Module 1- Administrative information and prescribing information

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

Summary Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Vildagliptin and Metformin Hydrochloride Tablets

Strength

Each film coated tablet contains:
Vildagliptin ……..… 50mg
Metformin Hydrochloride USP ……. 1000mg
Excipients …… q.s.
Color: Approved Colours used

Pharmaceutical form

Oral Solid dosage form

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration:

INGREDIENTS	SPECIFICATION
Metformin Hydrochloride	USP
Vildagliptin	IHS
Microcrystalline Cellulose 101	BP
Maize Starch	BP
Croscarmellose Sodium	BP
Povidone k 30	BP
Purified water	IHS
Magnesium Stearate	BP
Purified Talc	BP
Colloidal Anhydrous Silica	BP
Sodium Starch Glycolate	BP
Quinoline Yellow	IHS
Iso propyl alcohol	BP
Dichloromethane	BP

2.2 Quantitative Declaration:

Sr. No	Ingredients	Spec	mg per Tablet	(%) Overages	Category
Dry Mixing					
1.	Metformin Hydrochloride	USP	1000.0*	-	Active
2.	Vildagliptin	IHS	50.0*	-	Active
3.	Microcrystalline Cellulose 101	BP	139.0 @	-	Diluent
4.	Maize Starch	BP	90.0	-	Diluent
5.	Croscarmellose Sodium	BP	15.0	-	Disintegrant
Paste Preparation					
6.	P.V.P.K. 30	BP	45.000	-	Binder
7.	Purified water***	BP	Q. S	-	Solvent
Lubrication					
8.	Croscarmellose Sodium	BP	25.000	-	Disintegrant
9.	Magnesium Stearate	BP	10.000	-	Lubricant
10.	Purified Talc	BP	10.000	-	Lubricant
11.	Colloidal Anhydrous Silica	BP	6.000	-	lubricant
12.	Sodium Starch Glycolate	BP	10.000	-	Disintegrant
Total Weight of Uncoated Tablets			1400.0 mg		
Coating					
13.	Quinoline Yellow	In-House	35.000	-	Colouring agent
14.	Isopropyl alcohol	BP	280.000	-	Vehicle
15.	Dichloromethane	BP	420.000	-	Vehicle
Total Weight of coated Tablets			1435.0 mg		

BP = British Pharmacopeia

IH = In-House Specification

* Quantity of Metformin Hydrochloride and Vildagliptin is to be calculated on 100 % assay on dried basis.

@Quantity of Microcrystalline Cellulose 101 to be reduced against incremental increase in quantity of Metformin Hydrochloride and Vildagliptin.

Packing: 6 x 10 Alu-Alu Blister Pack

3. PHARMACEUTICAL FORM

Oral Solid dosage form

Yellow coloured, capsule shaped, biconvex, film coated tablets, one side break line and other side plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vildagliptin/metformin hydrochloride is indicated in the treatment of type 2 diabetes mellitus patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets.

4.2 Posology and method of administration

Adults

Based on the patient's current dose of metformin, Vildagliptin/metformin hydrochloride 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. The recommended daily dose is 100 mg vildagliptin plus 2000 mg metformin hydrochloride.

Patients receiving vildagliptin and metformin from separate tablets may be switched to Vildagliptin/metformin hydrochloride containing the same doses of each component.

Doses higher than 100 mg of vildagliptin are not recommended.

There is no clinical experience of vildagliptin and metformin in triple combination with other antidiabetic agents.

Taking Vildagliptin/metformin hydrochloride with or just after food may reduce gastrointestinal symptoms associated with metformin.

Additional information on special populations

Renal impairment

Vildagliptin/metformin hydrochloride should not be used in patients with creatinine clearance < 60 ml/min.

Hepatic impairment

Vildagliptin/metformin hydrochloride 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).

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 hydrochloride should have their renal function monitored regularly. Vildagliptin/metformin hydrochloride has not been studied in patients older than 75 years. Therefore, the use of Vildagliptin/metformin hydrochloride is not recommended in this population.

Paediatric population (< 18 years)

Vildagliptin/metformin hydrochloride is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

4.3 Contraindications

− Hypersensitivity to the active substances or to any of the excipients

− Diabetic ketoacidosis or diabetic pre-coma

− Renal failure or renal dysfunction defined as creatinine clearance < 60 ml/min

− 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

− Lactation

4.4 Special warnings and precautions for use

General

Vildagliptin/metformin hydrochloride 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 is a very rare but serious metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. In patients with impaired liver function, lactate clearance may be restricted. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors, such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia.

