Professional Information

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

VILEPTIN

2. QUALITATIVE AND QUANTITAIVE COMPOSITION

VILEPTIN

Each film coated tablet contains:

Vildagliptin 50 mg

Contains sugar: Lactose anhydrous 94,50 mg

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

3. PHARMACEUTICAL FORM

VILEPTIN

White to off white coloured, round tablets debossed with ‘50’ on one side and ‘V’ on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vildagliptin 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 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

The management of antidiabetic therapy should be individualised.

The recommended dose of **VILEPTIN** is 50 mg a day or 50 mg twice a day in combination with metformin or insulin (with or without metformin).

The recommended dose of **VILEPTIN** is 50 mg twice a day for triple combination with metformin and a SU.

When used in combination with a sulphonylurea, the recommended dose of **VILEPTIN** is 50 mg once daily administered in the morning. In this patient population, **VILEPTIN** 100 mg daily was reported to be more effective than vildagliptin 50 mg once daily.

Special populations

Patients with renal impairment

In patients with moderate or severe renal impairment or with End Stage Renal Disease (ESRD) on haemodialysis the recommended dose of **VILEPTIN** is 50 mg once daily (see section 5.2).

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

Elderly patients

In patients treated with **VILEPTIN** ≥ 65 years of age and ≥ 75 years of age no differences were reported 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

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

Method of administration

For oral use.

4.3 Contraindications

- **VILEPTIN** is contraindicated in patients with a known hypersensitivity to vildagliptin or to any of the excipients of **VILEPTIN** (see section 6.1).
- **VILEPTIN** 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

Hepatic impairment:

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

Liver enzyme monitoring:

There have been reported cases of hepatic dysfunction (including hepatitis) in patients using **VILEPTIN**. The patients were generally asymptomatic in these cases and liver function tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with **VILEPTIN**.

LFT-monitoring is imperative:

Liver function tests should be monitored during **VILEPTIN** 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, **VILEPTIN** should be discontinued.

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

Renal impairment:

There is limited experience reported in patients with ESRD on haemodialysis. Therefore **VILEPTIN** should be used with caution in these patients (see section 4.2 and 5.2).

Heart failure:

Vildagliptin is not recommended in patients with New York Heart Association (NYHA) Class III. The rates of reported cardiac events were higher in patients with NYHA functional Class III treated with vildagliptin than with a placebo. Since there is no experience of the use of vildagliptin in reported clinical trials in patients with NYHA functional Class IV, it is not recommended for use in these patients.

Skin disorders:

Skin lesions, including blistering and ulceration have been reported in

extremities of monkeys in reported non-clinical toxicology studies. Although skin lesions were not reported at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications. Furthermore, there have been 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:

Patients should be informed of the characteristic symptom of acute pancreatitis, since the use of vildagliptin has been reported to be associated with a risk of it being developed.

If pancreatitis is suspected, **VILEPTIN** should be discontinued and if acute pancreatitis is confirmed, **VILEPTIN** should not be restarted. Caution should thus be exercised in patients with a history of acute pancreatitis.

Hypoglycaemia:

Patients receiving **VILEPTIN** in combination association with a sulphonylurea may be at risk for hypoglycaemia, since sulphonylureas are known to cause hypoglycaemia. A lower dose of a sulphonylurea may therefore be considered, to reduce the risk of hypoglycaemia.

General:

Vildagliptin may cause arthralgia that can be severe.

VILEPTIN is not a substitute for insulin in insulin-requiring patients.

VILEPTIN should not be used in patients with type 1 diabetes for the treatment of diabetic ketoacidosis.

Excipients:

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

4.5 Interaction with other medicines and other forms of interaction

Since vildagliptin, as contained in **VILEPTIN**, is not a cytochrome P450 enzyme substrate nor does it inhibit nor induces cytochrome P450 enzymes, it is not likely to interact with co-medications that are substrates, inhibitors or inducers of these enzymes and thus has a low potential for interactions.
Furthermore, vildagliptin does not affect metabolic clearance of co-medications metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5.

