who experience dizziness should avoid driving vehicles or using machines.

4.8 Undesirable effects

a). Summary of the safety profile

The majority of adverse reactions in trials were mild and transient, not requiring treatment discontinuations. No association was found between adverse reactions and age, ethnicity, duration of exposure or daily dose.

Cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment.

Cases of angioedema have been reported during treatment with vildagliptin, as in VIDAMACE 50 mg. A greater proportion of cases were reported when vildagliptin was administered in combination with an ACE-Inhibitor. The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

b). *Tabulated summary of adverse reactions*

System Organ Class	**Frequency**	**Side effects**
Metabolism and nutrition disorders	Frequent	*** Decreased blood glucose, ****hypoglycaemia
Nervous system disorders	Frequent	*Tremor, *dizziness, headache, ***chills
***Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Nausea, gastroesophageal reflux disease, constipation Diarrhoea, flatulence Pancreatitis, intestinal obstruction

Hepatobiliary disorders	Frequency unknown	Cases of hepatitis, usually reversible upon medicine discontinuation, cholecystitis
**** Skin and subcutaneous tissue disorders	Frequent Frequency unknown	Hyperhidrosis Urticaria, localised exfoliation or blister
Musculoskeletal and connection tissue disorders	Frequency unknown	Arthralgia, sometimes severe
**General disorders and administration site conditions	Frequent	Asthenia, peripheral oedema

* Vildagliptin in combination with metformin and sulphonylurea only

** Vildagliptin in combination with sulphonylurea only

*** Vildagliptin in combination with insulin (with or without metformin)

****Vildagliptin in combination with metformin and sulphonylurea

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Muscle pain, paraesthesia, fever and oedema have been reported.

Increases in lipase levels (2 x ULN), creatine phosphokinase (CPK) levels, accompanied by elevations of aspartate aminotransferase (AST), C-reactive protein, and myoglobin may develop.

Management of overdose:

Treatment is symptomatic and supportive.

VIDAMACE 50 mg is not dialysable; however, the major hydrolysis metabolite (LAY151) can be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: A10BH02

Pharmacological classification: A 21.2. Oral hypoglycaemics

Mechanism of action

Vildagliptin is a selective dipeptidyl-peptidase-4 (DPP-4) inhibitor.

It increases endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide) by inhibiting the enzyme responsible for their degradation, DPP-4 (dipeptidyl-peptidase-4). The incretin hormones GLP-1 and GIP enhance glucose-dependent insulin secretion and exhibit other antihyperglycaemic actions following their release into the circulation from the gut in response to a meal. GLP-1 also suppresses inappropriate glucagon secretion. By increasing endogenous levels of these incretin hormones, vildagliptin enhances glucose-dependent insulin secretion by the pancreatic β-cell and suppresses inappropriately elevated glucagon secretion by the pancreatic α-cell.

The administration of vildagliptin results in a rapid and complete (> 90 %) inhibition of DPP-4 activity. The duration of DPP-4 inhibition is dose-dependent. The mean residence time of DPP-4 inhibition after 50 mg and 100 mg once-daily dosing with vildagliptin is 8,3 hours and 9,6 hours, respectively. This inhibition in DPP-4 activity by vildagliptin is associated with increases in basal as well as meal-stimulated GLP-1 and GIP levels throughout the day. Vildagliptin improves pancreatic islet function as evidenced by the improved ability of the α-cell and β-cell to sense and respond to glucose.

α-cell function: An indication of α-cell function is the ability to suppress inappropriate glucagon secretion in the presence of hyperglycaemia. In type 2 diabetes, glucagon is inappropriately suppressed, resulting in increased hepatic glucose production. After a single oral dose of vildagliptin (100 mg qd) in patients with type 2 diabetes glucagon levels were reduced before the evening meal, both in the prandial period and throughout the overnight post-absorptive period relative to placebo.

β-cell function: An indication of β-cell function is glucose-dependent insulin secretion. Vildagliptin improves pancreatic β-cell responsiveness to glucose leading to increased insulin secretion. This effect occurs only in the presence of elevated glucose concentrations in patients with type 2 diabetes. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion nor does it reduce glucose levels.

First phase insulin secretion: An early and sensitive indicator of β-cell function is first phase insulin secretion in response to intravenous glucose. In untreated type 2 diabetes patients, first

phase insulin secretion is virtually abolished, whereas patients treated with vildagliptin for 12 weeks demonstrated a clear improvement in restoration of first phase insulin secretion in response to a glucose stimulus. After discontinuation of vildagliptin for 2 weeks, this improvement is diminished.

Vildagliptin inhibits hepatic glucose production during meals as well as during the overnight post-absorptive period. Furthermore, the improvements in glycaemic control are associated with attenuated insulin resistance.

In addition, vildagliptin reduces postprandial lipaemia reflecting an effect to decrease both chylomicron and VLDL triglycerides.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration in the fasting state, vildagliptin is well absorbed with peak plasma concentrations observed at 1,75 hours.

Co-administration with food slightly decreases the rate of absorption of vildagliptin, as characterized 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).

Distribution:

The plasma protein binding of vildagliptin is low (9,3 %), and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady-state after intravenous administration (Vss) is 71 L, suggesting extravascular distribution.

Biotransformation:

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. *In-vitro* studies demonstrated that vildagliptin does not inhibit or induce cytochrome P450 enzymes.

Excretion and elimination:

Following oral administration of [14C] - vildagliptin, approximately 85 % of the dose is 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 approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours and is independent of dose.

Linearity/non-linearity:

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

Pharmacokinetics in special patient groups

Gender:

Although exposure in women was 13 % higher than in men, no statistically significant differences in the pharmacokinetics of vildagliptin were observed between male and female subjects with a diverse range of age and body mass index (BMI), DPP-4 inhibition by vildagliptin was unaffected by gender.

Obesity:

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

Hepatic impairment:

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 ~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 (see section 4.3).

Renal impairment:

In subjects with mild, moderate, and severe renal impairment, and end stage renal disease (ESRD) patients on haemodialysis, systemic exposure to vildagliptin was increased (C_{max} 8 % - 66 %; AUC 32 % - 134 %) compared to subjects with normal renal function. Exposure to the inactive metabolite (LAY151) increased with increasing severity of renal impairment (AUC 1,6- to 6,7-fold). Changes in exposure to vildagliptin did not correlate with severity of renal impairment, whereas changes in exposure to the inactive metabolite did correlate.
The elimination half-life of vildagliptin was not affected by renal impairment (see section 4.2).

Elderly:

In otherwise healthy elderly subjects (≥ 70 years), the overall exposure to vildagliptin (100 mg once daily) was increased by 32 % with an 18 % increase in peak plasma concentration compared to younger healthy subjects (18 - 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.

Paediatric population

No pharmacokinetic data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Croscarmellose sodium

Lactose

Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30˚C. Keep blisters in carton until use.

6.5 Nature and contents of container

OPA/ALU/PVC-Aluminium foil blisters.

Pack sizes of 30 or 60 tablets per outer carton. Not all pack sizes will be marketed.

6.6 Special precautions for disposal

No special precautions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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A56/21.2/0772

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