Diagnosis of lactic acidosis

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l and increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately.

Renal impairment

As metformin is excreted by the kidney, serum creatinine concentrations should be monitored regularly:

- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients.

Renal impairment in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID.

Hepatic impairment

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

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 hydrochloride in order to know the patient's baseline value. Liver function should be monitored during treatment with Vildagliptin/metformin hydrochloride at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent LFTs until the abnormality(ies) return(s) to normal. Should an increase in AST or in ALT of 3x ULN or greater persist, withdrawal of Vildagliptin/metformin hydrochloride therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Vildagliptin/metformin hydrochloride.

Following withdrawal of treatment with Vildagliptin/metformin hydrochloride and LFT normalisation, treatment with Vildagliptin/metformin hydrochloride should not be reinitiated.

Cardiac failure

Experience with vildagliptin therapy in patients with congestive heart failure of New York Heart Association (NYHA) functional class I-II is limited and therefore vildagliptin should be used cautiously in these patients. There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients.

Metformin is contraindicated in patients with heart failure, therefore Vildagliptin/metformin hydrochloride is contraindicated in this patient population.

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. Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.

Surgery

As Vildagliptin/metformin hydrochloride contains metformin, the treatment should be discontinued 48 hours before elective surgery with general anaesthesia and should not usually be resumed earlier than 48 hours afterwards.

Administration of iodinated contrast agent

The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure. Therefore, due to the metformin active substance, Vildagliptin/metformin hydrochloride should be discontinued prior to, or at the time of, the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for Vildagliptin/metformin hydrochloride . 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-drug interaction studies with digoxin (P-glycoprotein substrate) and warfarin (CYP2C9 substrate) in healthy subjects have shown no clinically relevant pharmacokinetic interactions after coadministration with vildagliptin.

Drug-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.

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

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the metformin active substance of Vildagliptin/metformin hydrochloride. Consumption of alcohol and medicinal products containing alcohol should be avoided.

Cationic active substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems and hence delay the elimination of metformin, which may increase the risk of lactic acidosis. A study in healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered.

Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation with the risk of lactic acidosis. Metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Combinations requiring precautions for use

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 hydrochloride 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.

4.6 Pregnancy and lactation

There are no adequate data from the use of Vildagliptin/metformin hydrochloride 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 hydrochloride should not be used during pregnancy.

Studies in animals have shown excretion of both metformin and vildagliptin in milk. It is not known 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 hydrochloride should not be used during lactation .

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 undesirable effect should avoid driving vehicles or using machines.

4.8 Undesirable effects

There have been no therapeutic clinical trials conducted with Vildagliptin/metformin hydrochloride. However, bioequivalence of Vildagliptin/metformin hydrochloride with co-administered vildagliptin and metformin has been demonstrated. The data presented here relate to the co-administration of vildagliptin and metformin, where vildagliptin has been added to metformin. There have been no studies of metformin added to vildagliptin.

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

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials of up to 24 weeks in duration, 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 once 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.

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 ACE inhibitor. The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

Adverse reactions reported in patients who received vildagliptin in double-blind studies as add-on therapy to metformin (Table 1) and as monotherapy (Table 2) are listed below by system organ class and absolute frequency. Adverse reactions listed in Table 3 are based on information available from the metformin Summary of Product Characteristics available in the EU. 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), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported in patients who received vildagliptin 100 mg daily as add-on therapy to metformin compared to placebo plus metformin in double-blind studies (N=208)

Nervous system disorders

Common Tremor

Common Headache

Common Dizziness

Uncommon Fatigue

Gastrointestinal disorders

Common Nausea

Metabolism and nutrition disorders

Common Hypoglycaemia

In controlled clinical trials with the combination of vildagliptin 100 mg daily plus metformin, no withdrawal due to adverse reactions was reported in either the vildagliptin 100 mg daily plus metformin or the placebo plus metformin treatment groups.

In clinical trials, the incidence of hypoglycaemia was common in patients receiving vildagliptin in combination with metformin (1%) and uncommon in patients receiving placebo + metformin (0.4%). No severe hypoglycaemic events were reported in the vildagliptin arms.

In clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was added to metformin (+0.2 kg and -1.0 kg for vildagliptin and placebo, respectively).

