VILDAGLIPTIN 50 MG & METFORMIN HYDROCHLORIDE 1000 MG TABLETS

1. Name of the medicinal product

Vildagliptin 50 mg & Metformin Hydrochloride 1000 mg Tablets

2. Qualitative and quantitative composition

Sr. No.	Ingredients	Grade	Qty. Req./ Tab. (mg)	Overages (%)	Function
Dry Mixing					
1	Metformin Hydrochloride*	USP	1000.000	-	Active
2	Magnesium stearate	BP	6.500	-	Lubricant
3	Hydroxypropyl cellulose	USP	37.000	-	Binder
4	Low substituted hydroxypropyl cellulose	USP	26.260		Disintegrant
Binder Solution (7.5 % w/w)					
5	Hydroxypropyl cellulose	USP	6.000	-	Binder
6	Purified Water***	BP	Q.S.	-	Vehicle
Blending#					
7	Vildagliptin*	IHS	50.000	-	Active
8	Microcrystalline cellulose PH 102**	BP	80.240		Diluent
9	Low substituted hydroxypropyl cellulose	USP	26.000	-	Disintegrant
Lubrication					
10	Magnesium Stearate	BP	18.000	-	Lubricant
	Weight of core tablet		**1250.000 mg/Tablet**		
Coating					
11	Instacoat Aqua II Brown@$	IHS	25.000	20.00	Coating agent
12	Purified water***	BP	Q.S		Vehicle
	Average Weight/Tablet		**1275.000 mg/Tablet**		

Note:

*Qty. to be calculated on basis of assay and LOD.

**Qty. to be compensate based on API quantities.

*** This will not remain in final product & will be evaporated during drying.

#Blending and Lubrication material to be taken as per actual yield of dried granules.

@ 20% overages are taken to compensate the process loss.

$ Instacoat aqua II brown is composition of Red oxide of iron & Titanium Dioxide.

3. Pharmaceutical form

Dosage form: Film coated tablet

Description: Light brown to brown colour, oval shape, film coated tablets plain on both side.

4. Clinical particulars

4.1 Therapeutic indications

Vildagliptin/Metformin is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus:
- in patients who are inadequately controlled with metformin hydrochloride alone
- in patients who are already being treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets.

4.2 Posology and method of administration

Posology

Adults with normal renal function (GFR ≥ 90 ml/min)
The dose of antihyperglycaemic therapy with Vildagliptin/Metformin should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Vildagliptin/Metformin may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening.
- For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy:
The starting dose of Vildagliptin/Metformin should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken.
- For patients switching from co-administration of vildagliptin and metformin as separate tablets:
Vildagliptin/Metformin should be initiated at the dose of vildagliptin and metformin already being taken.
- For patients inadequately controlled on dual combination with metformin and a sulphonylurea:
The doses of Vildagliptin/Metformin should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Vildagliptin/Metformin is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.
The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established.

<u>Special populations</u>

Elderly (≥ 65 years)
As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking Vildagliptin/Metformin should have their renal function monitored regularly.

Renal impairment

A GFR should be assessed before initiation of treatment with metformin-containing products 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 3-6 months.
The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR<60 ml/min.
If no adequate strength of Vildagliptin/Metformin is available, individual monocomponents should be used instead of the fixed dose combination.

GFR ml/min	Metformin	Vildagliptin
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	No dose adjustment.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximal daily dose is 50 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	
<30	Metformin is contraindicated.	

Hepatic impairment
Vildagliptin/Metformin should not be used in patients with hepatic impairment, including those with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN).

Paediatric population

Vildagliptin/Metformin is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Vildagliptin/Metformin in children and adolescents (< 18 years) have not been established. No data are available.

Method of administration

Oral use.
Taking Vildagliptin/Metformin with or just after food may reduce gastrointestinal symptoms associated with metformin.

Contraindications
- Hypersensitivity to the active substances or to any of the excipients
- Any type of acute metabolic acidosis
- Diabetic pre-coma
- Severe renal failure
- Acute conditions with the potential to alter renal function, such as:
    - dehydration,

- severe infection,
- shock,
- intravascular administration of iodinated contrast agents

- Acute or chronic disease which may cause tissue hypoxia, such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock.
- Hepatic impairment
- Acute alcohol intoxication, alcoholism
- Breast-feeding

4.4 Special warnings and precautions for use

General
Vildagliptin/Metformin is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes.

Lactic acidosis
Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function, or cardiorespiratory 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. Medicinal products that can acutely impair renal function 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 medicinal products that may cause lactic acidosis. 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.

