Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Vildaril M 50/500mg, 50/850mg and 50/1000mg film-coated tablets.

2. Qualitative and quantitative composition:

VILDARIL M 50/500
Each film coated tablet contains:
Vildagliptin … 50 mg
Metformin Hydrochloride… 500 mg
Contains Lactose

VILDARIL M 50/850
Each film coated tablet contains:
Vildagliptin … 50 mg
Metformin Hydrochloride USP … 850 mg
Contains Lactose

VILDARIL M 50/1000
Each film coated tablet contains:
Vildagliptin … 50 mg
Metformin Hydrochloride USP … 1000 mg
Contains Lactose

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

VILDARIL M 50/500

Beige to creamish yellow coloured, oval shaped, film coated tablets, plain on both sides.

VILDARIL M 50/850

Yellow to dark yellow coloured, oval shaped, film coated tablets, plain on both sides.

VILDARIL M 50/1000

Dark yellow to brownish yellow coloured, oval shaped, film coated tablets, plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

For patients with Type 2 diabetes mellitus (T2DM):
VILDARIL M

Its indicated as an adjunct to diet and exercise to improve glycemic control in patients whose diabetes is not adequately controlled on metformin hydrochloride alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets. Treatment should not be initiated with this fixed-dose combination.
Its indicated in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with metformin and a sulfonylurea.
Its indicated as add-on to insulin as an adjunct to diet and exercise to improve glycemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycemic control

4.2 Posology and method of administration

Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment, other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g per day. To minimise the risk of lactic acidosis, only one strength of Vildaril M should be prescribed and used at any one time. Patients should also be advised to discard their previous metformin medication when initiated on Vildaril M.

Adults

The use of anti-hyperglycemic therapy in the management of T2D should be individualized on the basis of effectiveness and tolerability. The recommended starting dose of Vildaril M should be based on the patient's current regimen of vildagliptin and/or metformin hydrochloride. Vildaril M should be given with meals to reduce the gastrointestinal side effects associated with metformin hydrochloride. When using Vildaril M the maximum daily dose of vildagliptin (100 mg) should not be exceeded.

Starting dose for patients inadequately controlled on metformin hydrochloride monotherapy:

Based on the patient's current dose of metformin hydrochloride, Vildaril M may be initiated at either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily.

Starting dose for patients switching from combination therapy of vildagliptin plus metformin hydrochloride as separate tablets:

Vildaril M may be initiated with either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1000 mg tablet strength based on the dose of vildagliptin or metformin already being taken.
Use in combination with a sulfonylurea or with insulin: The dose of Vildaril M 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

Renal impairment

A GFR should be assessed before initiation of treatment with metformin-containing products (such as Vildaril M) 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 should be reviewed before considering initiation of metformin-containing products (such as Vildaril M) in patients with GFR< 60 ml/min. Vildaril M is contraindicated in patients with GFR<30 ml/min because of its metformin component
The following dosing recommendations apply to metformin and vildagliptin, used separately or in combination, in patients with renal impairment. If no adequate strength of Vildaril M is available, individual components should be used instead of the fixed dose combination.

Table 1: Dose adjustments in patients with renal impairment

GFR	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 1000mg with a maximum daily dose of 2000 mg*	Maximal daily dose is 50 mg
30-44	Starting dose should not be more than 500mg with a maximum daily dose of 1000 mg.	
<30	Metformin is contraindicated.	

*If metformin doses higher than those achievable with Vildaril M alone are considered necessary.

Hepatic impairment

Vildaril M is not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal (see section WARNINGS AND PRECAUTIONS).

Geriatric patients (65 years or above)

As metformin is excreted via the kidneys, and elderly patients tend to exhibit decreased renal function, elderly patients taking metformin-containing products (such as Vildaril M) should have their renal function monitored regularly.

Paediatric patients (below 18 years) The safety and effectiveness of Vildaril M in paediatric patients have not been established. Therefore, Vildaril M is not recommended for use in children below 18 years of age.

Method of administration
Oral use.

4.3 Contraindications

Hypersensitivity
Vildagliptin/Metformin combination is contraindicated in patients with known hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients.

Patients with renal impairment
Vildagliptin/Metformin combination is contraindicated in patients with severe renal impairment (GFR<30ml/min)

Congestive Heart Failure
Vildagliptin/Metformin combination is contraindicated in patients with congestive heart failure requiring pharmacologic treatment.

Metabolic acidosis
Vildagliptin/Metformin combination is contraindicated in patients with acute or chronic metabolic acidosis, including lactic acidosis or diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Radiologic Studies
Vildagliptin/Metformin combination should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function

4.4 Special warnings and precautions for use

General
Vildagliptin/Metformin combination is not a substitute for insulin in patients requiring insulin. Vildagliptin/Metformin combination should not be used in patients with T1D or for the treatment of diabetic ketoacidosis.

Monitoring of Renal Function
GFR should be assessed before treatment initiation and regularly thereafter. Vildagliptin/Metformin combination is contraindicated in patients with GFR <30ml/min because of its metformin component and should be temporarily discontinued in the presence of conditions that alter renal function.
Metformin hydrochloride is known to be substantially excreted by the kidney and the risk of metformin hydrochloride accumulation and lactic acidosis increases with the degree of renal function impairment. Patients with serum creatinine levels above the ULN for their age should not receive Vildagliptin/Metformin combination. Since advancing age is

associated with reduced renal function, metformin containing products (such as Vildagliptin/Metformin combination) should be carefully titrated in the elderly to establish the minimum dose for adequate glycemic effect, and renal function should be monitored regularly.

Concomitant Medications that May Affect Renal Function or Metformin Hydrochloride Disposition

Concomitant medications that may affect renal function, result in significant hemodynamic change or interfere with the disposition of metformin hydrochloride, such as cationic drugs that are eliminated by renal tubular secretion should be used with caution.

Cardiac failure

Vildagliptin/Metformin combination is contraindicated in patients with congestive heart failure requiring pharmacologic treatment, which may potentially interact with metformin hydrochloride. A clinical study of vildagliptin in patients with NYHA functional class I-III showed that treatment with vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing CHF versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive. There is no experience of vildagliptin use in clinical studies in patients with NYHA functional class IV and therefore use is not recommended in these patients.

Use in hepatic impairment Vildagliptin, and hence Vildagliptin/Metformin combination is not recommended in patients with clinical or laboratory evidence of hepatic impairment, including patients with pretreatment ALT or AST > 2.5x the ULN.

Since impaired hepatic function has been associated with some cases of lactic acidosis (a risk associated with metformin hydrochloride), metformin-containing products (such as vildagliptin/metformin combination) should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Liver Enzyme Monitoring 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 tests (LFTs) returned to normal after discontinuation of treatment. LFTS should be performed prior to the initiation of treatment with vildagliptin/metformin combination. Vildagliptin/Metformin combination is not recommended in patients with a pre-treatment ALT or AST >2.5x the ULN.

LFTs should be monitored during Vildagliptin/Metformin combination 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 up thereafter with frequent liver function tests until the abnormality/abnormalities return to normal. Should an increase in AST or ALT of 3x the ULN or greater persist, withdrawal of therapy with vildagliptin/metformin combination is recommended. Patients who develop jaundice or other signs suggestive of liver

dysfunction should discontinue Vildagliptin/Metformin combination and contact their physician immediately.
Following withdrawal of treatment with Vildagliptin/Metformin combination and LFT normalization, Vildagliptin/Metformin combination should not be reinitiated. Vildagliptin/Metformin combination is not recommended in patients with hepatic impairment.

Lactic Acidosis
Lactic acidosis is a very rare but serious metabolic complication that most often occurs with acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs with acute worsening of renal function and increases the risk of lactic acidosis.
In case of dehydration (e.g. due to severe diarrhea or vomiting, fever or reduced fluid intake), the patient should stop taking metformin-containing products (such as vildagliptin/metformin combination) and seek immediate medical attention.
Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in patients treated with metformin containing products (such as vildagliptin/metformin combination). Other risk factors for lactic acidosis are excessive alcohol intake, hepatic impairment, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

Diagnosis of lactic acidosis
Patients and/or caregivers 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. If suspected symptoms occur, the patient should stop taking metformin - containing products (such as vildagliptin/metformin combination) 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. If metabolic acidosis is suspected, treatment with metformin containing products (such as vildagliptin/metformin combination) should be discontinued and the patient should be immediately hospitalized.

Paediatric use
The safety and effectiveness of vildagliptin/metformin combination in paediatric patients have not been established.
Therefore, vildagliptin/metformin combination is not recommended for use in children below 18 years of age.

Use in the elderly (≥ 65 Years)
As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking

metformin-containing products (such as Vildagliptin/Metformin combination) should have their renal function monitored regularly.
Vildagliptin/Metformin combination should only be used in elderly patients with normal renal function.

Administration of Intravascular Iodinated Contrast Materials

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Metformin-containing products (such as Vildagliptin/Metformin combination) should be discontinued prior to or at the time of the imaging procedures and not restarted until 48 hours subsequent to the procedure and reinstituted only after 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 hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotmeia. If such events occur in patients receiving metformin containing products (such as vildagliptin/metformin combination), the medication should be promptly discontinued.

Surgical Procedures

Metformin-containing products (such as Vildagliptin/Metformin combination) must be discontinued at the time of surgery under general, spinal or epidural anaesthesia (except minor procedures not associated with restricted intake of food and fluids) and may be restarted no earlier than 48 hours following surgery or until the patient's oral nutrition has resumed and renal function has been re-evaluated and found to be stable.

Alcohol Intake

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 Vildagliptin/Metformin combination). Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Vitamin B12 Levels

Metformin has been associated with a decrease in serum vitamin B12 levels without clinical manifestations, in approximately 7% of patients. Such a decrease is very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride and/or vitamin B12 supplementation. Measurement of hematological parameters on at least an annual basis is advised for patients receiving metformin-containing products (such as vildagliptin/metformin combination) 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 T2DM

A patient with T2DM previously well-controlled on Vildagliptin/Metformin combination 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, Vildagliptin/Metformin combination must be stopped immediately and appropriate measures initiated.

Hypoglycemia

Hypoglycemia does not usually occur in patients receiving Vildagliptin/Metformin combination alone, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or ethanol use. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people taking beta- adrenergic blocking drugs.

Loss of Control of Blood Glucose

When a patient stabilized 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 Vildagliptin/Metformin combination and temporarily administer insulin. Vildagliptin/Metformin combination may be reinstituted after the acute episode is resolved.

Effects on laboratory tests

Since impaired hepatic function has been associated with some cases of lactic acidosis (a risk associated with metformin hydrochloride), metformin-containing products (such as Vildagliptin/metformin combination) should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Rare cases of hepatic dysfunction (including hepatitis) have been reported with Vildagliptin. Vildagliptin/Metformin combination is not recommended in patients with a pre-treatment ALT or AST >2.5x the ULN. LFTs should be monitored during Vildagliptin/Metformin combination 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 up thereafter with frequent liver function tests until the abnormality/abnormalities return to normal. Should an increase in AST or ALT of 3x the ULN or greater persist, withdrawal of therapy with vildagliptin/metformin combination

is recommended. (For details, kindly refer Use in Hepatic Impairment, and Liver enzyme monitoring.)

Arthralgia
There have been post-marketing reports of joint pain, which may be severe, in patients taking DPP-4 inhibitors. Onset of symptoms following initiation of treatment may be rapid or may occur after longer periods. Discontinuation of therapy should be considered in patients who present with or experience an exacerbation of joint symptoms during treatment with DPP-4 inhibitors.

Bullous pemphigoid
Post-marketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Patients should be told to report any development of blisters or erosions while receiving Vildagliptin/Metformin combination. If bullous pemphigoid is suspected, Vildagliptin/Metformin combination should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Other
This medicine contains lactose monohydrate. “Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine”

4.5 Interaction with other medicinal products and other forms of interaction

No clinically relevant pharmacokinetic interactions have been observed when vildagliptin (100 mg once daily) was co-administered with metformin hydrochloride (1,000 mg once daily).
Drug interactions for each component of Vildagliptin/Metformin combination have been extensively studied. However, the concomitant use of the active substances in patients in clinical studies and in widespread clinical use has not resulted in any unexpected interactions. The following statements reflect the information available on the individual active substances (vildagliptin and metformin).

Vildagliptin Vildagliptin has low potential for drug interactions.
Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit or induce CYP 450 enzymes, it is not likely to interact with co-medications that are substrates, inhibitors or inducers of these enzymes. Furthermore, vildagliptin does not affect metabolic clearance of co-medications metabolized by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5.
Drug-drug interaction studies were conducted with commonly co-prescribed medications for patients with T2DM or medications with a

narrow therapeutic window. As a result of these studies no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, and metformin hydrochloride), amlodipine, digoxin, Ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.

Metformin Hydrochloride

Furosemide

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

Nifedipine

Nifedipine increased absorption, Cmax 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 Cmax, blood AUC of glyburide were observed, but were highly variable.

Iodinated contrast agents

Metformin-containing products (such as vildagliptin/metformin combination) 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.

Cationic drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential to interact 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 Vildagliptin/Metformin combination) and such medications are recommended.

Other

Some drugs 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 Vildagliptin/Metformin combination), close monitoring of renal function is necessary. Certain drugs tend to cause hyperglycemia and may lead

to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazine, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetic, calcium channel blocking drugs, and isoniazid. Close monitoring of glycemic control and metformin dose adjustments are recommended when such drugs are administered or withdrawn for these patients. There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to metformin. Consumption of alcohol and medicinal products containing alcohol should be avoided.

4.6 Fertility, pregnancy, and lactation

Pregnancy

Pregnancy Category C

Embryofetal development (teratology) studies have been conducted in rats and rabbits with the combination of vildagliptin and metformin hydrochloride in a 1:10 ratio There was no evidence of teratogenicity at oral doses yielding plasma exposure levels up to ca 14-20 times (rats) or 1.3- 2 times (rabbits) that anticipated in patients at the maximum recommended clinical dose. An increase in the incidence of incomplete ossification in rats and an increase in early resorptions in rabbits were observed at these doses.

However, there are no adequate and well-controlled studies in pregnant women, and animal studies are not always predictive of the human response. Therefore vildagliptin/metformin combination should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Lactation

No studies have been conducted with the combined components of Vildagliptin/Metformin combination. Metformin is excreted into human breast milk. It is not known whether vildagliptin is excreted in human milk or not. Vildagliptin/Metformin combination should not be administered to breast-feeding women.

4.7 Effects on ability to drive and use machines.

No studies on the effects on the ability to drive and use machines have been performed. Patients who are prone to dizziness should therefore avoid driving vehicles or using machines

4.8 Undesirable effects

The data presented here relate to the administration of vildagliptin and metformin as a free or fixed dose combination.
Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.
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 tests (LFTs) returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy studies lasting up to 24 weeks, the incidence of ALT or AST elevations ≥ 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for vildagliptin 50 mg daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.
In clinical studies with the combination of vildagliptin + metformin, 0.4% of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily + metformin treatment group, and no withdrawal due to adverse reactions was reported in either the vildagliptin 50 mg twice daily + metformin or the placebo + metformin treatment groups.
In clinical studies, the incidence of hypoglycemia was uncommon in patients receiving vildagliptin 50 mg once daily in combination with metformin (0.9%), patients receiving vildagliptin 50 mg twice daily in combination with metformin (0.5%) and in patients receiving placebo and metformin (0.4%). No severe hypoglycemic events were reported in the vildagliptin arms. Vildagliptin is weight-neutral when administered in combination with metformin.
Gastrointestinal adverse reactions including diarrhea and nausea, are known to occur very commonly during the introduction of metformin hydrochloride. Overall, gastrointestinal symptoms were reported in 13.2% (50 mg once daily or twice daily) of patients treated with the combination of vildagliptin and metformin hydrochloride compared to 18.1% of patients treated with metformin hydrochloride alone.
Adverse reactions reported in patients who received vildagliptin in double-blind studies as an add-on to metformin and as monotherapy, are listed in Table 1 for each indication, by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 - Other adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=233) or 50 mg twice daily (n=183) as add-on therapy to metformin compared to placebo plus metformin in double-blind studies

Nervous system disorders

Common: - Tremor, dizziness, headache

Long-term clinical studies of up to more than 2 years in duration, did not show any additional safety signals or unforeseen risks when vildagliptin was added on to metformin.

Combination with Insulin

Pooled safety data from two controlled clinical studies using vildagliptin 50 mg twice daily in combination with insulin, with or without concomitant metformin, identified the following adverse reactions:

Common: Headache, chills, nausea, gastro-esophageal reflux disease, decreased blood glucose

Uncommon: Diarrhea, flatulence

The overall incidence of withdrawals due to adverse reactions was 0.3% in the vildagliptin treatment group and there were no cases of withdrawal in the placebo group.

The incidence of hypoglycemia was similar in both treatment groups (14.0% in the vildagliptin group vs 16.4 % in the placebo group). Two patients reported severe hypoglycemic events in the vildagliptin group, and 6 patients in the placebo group.

At the end of the study, the effect on mean body weight was neutral (+ 0.6 kg change from baseline in the vildagliptin group and no weight change in the placebo group).

The adverse effect profiles for the vildagliptin and placebo arms of the 24-week study investigating vildagliptin as add-on to insulin treatment (with or without metformin) is shown in Table 2.

Table 2 - Adverse effects reported in patients who received vildagliptin 50 mg twice daily vs placebo in combination with insulin (with or without metformin)

	Vildagliptin N=227 (n,%)	Placebo N=221 (n,%)
Adverse effects reported (AE)	131(57.7%)	105 (47.5%)
Serious adverse effects (SAE)	9 (4.0%)	9 (4.1%)
Discontinuation due to AEs	9 (4.0%)	5 (2.3%)
Deaths	0 (0.0%)	1 (0.5%)
Hypoglycemia	19 (8.4%)	16 (7.2%)

Combination with SU

There were no cases of withdrawal reported due to adverse reactions in the vildagliptin + metformin + glimepiride treatment group. Vs. 0.6% in the placebo + metformin + glimepiride treatment group. The incidence of hypoglycemia was common (≥1/100,<1/10) in both treatment groups, but was numerically greater for the vildagliptin + metformin + glimepiride group (5.1%) than the placebo + metformin + glimepiride group (1.9%).

One severe hypoglycemic event was reported in the vildagliptin group. At the end of the study, the effect on mean body weight was neutral (+0.6 kg in the vildagliptin group and -0.1 kg in the placebo group).

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

Nervous system disorders

Common - Dizziness, tremor

General disorders and administration site condition

Common – Asthenia

Metabolism and nutritional disorders

Common – Hypoglycemia

Skin and subcutaneous tissue disorders

Common – Hyperhidrosis

Vildagliptin

Adverse reactions for vildagliptin component from monotherapy double blind studies are presented in Table 4.

Table 4: Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=409) or 50 mg twice daily (n=1,373) as monotherapy in double-blind studies

Nervous system disorders
Common- Dizziness, Uncommon - Headache
Gastrointestinal disorders
Uncommon - Constipation
General disorders and administration site conditions
Uncommon- Edema peripheral

None of the adverse reactions reported for the vildagliptin monotherapy were observed at clinically significantly higher rates when vildagliptin was administered concomitantly with metformin.

The overall incidence of withdrawal from monotherapy studies due to adverse reactions was no greater for patients treated with vildagliptin at a dose of 50 mg once daily (0.2%) or vildagliptin at a dose of 50 mg twice daily (0.1%) than for placebo (0.6%) or comparators (0.5%).

In monotherapy studies.

Hypoglycemia was uncommon reported in 0.5% (2 of 409) of patients treated with vildagliptin 50 mg once daily and 0.3% (4 of 1,373) of patients treated with vildagliptin 50 mg twice daily compared to 0.2% (2 of 1,082) of patients in the groups treated with an active comparator or placebo, with no serious or severe events reported. Vildagliptin is weight neutral when administered as monotherapy.

Long term clinical studies of up to 2 years did not show any additional safety signals or unforeseen risks with vildagliptin monotherapy.

Post-marketing Experience with vildagliptin

During post-marketing experience the following additional adverse drug reaction has been reported: Rare cases of hepatitis reversible upon drug discontinuation Frequency not known*:

• Urticaria, bullous and exfoliative skin lesions, including bullous pemphigoid

• Pancreatitis

• Arthralgia, sometimes severe.

*Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as “not known”.

Post-marketing Experience with Metformin Hydrochloride

Table 5: Known adverse reactions for metformin

Metabolism and nutrition disorders
Very rare - Decrease of vitamin B12 absorption*, lactic acidosis
Nervous system disorders
Common - Metallic taste
Gastrointestinal disorders
Very common - Flatulence, nausea, vomiting, diarrhoea, abdominal pain, loss of appetite
Hepatobiliary disorders Very rare - Liver function test abnormalities, hepatitis**
Skin and subcutaneous tissue disorders
Very rare - Skin reactions such as erythema, pruritus, urticaria

*A decrease of vitamin B12 absorption with decrease of serum levels has very rarely been observed in patients treated long-term with metformin and appears to generally not be of clinical significance. 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 effects 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

4.9 Overdose

Accidental overdose resulting from the continuance of previously prescribed products may occur. To avoid accidental overdose, patients should be advised to discard their previous metformin medication when prescribed with Vildagliptin/Metformin combination.

Symptoms and treatment

Vildagliptin In healthy subjects (seven to fourteen subjects per treatment group), vildagliptin was administered in once-daily doses of 25, 50, 100, 200, 400, and 600 mg for up to 10 consecutive days. Doses up to 200 mg were well tolerated. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, edema and transient increase in lipase levels (2x ULN). At 600 mg, one subject experienced edema of the hands and feet, and an

excessive increase in creatinine phosphokinase (CPK) levels, accompanied by elevations of aspartate aminotransferase (AST), C-reactive protein, and myoglobin. Three additional subjects in this dose group presented with edema of both feet, accompanied by paraesthesia in two cases.
All symptoms and laboratory abnormalities resolved after study drug discontinuation. Vildagliptin is not dialyzable, however the major hydrolysis metabolite (LAY151) can be removed by haemodialysis.

Metformin Hydrochloride
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycaemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin hydrochloride overdose cases. Metformin hydrochloride is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, haemodialysis may be useful for removal of the accumulated drug from patients in whom metformin hydrochloride overdosage is suspected.
In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group:
Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD08
Mechanism of action
Vildagliptin/Metformin combination combines two antihyperglycaemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes (T2D): vildagliptin, a member of the DPP-4 (dipeptidyl-peptidase-4) inhibitor class and metformin hydrochloride, a member of the biguanide class.

Vildagliptin
Vildagliptin, a member of the islet enhancer class, is a high affinity dipeptidyl-peptidase-4 (DPP4) inhibitor that improves glycemic control. The administration of vildagliptin results in rapid and near-complete inhibition of DPP-4 activity. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).
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 50 to 100 mg daily in patients with T2D significantly improved markers of beta cell function. The degree of improvement in beta-cell function is dependent on the initial degree of impairment; in non-diabetic (normal glycemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.
By increasing endogenous GLP-1 levels, vildagliptin enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion. The reduction in inappropriate glucagon during meals in turn attenuates insulin resistance.
The enhanced increase in the insulin/glucagon ratio during hyperglycemia (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 to delay gastric emptying is not observed with vildagliptin treatment. In addition, a reduction in postprandial lipaemia that is not associated with vildagliptin's incretin mediated effect to improve islet function has been observed.

Metformin Hydrochloride
Metformin hydrochloride improves glucose tolerance in patients with T2D, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin hydrochloride does not cause hypoglycemia in either patients with T2D or normal subjects (except in special circumstances), and does not cause hyperinsulinemia. With metformin hydrochloride therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.
Metformin hydrochloride 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, metformin hydrochloride has favourable effects on lipid metabolism, independent of its action on glycemia. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDLc and triglyceride levels.

5.2 Pharmacokinetic properties

Absorption In one of the published bioequivalence studies of Vildagliptin/Metformin combination (Innovator) at three dose strengths (50 mg/500 mg, 50 mg/850 mg and 50 mg/1,000 mg), versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses, the area under the curve (AUC) and maximum concentration (Cmax) of both the vildagliptin component and the metformin hydrochloride component of the Vildagliptin/Metformin combination tablets were demonstrated to be bioequivalent to that of free combination tablets.

Food does not affect the extent and rate of absorption of vildagliptin from Vildagliptin/Metformin combination. The Cmax and AUC of the metformin hydrochloride component from Vildagliptin/Metformin combination were decreased by 26% and 7%, respectively when given with food. The absorption of metformin hydrochloride was also delayed as reflected by the Tmax (2.0 to 4.0 hrs) when given with food. These changes in Cmax and AUC are consistent but lower than those observed when metformin hydrochloride was given alone under fed conditions. The effects of food on the pharmacokinetics of both the vildagliptin component and metformin hydrochloride component of Vildagliptin/Metformin combination were similar to the pharmacokinetics of vildagliptin and metformin hydrochloride when given alone with food.

Vildagliptin

Vildagliptin is rapidly absorbed with an absolute oral bioavailability of 85%. Peak plasma concentrations for vildagliptin and the area under the plasma concentration versus time curve increased in an approximately dose-proportional manner over the therapeutic dose range. Following oral administration in the fasting state, vildagliptin is rapidly 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).

Metformin Hydrochloride

Studies using single oral doses of metformin tablets indicate a lack of dose proportionality, due to increased absorption of metformin with increasing doses.

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximate 50 to 60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin hydrochloride, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve, and a 35-minute prolongation of the time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of metformin hydrochloride with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Vildagliptin

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 litres, suggesting extravascular distribution.

Metformin Hydrochloride

The apparent volume of distribution (V/F) of metformin hydrochloride following single oral doses of 850 mg averaged 654 ± 358 litres. Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound

Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride, steady state plasma concentrations of metformin hydrochloride are reached within 24 to 48 hours and are generally < 1 microgram/mL. During controlled clinical studies of metformin hydrochloride, maximum metformin hydrochloride plasma levels did not exceed 5 micrograms/mL, even at maximum doses.

Metabolism

Vildagliptin

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.

Metformin Hydrochloride

Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism. In patients with significantly decreased renal function, the plasma half-life of metformin is prolonged and renal clearance is decreased.

Excretion

Vildagliptin

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 litres/hour and 13 litres/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 the dose.

Metformin Hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin hydrochloride is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution

5.3 Preclinical safety data

Carcinogenicity No carcinogenicity studies have been conducted with the combined components of Vildagliptin/Metformin combination.

Long-term oral studies with vildagliptin in rats and mice showed evidence of haemangiosarcomas at high exposures. Tumour incidence was increased at exposure levels 46-235 times (mice) and 150 times (rats) human exposure at the maximum clinical dose, based on AUC. No significant increase in incidence was observed at 15 (males) to 80 (females) times human exposure in mice. No effect levels of ca 80 to 160 times the human exposure were established in rats. Mammary tumour incidence was increased in female mice at approximately 185 times the maximum anticipated human exposures to vildagliptin, but was not increased at ca 80 times. The tumours are thought to result from species-specific hormonal disturbances.