Additional information on the individual active substances of the fixed combination

Vildagliptin

Table 2 Adverse reactions reported in patients who received vildagliptin 100 mg daily as monotherapy in double-blind studies (N=1855)

Nervous system disorders

Common Dizziness

Uncommon Headache

Gastrointestinal disorders

Uncommon Constipation

Musculoskeletal and connective tissue disorders

Uncommon Arthralgia

Metabolism and nutrition disorders

Uncommon Hypoglycaemia

Infections and infestations

Very rare Upper respiratory tract infection

Very rare Nasopharyngitis

Vascular disorders

Uncommon Oedema peripheral

The overall incidence of withdrawals from controlled monotherapy trials due to adverse reactions was no greater for patients treated with vildagliptin at doses of 100 mg daily (0.3%) than for placebo (0.6%) or comparators (0.5%).

In comparative controlled monotherapy studies, hypoglycaemia was uncommon, reported in 0.4% (7 of 1,855) of patients treated with vildagliptin 100 mg 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.

In clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was administered as monotherapy (-0.3 kg and -1.3 kg for vildagliptin and placebo, respectively).

Metformin

Table 3 Known adverse reactions for metformin component

Metabolism and nutrition disorders

Very Rare Decrease of vitamin B12 absorption and lactic acidosis*

Nervous system disorders

Common Metallic taste

Gastrointestinal disorders

Very common Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite

Hepatobiliary disorders

Very rare Liver function test abnormalities or hepatitis**

Skin and subcutaneous tissue disorders

Very rare Skin reactions such as erythema, pruritus and urticaria

**A decrease in vitamin B12 absorption with decrease in serum levels has been very rarely observed in patients treated long-term with metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.*

***Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.*

Gastrointestinal undesirable 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

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

Vildagliptin

Information regarding overdose with vildagliptin is limited.

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: Combinations of oral blood glucose lowering drugs, ATC code: A10BD08

Vildagliptin/metformin hydrochloride 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.

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%).

Vildagliptin

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

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

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with vildagliptin 50-100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function including HOMA-β (Homeostasis Model Assessment–β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-

sampled meal tolerance test. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

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

The enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia.

The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptin treatment.

Metformin

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

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

- by reduction of hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis;
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation;
- by delaying intestinal glucose absorption.

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

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

The prospective randomised UKPDS (UK Prospective Diabetes Study) 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 sulphonyl urea 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 sulphonyl urea 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).

5.2 Pharmacokinetic properties

Vildagliptin/metformin hydrochloride

Absorption

Bioequivalence has been demonstrated between Vildagliptin/metformin hydrochloride 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 hydrochloride. The rate and extent of absorption of metformin from Vildagliptin/metformin hydrochloride 50 mg/1000 mg were decreased when given with food as reflected by the decrease in Cmax by 26%, AUC by 7% and delayed Tmax (2.0 to 4.0 h). The following statements reflect the pharmacokinetic properties of the individual active substances of Vildagliptin/metformin hydrochloride .

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 Cmax (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 comedications 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 [14C] 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 Cmax 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 (Cmax 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 (Cmax) is achieved after about 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

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

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

Distribution

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

Metabolism

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 hydrochloride. 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 C_{max}).

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

INGREDIENTS	SPECIFICATION
Microcrystalline Cellulose 101	BP
Maize Starch	BP
Croscarmellose Sodium	BP
Povidone k 30	BP
Purified water	IHS
Magnesium Stearate	BP
Purified Talc	BP
Colloidal Anhydrous Silica	BP
Sodium Starch Glycolate	BP
Quinoline Yellow	IHS
Iso propyl alcohol	BP
Dichloromethane	BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30° C temperature. Protect from light and moisture

6.5 Nature and contents of container

6 x 10 Alu-Alu Blister Pack

6.6 Special precautions for disposal and other handling

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. APPLICANT/MANUFACTURER

Manufactured by:

STIVAPH HEALTHCARE PVT. LTD.

PF-01, Sanand GIDC-II,

Village-Bol, Ta. Sanand,

Dist. Ahmedabad-382170

Gujarat, India.

Manufactured for:

BEZIK PHARMA LTD

18 Jesse Jackson Street, Asokoro, Abuja, Nigeria.

Exported by:

GENAIDE PHARMACEUTICAL LLP

12/A, Sun Residency Bungalows,

Opp. Upvan Bungalows, Thaltej,

Ahmedabad-380059, Gujarat,

India.

8. FDA APPLICATION NUMBER

9. DATE OF <REGISTRATION> / <RENEWAL OF REGISTRATION>

10. DATE OF REVISION OF THE TEXT: