PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

Viglymak Plus 50/850 mg film coated tablets

Viglymak Plus 50/1000 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Viglymak Plus 50/850 mg

Each film - coated tablet contains 50 mg Vildagliptin and 850 mg metformin hydrochloride.

Viglymak Plus 50/1000 mg

Each film - coated tablet contains 50 mg Vildagliptin and 1000 mg metformin hydrochloride.

Sugar free

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

Viglymak Plus 50/850 mg: Yellow colored, oval shaped, biconvex, film-coated tablets, debossed with “F59” on one side and plain on other side

Viglymak Plus 50/1000 mg: Dark yellow colored, oval shaped, biconvex, film- coated tablets, debossed with “F60” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For patients with Type 2 diabetes mellitus (T2DM).

Viglymak Plus 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.

Viglymak Plus is indicated as an add-on to insulin as an adjunct to diet and exercise in patients on a stable dose of insulin plus vildagliptin and metformin hydrochloride.

Viglymak Plus 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.

Viglymak Plus can be used to replace the ~~V~~vildagliptin and metformin hydrochloride at the same dosages as the separate tablets.

4.2 Posology and method of administration

Posology

In using Viglymak Plus do not exceed the maximum daily dose of vildagliptin (100 mg).

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

Use by combination with sulphonylurea or with insulin:

The dose of Viglymak Plus 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.

Special populations

Patients with renal impairment:

A GFR should be assessed before initiation of treatment with metformin-containing products (such as Viglymak Plus) 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 Viglymak Plus) in patients with GFR < 60 ml/min. Viglymak Plus 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 Viglymak Plus 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 Viglymak Plus alone are considered necessary

Patients with hepatic impairment:

Viglymak Plus is not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment ALT or AST > 2,5 X the upper limit of normal (see section 4.4 “Monitoring of renal function”).

Elderly

As metformin is excreted via the kidney, and elderly patients have a tendency to exhibit decreased renal function, elderly patients taking Viglymak Plus should have their renal function monitored regularly. The dosage of [PRODCT NAME] for elderly patients should be adjusted based on renal function (see section 4.3 “Renal disease” and section 4.4 “Monitoring of renal function”).

Paediatric population

Safety and efficacy of Viglymak Plus in paediatric patients have not been established. Therefore, Viglymak Plus is not recommended for use in children below 18 years of age.

Method of administration

Oral use.

4.3 Contraindications

Viglymak Plus is contraindicated in:

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Any type of acute or chronic metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis), with or without coma. Diabetic ketoacidosis should be treated with insulin.
- Severe renal failure (GFR < 30 mL/min) (see section 4.2 and 4.4)
- 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)
- Patients with congestive heart failure requiring pharmacological treatment (see section 4.4)

4.4 Special warnings and precautions for use

General

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

Lactic acidosis

Lactic acidosis, serious metabolic complication, most often occurs at acute worsening of renal function,

or cardio respiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

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.

Medicines that can acutely impair renal function (such as antihypertensive, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicines that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7,35), increased plasma lactate levels (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Administration of iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Metformin should 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 4.5).

Renal function

GFR should be assessed before treatment initiation and regularly thereafter (see section 4.2). Metformin is 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 kidneys, 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, metformin-containing products (such as Viglymak Plus) should be carefully titrated in the elderly to establish the minimum dose for adequate glycaemic effect, and renal function should be monitored regularly (see section 4.2).

Concomitant medicines that may affect renal function, result in significant haemodynamic change, or inhibit renal transport and increase metformin systemic exposure, should be used with caution (see section 4.5).

Viglymak Plus should be discontinued if evidence of renal impairment is present.

Hepatic impairment

Patients with hepatic impairment, including those with pre-treatment ALT or AST > 2,5 x ULN, should not be treated with Viglymak Plus (see sections 4.2, 4.3 and 4.8).

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 Viglymak Plus in order to know the patient's baseline value. Liver function should be monitored during treatment with Viglymak Plus 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 LFTs until the abnormality (ies) return(s) to normal. Should an increase in AST or in ALT of 3x ULN or greater persist, withdrawal of Viglymak Plus therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Viglymak Plus.

Following withdrawal of treatment with Viglymak Plus and LFT normalisation, treatment with Viglymak Plus should not be re-initiated.

Skin disorders

Skin lesions, including blistering and ulceration have been reported with vildagliptin 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.

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 Viglymak Plus. SCARs are regarded as a class effect of DPP-4 inhibitors such as Viglymak Plus. If a patient develops SCAR, treatment with DPP-4 inhibitors such as Viglymak Plus 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 Viglymak Plus. 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.

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.

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.

Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Hypoxic states

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxaemia have been associated with lactic acidosis and may also cause prerenal uraemia. If such events occur in patients receiving Viglymak Plus therapy, the medication should be promptly discontinued.

Vitamin B12 levels

The metformin component of Viglymak Plus has been associated with a decrease in serum vitamin B12 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 B12 supplementation. Measurement of haematological parameters on at least an annual basis is advised for patients receiving metformin-containing products (such as Viglymak Plus) and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (e.g. those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 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 Viglymak Plus 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, Viglymak Plus must be stopped immediately and appropriate measures initiated.

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 Viglymak Plus and temporarily administer insulin. Viglymak Plus may be reinstituted after the acute episode is resolved.

4.5 Interaction with other medicines and other forms of interaction

There have been no formal interaction studies for Viglymak Plus. The following statements reflect the information available on the individual active substances.

Vildagliptin

Vildagliptin has a low potential for interactions with co-administered medicines. 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.

Results from clinical trials conducted with the oral antidiabetics pioglitazone, metformin and glyburide in combination with vildagliptin have shown no clinically relevant pharmacokinetic interactions in the target population.

Interaction studies with digoxin (P-glycoprotein substrate) and warfarin (CYP2C9 substrate) in healthy subjects have shown no clinically relevant pharmacokinetic interactions after co-administration with vildagliptin.

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. However, this has not been established in the target population.

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

Combinations not recommended

Alcohol

Alcohol is known to potentiate the effect of metformin hydrochloride on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving metformin containing products such as Viglymak Plus. Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

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 Viglymak Plus 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 medcines and on its discontinuation.

Concomitant use of medicines 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.

Furosemide

Furosemide increased Cmax and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreased C_{max} blood AUC of furosemide, with no change in renal clearance of furosemide.

Nifedipine

Nifedipine increased absorption, C_{max} 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 C_{max} 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-containing products (such as Viglymak Plus) and such medications are recommended.

Other

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-containing products (such as Viglymak Plus), close monitoring of renal function is necessary. Certain medicines tend to cause 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Viglymak Plus in pregnant women. 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. Viglymak Plus should not be used during pregnancy.

Breast-feeding

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, Viglymak Plus should not be used during breast-feeding (see section 4.3).

Fertility

No studies on the effect on human fertility have been conducted for Viglymak Plus (see section 5.3).

4.7 Effects on ability to drive and use machines

Viglymak Plus may cause dizziness. Patients who experience dizziness should avoid driving or using machines.

4.8 Undesirable effects

Viglymak Plus frequently causes decreased blood glucose levels, tremor, dizziness, headache, chills, metallic taste, nausea, gastroesophageal reflux disease, diarrhoea, abdominal pain, loss of appetite, hyperhidrosis and asthenia.

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

Rare 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 returned to normal after discontinuation of treatment.

Rare cases of angioedema have been reported on vildagliptin. 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.

Tabulated summary of adverse reactions

Table 1 Adverse reactions reported in patients who received vildagliptin 100 mg daily as add-on therapy to metformin

System organ class	**Frequent**	**Less frequent**	**Frequency unknown**
Metabolism and nutrition disorders	Hypoglycaemia		

Nervous system disorders	Tremor, dizziness, headache	Fatigue	
Gastrointestinal disorders	Nausea		

Table 2 Adverse reactions reported in patients who received vildagliptin 100 mg daily in combination with insulin (with or without metformin)

Metabolism and nutrition disorders	Hypoglycaemia		
Nervous system disorders	Headache, chills		
Gastrointestinal disorders	Nausea, gastroesophageal reflux disease	Diarrhoea, flatulence	

Table 3 Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with metformin and a sulphonylurea

Metabolism and nutrition disorders	Hypoglycaemia		

Nervous system disorders	Dizziness, tremor		
Skin and subcutaneous tissue disorders	Hyperhidrosis		
General disorders and administration site conditions	Asthenia		

Vildagliptin:

Adverse reactions for vildagliptin component from mono therapy

Table 4 Adverse reactions reported in patients who received vildagliptin 100 mg daily as mono therapy

Infections and infestations		Upper respiratory tract infection, nasopharyngitis	
Metabolism and nutrition disorders		Hypoglycaemia	
Nervous system disorders	Dizziness	Headache	

Vascular disorders		Oedema peripheral	
Gastrointestinal disorders		Constipation	
Musculoskeletal and connective tissue disorders		Arthralgia	

Metformin

Table 5 Adverse reactions for metformin component

Metabolism and nutrition disorders	Decreased appetite	Decrease of vitamin B_{12} absorption and lactic acidosis*	
Nervous system disorders	Metallic taste		
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain and flatulence		
Hepatobiliary disorders		Liver function test abnormalities or hepatitis**	
Skin and subcutaneous tissue disorders		Skin reactions such as erythema, pruritus, urticaria	

*A decrease in vitamin B12 absorption with decrease in serum levels has been very rarely observed in patients treated long-term with metformin. 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.

Gastrointestinal adverse reactions 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.

Table 6

Other adverse reactions reported

Gastrointestinal disorders			Pancreatitis
Hepatobiliary disorders			Hepatitis (reversible upon discontinuation of the medicine) Abnormal liver function tests (reversible upon discontinuation of the medicine)

Musculoskeletal and connective tissue disorders			Myalgia
Skin and subcutaneous			Urticarial, Exfoliative and bullous skin lesions, including bullous pemphigoid

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Macleods Pharmaceuticals SA (Pty) Ltd. at safety@macleodspharma.com

4.9 Overdose

No data are available with regard to overdose of Viglymak Plus.

Vildagliptin

Information regarding overdose with vildagliptin is limited.

Symptoms

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

Metformin

A large overdose of metformin (or co-existing risk of lactic acidosis) may lead to lactic acidosis, which is a medical emergency and must be treated in hospital. Hypoglycaemia may develop and should be monitored for.

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 hypoglycaemic

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

ATC code: A10BD08

Mechanism of action

Viglymak Plus combines two antihyperglycaemic medicines with complimentary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: vildagliptin, a member of the islet enhancer class, and metformin hydrochloride, a member of the biguanide class.

Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor. Metformin acts primarily by decreasing endogenous hepatic glucose production.

Pharmacodynamic effects

Vildagliptin

Vildagliptin acts primarily by inhibiting DPP-4, the enzyme responsible for the degradation of the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide).

The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 and GIP.

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 vildagliptin 50-100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function including HOMA-β (Homeostasis Model Assessment–β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion.

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 delaying gastric emptying is not observed with vildagliptin treatment.

Metformin

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia or increased weight gain.

Metformin may exert its glucose-lowering effect via three mechanisms:

- by reduction of hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis;

- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation;

- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase and increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

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

5.2 Pharmacokinetic properties

Viglymak Plus

Absorption

Food does not affect the extent and rate of absorption of vildagliptin from Viglymak Plus. The rate and extent of absorption of metformin from Viglymak Plus 50 mg/1000 mg were decreased when given with food as reflected by the decrease in C_{max} by 26 %, AUC by 7 % and delayed T_{max}(2,0 to 4,0 h).

The following statements reflect the pharmacokinetic properties of the individual active substances of Viglymak Plus.

