Professional Information

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

VILDAGLIPTIN 50 UNICORN tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **VILDAGLIPTIN 50 UNICORN** tablet contains 50 mg vildagliptin.

VILDAGLIPTIN 50 UNICORN contains sugar (47,00 mg lactose).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to off-white, round, flat tablets, engraved with 'VLD' on the one side, plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VILDAGLIPTIN 50 UNICORN 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.

VILDAGLIPTIN 50 UNICORN 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 dose of **VILDAGLIPTIN 50 UNICORN** is 50 mg a day or 50 mg twice a day in combination with metformin or insulin (with or without metformin).

For triple combination, the recommended dose of **VILDAGLIPTIN 50 UNICORN** is 50 mg twice a day with metformin and a sulphonylurea.

When used in combination with a sulphonylurea, the recommended dose of **VILDAGLIPTIN 50 UNICORN** is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 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 **VILDAGLIPTIN 50 UNICORN** is 50 mg once daily (see section 5.2). The maximum dose should be 50 mg in patients with mild renal impairment.

Elderly

In patients treated with vildagliptin ≥ 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 dosage adjustments are therefore necessary in the elderly patients without renal impairment (see section 5.2).

Paediatric population

VILDAGLIPTIN 50 UNICORN has not been studied in patients under 18 years of age; therefore, the use **VILDAGLIPTIN 50 UNICORN** in paediatric patients is not recommended (see section 5.2).

Method of administration

Oral

4.3 Contraindications

- **VILDAGLIPTIN 50 UNICORN** is contraindicated in patients with known hypersensitivity to vildagliptin or to any of the excipients of **VILDAGLIPTIN 50 UNICORN**

- **VILDAGLIPTIN 50 UNICORN** is contraindicated 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

General

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

VILDAGLIPTIN 50 UNICORN may cause arthralgia that can be severe.

Renal impairment

There is limited experience in patients with End-Stage-Renal-Disease (ESRD) on haemodialysis. Therefore, **VILDAGLIPTIN 50 UNICORN** should be used with caution in these patients (see sections 4.2, 5.1 and 5.2).

Hepatic impairment

VILDAGLIPTIN 50 UNICORN should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3 x ULN (see sections 4.2 and 5.2).

Liver enzyme monitoring

Cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function test results returned to normal after discontinuation of treatment. Liver function tests should be performed prior to the initiation of treatment with **VILDAGLIPTIN 50 UNICORN** in order to know the patient's baseline value.
Liver function should be monitored during treatment with **VILDAGLIPTIN 50 UNICORN** 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 ULN or greater persist, withdrawal of **VILDAGLIPTIN 50 UNICORN** therapy is recommended.

Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue **VILDAGLIPTIN 50 UNICORN.**

Following withdrawal of treatment with **VILDAGLIPTIN 50 UNICORN** and LFT normalisation, treatment with **VILDAGLIPTIN 50 UNICORN** should not be reinitiated.

Cardiac failure

VILDAGLIPTIN 50 UNICORN 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 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 non-clinical toxicology studies. Although skin lesions were not observed at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications. Furthermore, there have been post-marketing reports of bullous and exfoliative skin lesions. Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.

Acute pancreatitis

Use of vildagliptin has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis. If pancreatitis is suspected, **VILDAGLIPTIN 50 UNICORN** should be discontinued; if acute pancreatitis is confirmed, **VILDAGLIPTIN 50 UNICORN** should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.

Hypoglycaemia

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

Excipients

VILDAGLIPTIN 50 UNICORN contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **VILDAGLIPTIN 50 UNICORN**.

4.5 Interaction with other medicines and other forms of interaction

Vildagliptin has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate and does not inhibit or induce CYP 450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes.

Furthermore, vildagliptin 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.

Combination with pioglitazone, metformin and glyburide

Results from studies conducted with these oral antidiabetics have shown no clinically relevant pharmacokinetic interactions.

***Digoxin* (Pgp substrate), warfarin (CYP2C9 substrate)**

Clinical studies performed with healthy subjects have shown no clinically relevant pharmacokinetic interactions. However, this has not been established in the target population.

Combination with amlodipine, ramipril, valsartan or simvastatin

Interaction studies in healthy subjects were conducted with amlodipine, ramipril, valsartan and simvastatin. In these studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin.

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 medicines and sympathomimetics.

4.6 Fertility, pregnancy and lactation (see section 4.2 and 4.3 and 4.4)

Pregnancy

There are no adequate data from the use of vildagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Due to lack of human data, **VILDAGLIPTIN 50 UNICORN** should not be used during pregnancy.

Breast-feeding

It is unknown whether vildagliptin is excreted in human milk. Animal studies have shown excretion of vildagliptin in milk. **VILDAGLIPTIN 50 UNICORN** should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted for **VILDAGLIPTIN 50 UNICORN**.

4.7 Effects on ability to drive and use machines

VILDAGLIPTIN 50 UNICORN may cause dizziness. Patients who experience dizziness as an adverse reaction should avoid driving vehicles or using machines.

4.8 Undesirable effects

Cases of angioedema have been reported during treatment with vildagliptin. Cases of hepatic dysfunction (including hepatitis) have been reported.

Table 1: Adverse reactions reported in patients who received **VILDAGLIPTIN 50 UNICORN** as add-on therapy, by system organ class and absolute frequency.

MedDRA system organ class	**Adverse reaction**	**Frequency of adverse reaction**
Nervous system disorders	*Tremor, *dizziness, headache, ***chills	*Frequent*
**General disorders and administration site conditions	Asthenia, peripheral oedema	*Frequent*
***Gastrointestinal disorders	Nausea, gastroesophageal reflux disease, constipation	*Frequent*
	Diarrhoea, flatulence	*Less frequent*
	Pancreatitis	*Frequency unknown*
Metabolism and nutritional disorders	*** Decreased blood glucose, **** hypoglycaemia	*Frequent*
**** Skin and subcutaneous tissue disorders	Hyperhidrosis	*Frequent*
	Urticaria, localised exfoliation or blisters	*Frequency unknown*

Hepatobiliary disorders	Cases of hepatitis, usually reversible upon medicine discontinuation	*Frequency unknown*
Musculoskeletal and connective tissue disorders	Arthralgia	*Frequency unknown*

* 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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

Adverse reactions may also be reported directly to Unicorn using the following email: vigilance@unicornpharma.co.za

4.9 Overdose

Information regarding overdose with vildagliptin is limited.

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

In the event of an overdose, supportive management is recommended. Vildagliptin cannot be removed by haemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.2. Oral hypoglycaemics

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

ATC code: A10BH02

Vildagliptin, a member of the islet enhancer class, is a potent and selective DPP-4 inhibitor.

Mechanism of action

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 antihyperglycemic 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 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).

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.

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:

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.

Special populations:

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 (Cmax 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 4.3 and 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:

No pharmacokinetic data available.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose

Lactose

Pregelatinised maize starch

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C

Keep out of the reach of children

6.5 Nature and contents of container

VILDAGLIPTIN 50 UNICORN tablets are packed in aluminium / aluminium blisters of 28 or 56 tablets. The blisters are packed in an outer cardboard boxes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBERS

59/21.2/0605

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 July 2026

10 DATE OF REVISION OF THE TEXT

Not applicable