1.3.1: SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Vilza Plus 50 mg/850 mg tablets

Vilza Plus 50 mg/500 mg tablets

Vilza Plus 50 mg/1000 mg tablets

2. Qualitative and quantitative composition

Vilza Plus 50 mg/500 mg tablets: Each film-coated tablet contains 50 mg of vildagliptin and 500 mg of metformin hydrochloride

Vilza Plus 50 mg/850 mg tablets: Each film-coated tablet contains 50 mg of vildagliptin and 850 mg of metformin hydrochloride

Vilza Plus 50 mg/1000 mg tablets: Each film-coated tablet contains 50 mg of vildagliptin and 1000 mg of metformin hydrochloride

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Vilza Plus 50 mg/500 tablets: Green color oval shape film coated tablet plain from both side

Vilza Plus 50 mg/850 mg tablets: White color oval shape film coated tablet plain from both side

Vilza Plus 50 mg/1000 mg tablets: Light pink color oval shape film coated tablet plain from both side

4. Clinical particulars

4.1 Therapeutic indications

Vilza Plus 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.

- in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

4.2 Posology and method of administration

Posology

Adults with normal renal function (GFR ≥ 90 ml/min)

The dose of antihyperglycaemic therapy with Vilza Plus 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. Vilza Plus 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 Vilza Plus 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:

Vilza Plus 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 Vilza Plus 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 Vilza Plus is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.

- For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin:

The dose of Vilza Plus should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.

The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established.

Special populations

Elderly (≥ 65 years)

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking Vilza Plus should have their renal function monitored regularly (see sections 4.4 and 5.2).

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 Vilza Plus 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

Vilza Plus 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) (see sections 4.3, 4.4 and 4.8).

Paediatric population

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

Method of administration

Oral use.

Taking Vilza Plus with or just after food may reduce gastrointestinal symptoms associated with metformin (see also section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (GFR < 30 ml/min) (see section 4.4)
- Acute conditions with the potential to alter renal function, such as:
    - dehydration,
    - severe infection,
    - shock,
    - intravascular administration of iodinated contrast agents (see section 4.4).
- Acute or chronic disease which may cause tissue hypoxia, such as:
    - cardiac or respiratory failure,
    - recent myocardial infarction,
    - shock.
- Hepatic impairment (see sections 4.2, 4.4 and 4.8)
- Acute alcohol intoxication, alcoholism
- Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

General

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

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (> 5 mmol/l) and an increased anion gap and lactate/pyruvate ratio.

Administration of iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.5).

Renal function

GFR should be assessed before treatment initiation and regularly thereafter (see section 4.2). Metformin is contraindicated in patients with GFR < 30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function (see section 4.3).

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 (see section 4.5).

Hepatic impairment

Patients with hepatic impairment, including those with pre-treatment ALT or AST > 3x ULN, should not be treated with Vilza Plus (see sections 4.2, 4.3 and 4.8).

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

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

Skin disorders

Skin lesions, including blistering and ulceration have been reported with vildagliptin in extremities of monkeys in non-clinical toxicology studies (see section 5.3). 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 Vilza Plus. 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 co-administration 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.

Combination with ACE inhibitors

There may be an increased risk of angioedema in patients concomitantly taking ACE inhibitors.(see section 4.8).

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 (see sections 4.2 and 4.4).

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 Vilza Plus may need to be adjusted during concomitant therapy and on its discontinuation.

Angiotensin converting enzyme (ACE) inhibitors may decrease the blood glucose levels. If necessary, the dosage of the antihyperglycaemic 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 (e.g. organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir and cimetidine) could increase systemic exposure to metformin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Vilza Plus 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 (see section 5.3). The potential risk for humans is unknown. Vilza Plus should not be used during pregnancy.

Breast-feeding

Studies in animals have shown excretion of both metformin and vildagliptin in milk. It is unknown whether vildagliptin is excreted in human milk, but metformin is excreted in human milk in low amounts. Due to both the potential risk of neonate hypoglycaemia related to metformin and the lack of human data with vildagliptin, Vilza Plus should not be used during breast-feeding (see section 4.3).

Fertility

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

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

4.8 Undesirable effects

There have been no therapeutic clinical trials conducted with Vilza Plus. However, bioequivalence of Vilza Plus with co-administered vildagliptin and metformin has been demonstrated (see section 5.2). 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.

Summary of the safety profile

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.

Tabulated list of adverse reactions

Adverse reactions reported in patients who received vildagliptin in double-blind studies as monotherapy and add-on therapies are listed below by system organ class and absolute frequency. Adverse reactions listed in Table 5 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 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions 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)

Metabolism and nutrition disorders	
Common	Hypoglycaemia
Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness

Uncommon	Fatigue
Gastrointestinal disorders	
Common	Nausea

Description of selected adverse reactions

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).

Clinical trials of up to more than 2 years' duration did not show any additional safety signals or unforeseen risks when vildagliptin was added on to metformin.

Combination with a sulphonylurea

Table 2 Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with metformin and a sulphonylurea (N=157)

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

Description of selected adverse reactions

There were no withdrawals due to adverse reactions reported in the vildagliptin + metformin + glimepiride treatment group versus 0.6% in the placebo + metformin + glimepiride treatment group.

The incidence of hypoglycaemia was common in both treatment groups (5.1% for the vildagliptin + metformin + glimepiride group versus 1.9% for the placebo + metformin + glimepiride group). One severe hypoglycaemic event was reported in the vildagliptin group.

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

Combination with insulin

Table 3 Adverse reactions reported in patients who received vildagliptin 100 mg daily in combination with insulin (with or without metformin) in double-blind studies (N=371)

Metabolism and nutrition disorders	
Common	Decreased blood glucose
Nervous system disorders	
Common	Headache, chills
Gastrointestinal disorders	
Common	Nausea, gastro-oesophageal reflux disease
Uncommon	Diarrhoea, flatulence

Description of selected adverse reactions

In controlled clinical trials using vildagliptin 50 mg twice daily in combination with insulin, with or without concomitant metformin, the overall incidence of withdrawals due to adverse reactions was 0.3% in the vildagliptin treatment group and there were no withdrawals in the placebo group.

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

At the end of the study, 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).

Additional information on the individual active substances of the fixed combination

Vildagliptin

Table 4 Adverse reactions reported in patients who received vildagliptin 100 mg daily as monotherapy in double-blind studies (N=1855)

Infections and infestations	
Very rare	Upper respiratory tract infection
Very rare	Nasopharyngitis
Metabolism and nutrition disorders	
Uncommon	Hypoglycaemia
Nervous system disorders	
Common	Dizziness
Uncommon	Headache
Vascular disorders	
Uncommon	Oedema peripheral
Gastrointestinal disorders	
Uncommon	Constipation
Musculoskeletal and connective tissue disorders	
Uncommon	Arthralgia

Description of selected adverse reactions

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).

Clinical trials of up to 2 years' duration did not show any additional safety signals or unforeseen risks with vildagliptin monotherapy.

Metformin

Table 5 Adverse reactions for metformin component

Metabolism and nutrition disorders	
Very rare	Decrease of vitamin B_{12} 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 adverse reactions occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 daily doses during or after meals. A slow increase in the dose may also improve gastrointestinal tolerability.

Post-marketing experience

Table 6 Post-marketing adverse reactions

Gastrointestinal disorders	
Not known	Pancreatitis
Hepatobiliary disorders	
Not known	Hepatitis (reversible upon discontinuation of the medicinal product) Abnormal liver function tests (reversible upon discontinuation of the medicinal product)
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Skin and subcutaneous tissue disorders	
Not known	Urticaria Exfoliative and bullous skin lesions, including bullous pemphigoid

4.9 Overdose

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

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

Galvecta Plus 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 (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 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} were -0.4% with vildagliptin added to metformin and -0.5% with glimepiride added to metformin, from a mean baseline HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} were -0.81% with vildagliptin added to metformin (mean baseline HbA_{1c} 8.4%) and -0.85% with gliclazide added to metformin (mean baseline HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} of 8.6%. The decrease in HbA_{1c} 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

HbA_{1c} compared with placebo. The placebo-adjusted mean reduction from a mean baseline HbA_{1c} 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" (HbA_{1c} 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 (HbA_{1c} value ≥7%) was 429 (43.6%) patients in the combination treatment group and 614 (62.1%) patients in the sequential treatment group.

A 24-week randomised, double-blind, placebo-controlled trial was conducted in 449 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with a stable dose of basal or premixed insulin (mean daily dose 41 units), with concomitant use of metformin (N=276) or without concomitant metformin (N=173). Vildagliptin in combination with insulin significantly decreased HbA_{1c} compared with placebo. In the overall population, the placebo-adjusted mean reduction from a mean baseline HbA_{1c} 8.8% was -0.72%. In the subgroups treated with insulin with or without concomitant metformin the placebo-adjusted mean reduction in HbA_{1c} was -0.63% and -0.84%, respectively. The incidence of hypoglycaemia in the overall population was 8.4% and 7.2% in the vildagliptin and placebo groups, respectively. Patients receiving vildagliptin experienced no weight gain (+0.2 kg) while those receiving placebo experienced weight reduction (-0.7 kg).

In another 24-week study in patients with more advanced type 2 diabetes not adequately controlled on insulin (short and longer acting, average insulin dose 80 IU/day), the mean reduction in HbA_{1c} when vildagliptin (50 mg twice daily) was added to insulin was statistically significantly greater than with placebo plus insulin (0.5% vs. 0.2%). The incidence of hypoglycaemia was lower in the vildagliptin group than in the placebo group (22.9% vs. 29.6%).

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 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Vilza Plus

Absorption

Bioequivalence has been demonstrated between Vilza Plus 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 Vilza Plus. The rate and extent of absorption of metformin from Vilza Plus 50 mg/1000 mg were decreased when given with food as reflected by the decrease in C_{max} by 26%, AUC by 7% and delayed T_{max} (2.0 to 4.0 h).

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

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. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/ml, even at maximum doses.

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

Distribution

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

Biotransformation

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

Elimination

Metformin is eliminated by renal excretion. Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

Animal studies of up to 13-week duration have been conducted with the combined substances in Vilza Plus. 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

Microcrystalline Cellulose -102
Povidone (PVP) K-30
Sodium Dodecyl Sulphate
Sodium Stearyl Fumarate
Purified water
Opadry white 85G68918

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30°C.

For details please see enclosed leaf insert.

6.5 Nature and contents of container
Alu-Alu blister pack of 56's tablets.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

PharmEvo (Pvt) Ltd.
A-29, North Western Industrial Zone Port Qasim Authority Karachi 75020. Pakistan
Tel : +92-21-34720155-159 FAX: +92-21-34720161
Web: www.pharmevo.biz

8. Marketing authorisation number(s)

50/1000mg = 082239

50/850mg = 082240

50/500mg = 103032

9. Date of first authorisation/renewal of the authorisation

50/1000mg, 50/850mg = 26th September 2017/4th June 2022

50/500mg = 3rd April 2020