Based on the available data vildagliptin is not anticipated to present a carcinogenic risk at clinically relevant exposures.

Long-term carcinogenicity studies with metformin were performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 and 1,500 mg/kg/day respectively. These doses are approximately three to four times the recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day.

Genotoxicity

Vildagliptin was not mutagenic in a bacterial reverse mutation assay and a human lymphocyte chromosomal aberration assay. Some clastogenic potential was exhibited in an in vitro micronucleus test in V79 Chinese hamster cells after long exposure to high, cytotoxic concentrations. However, no clastogenicity was observed in either mouse or rat micronucleus tests in vivo at up to ca 400 times the

maximum human exposure, based on AUC. Furthermore, an in vivo mouse liver comet assay using the same dose was also negative. The weight of evidence indicates vildagliptin is unlikely to be genotoxic in humans at clinically relevant doses.
Metformin was not mutagenic in the bacterial reverse mutation assay, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or in vivo micronuclei formation test (mouse bone marrow).

Effects on skin

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at all oral doses administered (5 to 160 mg/kg/day). These were consistently located on the extremities (hands, feet, ears and tail) and included flaking skin, peeling skin, scabs, tail sores and blisters. At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), lesions were reversible despite continued treatment. Necrotic lesions of the tail were observed at ≥ 80 mg/kg/day (18 times human AUC exposure at the maximum recommended clinical dose). Skin lesions were not reversible in monkeys treated at 160 mg/kg/day (35 times human AUC exposure) during a 4-week recovery period. Skin lesions have not been observed in other animal species and no excess of skin lesions with vildagliptin treatment relative to comparator treatments have been observed in the clinical trial programme.

6. Pharmaceutical particulars

6.1 List of excipients

VILDARIL M 50/500

Lactose (Monohydrate), Hydroxypropyl cellulose, Isopropyl Alcohol, Sodium Starch Glycolate Type B, Microcrystalline Cellulose, Hydrophobic Colloidal Silica, Magnesium Stearate, Insta Moistshield A21R01476 Yellow (Hypromellose, Ethyl Cellulose, Triacetin, Talc, Titanium Dioxide, Yellow iron oxide, Red iron oxide) and Dichloromethane
VILDARIL M 50/850
Lactose (Monohydrate), Hydroxypropyl cellulose, Isopropyl Alcohol, Sodium Starch Glycolate Type B, Microcrystalline Cellulose, Hydrophobic Colloidal Silica, Magnesium Stearate, Insta Moistshield A21R01474 Yellow (Hypromellose, Ethyl Cellulose, Triacetin, Talc, Titanium Dioxide, Yellow iron oxide, Red iron oxide) and Dichloromethane
VILDARIL M 50/1000
Lactose (Monohydrate), Hydroxypropyl cellulose, Isopropyl Alcohol, Sodium Starch Glycolate Type B, Microcrystalline Cellulose,

Hydrophobic Colloidal Silica, Magnesium Stearate, Insta Moistshield A21R01475 Yellow (Hypromellose, Ethyl Cellulose, Triacetin Talc, Titanium Dioxide, Yellow iron oxide, Red iron oxide) and Dichloromethane.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage:
Store below 30°C. Protect from moisture.

6.5 Nature and contents of container
10 tablets in Alu-Alu blister pack, 3 such blisters in a printed carton along with Pack Insert

6.6 Special precautions for disposal and other handling:
No special requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Ajanta Pharma Limited
Ajanta House, Charkop, Kandivli (West),
Mumbai- 400067,
India

Manufacturing site address:
Ajanta Pharma Limited
Plot No. Z/103/A, Dahej SEZ II, Bharuch,
Gujarat – 392130.
India
e-mail : info@ajantapharma.com

8. Marketing authorization number
CTD9462

9. Date of first registration
22/02/2022

10. Date of revision of the text:
September 2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable

S.K.M