Renal function
GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR < 30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function. Concomitant medicinal products that

may affect renal function, result in significant haemodynamic change, or inhibit renal transport and increase metformin systemic exposure, should be used with caution.

Hepatic impairment
Patients with hepatic impairment, including those with pre-treatment ALT or AST > 3x ULN, should not be treated with Vildagliptin/Metformin.

Liver enzyme monitoring
Rare cases of hepatic dysfunction have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with Vildagliptin/Metformin in order to know the patient's baseline value. Liver function should be monitored during treatment with Vildagliptin/Metformin 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 return(s) to normal. Should an increase in AST or in ALT of 3x ULN or greater persist, withdrawal of Vildagliptin/Metformin therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Vildagliptin/Metformin. Following withdrawal of treatment with Vildagliptin/Metformin and LFT normalisation, treatment with Vildagliptin/Metformin 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Vildagliptin

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

As with other oral antidiabetic medicinal products 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 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.

Combinations requiring precautions for use

Some medicinal products 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 Vildagliptin/Metformin 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 medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation. Concomitant use of medicinal products that interfere with common renal tubular transport systems involved in the renal elimination of metformin could increase systemic exposure to metformin.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of Vildagliptin/Metformin in pregnant women. For vildagliptin studies in animals have shown reproductive toxicity at high doses. For metformin, studies in animals have not shown reproductive toxicity. 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. Vildagliptin/Metformin 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, Vildagliptin/Metformin should not be used during breast-feeding.

Fertility
No studies on the effect on human fertility have been conducted for Vildagliptin/Metformin

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 may experience dizziness as an adverse reaction should avoid driving vehicles or using machines.

4.8 Undesirable effects

Metabolism and nutrition disorders: Hypoglycaemia, Decreased blood glucose, Decrease of vitamin B_{12} absorption and lactic acidosis*
Nervous system disorders: Tremor, Headache, Dizziness, Fatigue, Diarrhoea, flatulence, chills, Metallic taste
Gastrointestinal disorders: Nausea, gastro-oesophageal reflux disease, Constipation, vomiting, diarrhoea, abdominal pain and loss of appetite, Pancreatitis
Skin and subcutaneous tissue disorders: Hyperhidrosis

General disorders and administration site conditions: Asthenia
Infections and infestations: Upper respiratory tract infection, Nasopharyngitis
Vascular disorders: Oedema peripheral
Musculoskeletal and connective tissue disorders: Arthralgia, Myalgia
Hepatobiliary disorders: Liver function test abnormalities or hepatitis**
Skin and subcutaneous tissue disorders: Skin reactions such as erythema, pruritus and urticaria, Exfoliative and bullous skin lesions, including bullous pemphigoid.

4.9 Overdose

No data are available with regard to overdose of Vildagliptin/Metformin.

Vildagliptin
Information regarding overdose with vildagliptin is limited.
Symptoms
Information on the likely symptoms of overdose with vildagliptin was taken from a rising dose tolerability study in healthy subjects given vildagliptin for 10 days. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels. At 600 mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), AST, C-reactive protein (CRP) and myoglobin levels. Three other subjects experienced oedema of the feet, with paraesthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product.

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.
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

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD08

Mechanism of action
Vildagliptin/Metformin combines two antihyperglycaemic agents 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 and GIP. 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. 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. The prospective randomised UKPDS study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction in the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034;
- a significant reduction in the absolute risk of diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017;

- a significant reduction in the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years (p=0.01).

Clinical efficacy and safety

Vildagliptin added to patients whose glycaemic control was not satisfactory despite treatment with metformin monotherapy resulted after 6-month treatment in additional statistically significant mean reductions in HbA1c compared to placebo (between group differences of -0.7% to -1.1% for vildagliptin 50 mg and 100 mg, respectively). The proportion of patients who achieved a decrease in HbA1c of ≥ 0.7% from baseline was statistically significantly higher in both vildagliptin plus metformin groups (46% and 60%, respectively) versus the metformin plus placebo group (20%).

In a 24-week trial, vildagliptin (50 mg twice daily) was compared to pioglitazone (30 mg once daily) in patients inadequately controlled with metformin (mean daily dose: 2020 mg). Mean reductions from baseline HbA1c of 8.4% were -0.9% with vildagliptin added to metformin and -1.0% with pioglitazone added to metformin. A mean weight gain of +1.9 kg was observed in patients receiving pioglitazone added to metformin compared to +0.3 kg in those receiving vildagliptin added to metformin.