Interaction studies have been reported with commonly co-prescribed medicines 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, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin have been reported after co-administration with vildagliptan.

Taking ACE-inhibitors concomitantly simultaneously with vildagliptin may lead to an increased risk of angioedema.

The hypoglycaemic effect of vildagliptin may be reduced by certain active substances such as thiazides, corticosteroids, thyroid products and sympathomimetics.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

It is unknown whether vildagliptin is excreted in human milk. Reported animal studies have shown excretion of vildagliptin in milk. **VILEPTIN**. should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been reported for **VILEPTIN**.

4.7 Effects on ability to drive and use machines

VILEPTIN may cause dizziness. Patients who experience dizziness should avoid driving vehicles or using machines.

4.8 Undesirable effects

Cases of angioedema have been reported during treatment with **VILEPTIN**.

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

Table: Adverse reactions reported with vildagliptin as monotherapy or as add on therapy			
	Frequent	**Less frequent**	**Frequency unknown**
Infections and infestations		[**]nasopharyngitis; upper respiratory tract infection	
Metabolism and nutrition disorders	[***]decreased blood glucose; [****]hypoglycaemia; weight increase		
Nervous system disorders	[*]tremor, [*]dizziness, headache; [***]chills		
[***]**Gastrointestinal disorders**	nausea, gastroesophageal reflux disease, constipation	diarrhoea, flatulence	pancreatitis
Hepatobiliary disorders			Cases of hepatitis, usually reversible upon medicine discontinuation; abnormal liver function

			tests, reversible upon medicine discontinuation (see Section 4.4)
****Skin and subcutaneous tissue disorders**	hyperhidrosis		Localised exfoliation or blisters including bullous pemphigoid, Urticaria
Musculoskeletal, connective tissue and bone disorders			Arthralgia, sometimes severe; myalgia
****General disorders and administration site conditions**	asthenia, peripheral oedema	fatigue	

* 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 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/document/adverse-drug-reactions-and-quality-problem-reporting-form/

4.9 Overdose

Signs and symptoms:

Muscle pain, paraesthesia, fever and oedema have been reported. Increases in lipase levels (2 x upper

level of normal), 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, symptomatic and supportive treatment is recommended.

VILEPTIN cannot be removed via haemodialysis; 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

Category and class: A21.2 Oral hypoglycaemics

Pharmacodynamic properties

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 and 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 reported to be 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 nondiabetic (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. First phase insulin secretion is virtually abolished in untreated type 2 diabetes patients, whereas patients treated with vildagliptin for 12 weeks demonstrated a clear improvement in restoration of first phase insulin secretion in response to 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

Linearity:

The 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.

Absorption:

Vildagliptin is well absorbed following oral administration in the fasting state, with an absolute bioavailability of 85 % and 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.

Metabolism:

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. Vildagliptin is not metabolised by cytochrome P450 enzymes to any quantifiable extent. Vildagliptin does not inhibit or induce cytochrome P450 enzymes.

Excretion and elimination:

Following oral administration of [^{14}C] - 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.

Special populations:

Gender:

Although exposure in women was reported to be 13 % higher than in men, no statistically significant differences in the pharmacokinetics of vildagliptin were reported 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 pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2,5x the upper limit of normal (see sections 4.2, 4.3 and 4.4).

Renal impairment:

In subjects with mild, moderate, 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 reported to be 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous, microcrystalline cellulose, sodium starch glycolate and magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at or below 25ºC. Protect from moisture.

Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

Each carton contains 30 or 60 tablets packed in cold form blister pack which comprises of cold form blister laminate composed of oriented polyamide, aluminium foil and PVC film with backing of hard tempered aluminium foil coated with heat seal lacquer on the inner side.

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)

Will be allocated by SHAPRA upon registration

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Will be allocated by SAHPRA upon registration

10 DATE OF REVISON OF THE TEXT