SCHEDULING STATUS
S3

1. NAME OF THE MEDICINE

ZOMVIL 50 (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg vildagliptin.
Excipient with known effect: Each tablet contains 10,00 mg lactose (anhydrous).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.
White to light yellowish, round, flat faced, bevelled-edge, plain tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ZOMVIL is indicated in the treatment of type 2 diabetes mellitus in adults:

As monotherapy
- As an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus.

As dual oral therapy in combination with
- 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.

As triple oral therapy in combination with
- As a 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

Adults
The management of antidiabetic therapy should be individualised.
The recommended dose of ZOMVIL 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 ZOMVIL is 50 mg twice a day for triple combination with metformin and a sulphonylurea.
When used in combination with a sulphonylurea, the recommended dose of ZOMVIL is 50 mg once daily administered in the morning. In this patient population, ZOMVIL 100 mg daily is no more effective than ZOMVIL 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 ZOMVIL is 50 mg once daily. The maximum dose should be 50 mg in patients with mild renal impairment.

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 ZOMVIL is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST > 2,5x the upper limit of normal (see section 4.3).

Elderly (≥ 65 years)
In patients treated with vildagliptin 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 dosage adjustments are necessary in the elderly patients without renal impairment.

Paediatric populations
ZOMVIL is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of ZOMVIL in children and adolescents (< 18 years) have not been established.

Method of administration
For oral use.

4.3 Contraindications

ZOMVIL is contraindicated in:
- Patients with known hypersensitivity to vildagliptin or to any of the excipients listed in section 6.1;
- Patients with hepatic impairment, including patients with a pre-treatment ALT or AST > 2,5 times (2,5x) the upper limit of normal.

4.4 Special warnings and precautions for use

General
ZOMVIL is not a substitute for insulin in insulin-requiring patients. ZOMVIL 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. ZOMVIL should be used with caution in renal impaired patients (also see sections 4.2, 5.1 and 5.2).

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

Liver function tests monitoring
Cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic and liver function tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with vildagliptin.
Liver function tests (LFT) should be performed prior to the initiation of treatment with ZOMVIL as well as during ZOMVIL 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 2,5x upper limit of normal or greater persist, ZOMVIL should be discontinued (see section 4.3).
Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue ZOMVIL and contact their medical practitioner immediately. Following withdrawal of treatment with ZOMVIL and LFT normalisation, ZOMVIL treatment should not be reinitiated.

Heart failure
ZOMVIL is not recommended in patients diagnosed with New York Heart Association (NYHA) Class III. Rates of 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 patients with NYHA functional class IV and therefore use is not recommended in these patients.

Arthralgia
ZOMVIL may cause severe arthralgia.

Skin disorders
Although skin lesions were not observed at an increased incidence in clinical trials with vildagliptin, 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 may be associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis.
If pancreatitis is suspected, ZOMVIL should be discontinued. If acute pancreatitis is confirmed, ZOMVIL 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 ZOMVIL 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
ZOMVIL contains lactose (see section 6.1). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ZOMVIL.

4.5 Interaction with other medicines and other forms of interaction

Vildagliptin has a low potential for interactions when co-administered with other 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 medicines that are substrates, inhibitors or inducers of these enzymes.

Combination with pioglitazone, metformin, glibenclamide and glyburide
Results from studies conducted with these oral antidiabetics have shown no clinically relevant pharmacokinetic interactions.

Digoxin (Pgp substrate) or 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).

Other
The hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including hydrochlorothiazide, corticosteroids, thyroid products and sympathomimetics.

4.6 Fertility, pregnancy and lactation

ZOMVIL should not be used during pregnancy and breastfeeding as the safety of vildagliptin have not been established.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Infections and infestations	*Less frequent*	Nasopharyngitis[2,6], upper respiratory tract infection[6]
Metabolism and nutritional disorders	*Frequent*	Decreased blood, glucose[3]; hypoglycaemia[1,2,3,4,5,6], weight increase[5]
Nervous system disorders	*Frequent*	Tremor[1,2,4], dizziness[1,2,4,6], headache[1,2,3,5,6]; chills[3], fatigue[1], asthenia[2,4,5]
Vascular disorders	*Frequent*	Peripheral oedema[2,5,6]
Gastrointestinal disorders	*Frequent*	Nausea[1,3], gastroesophageal reflux disease[3], constipation[2,6]
	Less frequent	Diarrhoea[3], flatulence[3]
Skin and subcutaneous tissue disorders	*Frequent*	Hyperhidrosis[4]
Musculoskeletal and connective tissue disorders	*Less frequent*	Arthralgia[6]

b. Description of selected adverse reactions

[1] Side-effects that may occur with ZOMVIL in combination with metformin only.
[2] Side effects that may occur with ZOMVIL in combination with sulphonylurea only.
[3] Side effects that may occur with ZOMVIL in combination with insulin (with or without metformin).
[4] Side effects that may occur with ZOMVIL in combination with metformin and sulphonylurea.
[5] Side effects that may occur with ZOMVIL in combination with thiazolidinedione only.
[6] Side effects that may occur with ZOMVIL as monotherapy.

c. Post-marketing experience

The following additional side effects may occur:

System Organ Class	Frequency	Undesirable effect
Gastrointestinal disorders	*Frequency unknown*	Pancreatitis
Hepato-biliary disorders	*Frequency unknown*	Cases of hepatitis, usually reversible upon medicine discontinuation
Skin and subcutaneous tissue disorders	*Frequency unknown*	Urticaria, localised exfoliation or blisters
Musculoskeletal and connective tissue disorders	*Frequency unknown*	Arthralgia, sometimes severe

d. Paediatric populations
The safety of ZOMVIL for use in children and adolescents (< 18 years) have not been established.

e. 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 "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms
Muscle pain, paraesthesia, fever and oedema have been reported. Increases in lipase levels (2x ULN), creatine phosphokinase (CPK) levels, accompanied by elevations of aspartate aminotransferase (AST), C-reactive protein, and myoglobin may develop.

Management
Treatment is symptomatic and supportive. ZOMVIL is not dialysable; however, the major hydrolysis metabolite (LAY151) can be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.2. Oral hypoglycaemics.

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 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. 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

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.

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 is distributed equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady state after intravenous administration (Vss) is 71 litres, 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 as shown in an *in vivo* study using DPP-4 deficient rats. Vildagliptin is not metabolized 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 [^{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 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 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 > 2.5x the ULN (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 sections 4.2 and 4.3).

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 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.

Paediatric population
No pharmacokinetic data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, Microcrystalline
Lactose Anhydrous
Low-Substituted Hydroxypropylcellulose
Magnesium Stearate

6.2 Incompatibilities

Unknown.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 ºC.
Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

Aluminium/Aluminium (OPA/ALU/PVC) blisters.
Available in packs containing 7, 14, 28, 30, 56, 60, 90, 112 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDERS OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.
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8 REGISTRATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

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N.A

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