In a clinical trial of 2 years' duration, vildagliptin (50 mg twice daily) was compared to glimepiride (up to 6 mg/day – mean dose at 2 years: 4.6 mg) in patients treated with metformin (mean daily dose: 1894 mg). After 1 year mean reductions in HbA1c were -0.4% with vildagliptin added to metformin and -0.5% with glimepiride added to metformin, from a mean baseline HbA1c of 7.3%. Body weight change with vildagliptin was -0.2 kg vs +1.6 kg with glimepiride. The incidence of hypoglycaemia was significantly lower in the vildagliptin group (1.7%) than in the glimepiride group (16.2%). At study endpoint (2 years), the HbA1c was similar to baseline values in both treatment groups and the body weight changes and hypoglycaemia differences were maintained.

In a 52-week trial, vildagliptin (50 mg twice daily) was compared to gliclazide (mean daily dose: 229.5 mg) in patients inadequately controlled with metformin (metformin dose at baseline 1928 mg/day). After 1 year, mean reductions in HbA1c were -0.81% with vildagliptin added to metformin (mean baseline HbA1c 8.4%) and -0.85% with gliclazide added to metformin (mean baseline HbA1c 8.5%); statistical non-inferiority was achieved (95% CI -0.11 – 0.20). Body weight change with vildagliptin was +0.1 kg compared to a weight gain of +1.4 kg with gliclazide.

In a 24-week trial the efficacy of the fixed dose combination of vildagliptin and metformin (gradually titrated to a dose of 50 mg/500 mg twice daily or 50 mg/1000 mg twice daily) as initial therapy in drug-naïve patients was evaluated. Vildagliptin/metformin 50 mg/1000 mg twice daily reduced HbA1c by -1.82% ,vildagliptin/metformin 50 mg/500 mg twice daily by -1.61%, metformin 1000 mg twice daily by -1.36% and vildagliptin 50 mg twice daily by -1.09% from a mean baseline HbA1c of 8.6%. The decrease in HbA1c observed in patients with a baseline ≥10.0% was greater.

A 24-week randomised, double-blind, placebo-controlled trial was conducted in 318 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in

combination with metformin (≥1500 mg daily) and glimepiride (≥4 mg daily). Vildagliptin in combination with metformin and glimepiride significantly decreased HbA1c compared with placebo. The placebo-adjusted mean reduction from a mean baseline HbA1c of 8.8% was -0.76%.
A five-year multi-centre, randomised, double-blind study (VERIFY) was conducted in patients with type 2 diabetes to evaluate the effect of an early combination therapy with vildagliptin and metformin (N = 998) against standard-of-care initial metformin monotherapy followed by combination with vildagliptin (sequential treatment group) (N = 1,003) in newly diagnosed patients with type 2 diabetes. The combination regimen of vildagliptin 50 mg twice daily plus metformin resulted in a statistically and clinically significant relative reduction in hazard for "time to confirmed initial treatment failure" (HbA1c value ≥7%) vs metformin monotherapy in treatment-naïve patients with type 2 diabetes over the 5-year study duration (HR [95%CI]: 0.51 [0.45, 0.58]; p<0.001). The incidence of initial treatment failure (HbA1c value ≥7%) was 429 (43.6%) patients in the combination treatment group and 614 (62.1%) patients in the sequential treatment group.

Cardiovascular risk
A meta-analysis of independently and prospectively adjudicated cardiovascular events from 37 phase III and IV monotherapy and combination therapy clinical studies of up to more than 2 years duration (mean exposure 50 weeks for vildagliptin and 49 weeks for comparators) was performed and showed that vildagliptin treatment was not associated with an increase in cardiovascular risk versus comparators. The composite endpoint of adjudicated major adverse cardiovascular events (MACE) including acute myocardial infarction, stroke or cardiovascular death was similar for vildagliptin versus combined active and placebo comparators [Mantel–Haenszel risk ratio (M-H RR) 0.82 (95% CI 0.61-1.11)]. A MACE occurred in 83 out of 9,599 (0.86%) vildagliptin-treated patients and in 85 out of 7,102 (1.20%) comparator-treated patients. Assessment of each individual MACE component showed no increased risk (similar M-H RR). Confirmed heart failure (HF) events defined as HF requiring hospitalisation or new onset of HF were reported in 41 (0.43%) vildagliptin-treated patients and 32 (0.45%) comparator-treated patients with M-H RR 1.08 (95% CI 0.68-1.70).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with vildagliptin in combination with metformin in all subsets of the paediatric population with type 2 diabetes mellitus.