Vildagliptin

Absorption

Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1,75 hours. Food slightly delays the time to peak plasma concentration to 2,5 hours, but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased C_{max} (19 %) compared to dosing in the fasting state. However, the magnitude

of change is not clinically significant, so that vildagliptin can be given with or without food. The absolute bioavailability is 85 %.

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 (V_{ss}) is 71 litres, suggesting extravascular distribution.

Biotransformation

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69 % of the dose. The major metabolite (LAY 151) 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 dose). DPP-4 contributes partially to the hydrolysis of vildagliptin based on an in vivo study using DPP-4 deficient rats. Vildagliptin is not metabolised by CYP 450 enzymes to any quantifiable extent, and accordingly the metabolic clearance of vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. In vitro studies demonstrated that vildagliptin does not inhibit/induce CYP 450 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.

Elimination

Following oral administration of [^{14}C] vildagliptin, approximately 85 % of the dose was excreted into the urine and 15 % of the dose was recovered in the faeces. Renal excretion of the unchanged vildagliptin accounted for 23 % of the dose after oral administration. After intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 and 13 L/h, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours.

Linearity/non-linearity

The C_{max} for vildagliptin and the area under the plasma concentrations versus time curves (AUC) increased in an approximately dose proportional manner over the therapeutic dose range.

Characteristics in patients

Gender: No clinically relevant differences in the pharmacokinetics of vildagliptin were observed between male and female healthy subjects within a wide range of age and body mass index (BMI). DPP-4 inhibition by vildagliptin is not affected by gender.

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

Hepatic impairment: In subjects with mild, moderate or severe hepatic impairment (Child-Pugh A-C) there were no clinically significant changes (maximum ~30 %) in exposure to vildagliptin.

Renal impairment: In subjects with mild, moderate, or severe renal impairment, systemic exposure to vildagliptin was increased (C_{max} 8 – 66 %; AUC 32 – 134 %) and total body clearance was reduced compared to subjects with normal renal function.

Ethnic group: Limited data suggest that race does not have any major influence on vildagliptin pharmacokinetics.

Metformin

Absorption

After an oral dose of metformin, the maximum plasma concentration (C_{max}) is achieved after about 2,5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50 – 60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20 – 30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 - 48 h and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels ($C_{max)}$ did not exceed 4 µg/mL, even at maximum doses.

Food slightly delays and decreases the extent of the absorption of metformin. Following administration of a dose of 850 mg, the plasma peak concentration was 40 % lower, AUC was decreased by 25 % and time to peak plasma concentration was prolonged by 35 minutes. The clinical relevance of this decrease is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The mean volume of distribution (V_d) ranged between 63- 276 litres.

Biotransformation

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

Elimination

Metformin is eliminated by renal excretion. Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6,5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl Cellulose HPC-L

Microcrystalline Cellulose Avicel PH 101

Isopropyl alcohol

Magnesium stearate

Film coating containing:

HPMC 2910/Hypromellose 6 mPas

Titanium Dioxide

Macrogol/PEG

Iron oxide yellow

Talc

6.2 Incompatibilities

Not applicable.

6.3 shelf life

24months from the date of manufacture for container and blister pack.

6.4 Special precaution for storage

Store at or below 30 °C.

Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and Contain of container

Blister pack :

Tablets are packed in a blister containing plain aluminium foil with heat seal lacquered as the lidding material and clear PVC/PVDC as the forming material. The blister is packed in an outer carton.

Blister pack cold form:

Tablets are packed in a blister containing plain aluminium foil with heat seal lacquered as the lidding material and cold form laminate as the forming material. The blister is packed in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

8. REGISTRATION NUMBERS

Viglymak Plus 50/850: 57/21.2/0368.366

Viglymak Plus 50/1000: 57/21.2/0369.367

9. DATE OF FIRST AUTHORISATION

24 June 2025

10. DATE OF REVISION OF THE TEXT

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PM0259-01

20/11/2025