5.2 Pharmacokinetic properties

Vildagliptin/Metformin

Absorption
Bioequivalence has been demonstrated between Vildagliptin/Metformin at three dose strengths (50 mg/500 mg, 50 mg/850 mg and 50 mg/1000 mg) versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses. Food does not affect the extent and rate of absorption of vildagliptin from Vildagliptin/Metformin. The rate and extent of absorption of metformin from Vildagliptin/Metformin 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 Vildagliptin/Metformin.

Vildagliptin

Absorption

Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.7 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. 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.

5.3 Preclinical safety data

Animal studies of up to 13-week duration have been conducted with the combined substances in Vildagliptin/Metformin. No new toxicities associated with the combination were identified. The following data are findings from studies performed with vildagliptin or metformin individually.

Vildagliptin
Intra-cardiac impulse conduction delays were observed in dogs with a no-effect dose of 15 mg/kg (7-fold human exposure based on Cmax).
Accumulation of foamy alveolar macrophages in the lung was observed in rats and mice. The no-effect dose in rats was 25 mg/kg (5-fold human exposure based on AUC) and in mice 750 mg/kg (142-fold human exposure).
Gastrointestinal symptoms, particularly soft faeces, mucoid faeces, diarrhoea and, at higher doses, faecal blood were observed in dogs. A no-effect level was not established.
Vildagliptin was not mutagenic in conventional in vitro and in vivo tests for genotoxicity.
A fertility and early embryonic development study in rats revealed no evidence of impaired fertility, reproductive performance or early embryonic development due to vildagliptin. Embryofoetal toxicity was evaluated in rats and rabbits. An increased incidence of wavy ribs was observed in rats in association with reduced maternal body weight parameters, with a no-effect dose of 75 mg/kg (10-fold human exposure). In rabbits, decreased foetal weight and skeletal variations indicative of developmental delays were noted only in the presence of severe maternal toxicity, with a no-effect dose of 50 mg/kg (9-fold human exposure). A pre- and postnatal development study was performed in rats. Findings were only observed in association with maternal toxicity at ≥ 150 mg/kg and included a transient decrease in body weight and reduced motor activity in the F1 generation.
A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times human exposure at the maximum recommended dose). No increases in tumour incidence attributable to vildagliptin were observed. Another two-year carcinogenicity study was conducted in mice at oral doses up to 1000 mg/kg. An increased incidence of mammary adenocarcinomas and haemangiosarcomas was observed with a no-effect dose of 500 mg/kg (59-fold human exposure) and 100 mg/kg (16-fold human exposure), respectively. The increased incidence of these tumours in mice is considered not to represent a significant risk to humans based on the lack of genotoxicity of vildagliptin and its principal metabolite, the occurrence of tumours only in one species, and the high systemic exposure ratios at which tumours were observed.
In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at doses ≥ 5 mg/kg/day. These were consistently located on the extremities (hands, feet, ears and tail). At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100

mg dose), only blisters were observed. They were reversible despite continued treatment and were not associated with histopathological abnormalities. Flaking skin, peeling skin, scabs and tail sores with correlating histopathological changes were noted at doses ≥ 20 mg/kg/day (approximately 3 times human AUC exposure at the 100 mg dose). Necrotic lesions of the tail were observed at ≥ 80 mg/kg/day. Skin lesions were not reversible in the monkeys treated at 160 mg/kg/day during a 4-week recovery period.

Metformin

Non-clinical data on metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6. Pharmaceutical particulars

6.1 List of excipients

Magnesium stearate BP
Hydroxypropyl cellulose USP
Low substituted hydroxypropyl cellulose USP
Purified water BP
Microcrystalline cellulose BP
Instacoat Aqua II Brown IHS

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C in cool & dry place. Protect from light & moisture.

6.5 Nature and contents of container

6 X 10 ALU/ALU Blister pack

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorization holder

RLPHONES PHARMACEUTICALS COMPANY LIMITED.
1, Ralphones Lane Lagos, Nigeria.

Manufacturer
Ratnatris Pharmaceuticals Pvt. Ltd,
Survey No 416, AT, Indrad, Ta. Kadi, Dist. Mehsana, Gujarat, India.

8. Marketing authorisation number(s)

Not Applicable

9. Date of first authorisation/renewal of the authorization
Not Applicable

10. Date of revision of the text
Not Applicable.