UNILAB

Vildagliptin + Metformin

ProglinMet®

50 mg/500 mg, 50 mg/850 mg and 50 mg/1 g Film-Coated Tablet
combination of oral blood glucose lowering drugs ℞

DESCRIPTION AND COMPOSITION

Pharmaceutical Forms

- **50 mg/500 mg:** light yellow, ovaloid beveled-edged, film-coated tablet imprinted with “NVR” on one side and “LLO” on the other side
- **50 mg/850 mg:** yellow, ovaloid beveled-edged, film-coated tablet imprinted with “NVR” on one side and “SEH” on the other side
- **50 mg/1,000 mg:** dark yellow, ovaloid beveled-edged, film-coated tablet imprinted with “NVR” on one side and “FLO” on the other side

Certain dosage strengths and dosage forms may not be available in all countries.

Active substances

Vildagliptin
Metformin hydrochloride

Three strengths are available. One tablet of vildagliptin + metformin (ProglinMet®) contains:

- 50 mg vildagliptin and 500 mg metformin hydrochloride.
- 50 mg vildagliptin and 850 mg metformin hydrochloride.
- 50 mg vildagliptin and 1 g metformin hydrochloride.

Active moieties

Vildagliptin and metformin

Excipients

Hydroxypropyl cellulose, hypromellose, iron oxide yellow, iron oxide red, macrogol, magnesium stearate, talc and titanium dioxide

INDICATIONS

ProglinMet® is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control:

- as initial therapy when diabetes is not adequately controlled by diet and exercise alone
- as therapy in patients inadequately controlled with metformin hydrochloride or vildagliptin alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets
- as combination therapy - in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycemic control (see sections **WARNINGS AND PRECAUTIONS, INTERACTIONS** and **CLINICAL STUDIES** for available data on different combinations)

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

The use of antihyperglycemic therapy in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability. Do not exceed the maximum daily dose of vildagliptin (100 mg).

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

Starting dose for patients inadequately controlled on vildagliptin monotherapy

Based on the usual starting doses of metformin hydrochloride (500 mg twice daily or 850 mg once daily), initiate treatment at the 50 mg/500 mg tablet strength twice daily and gradually titrate after assessing the adequacy of therapeutic response.

Starting dose for patients inadequately controlled on metformin hydrochloride monotherapy

Based on the patient’s current dose of metformin hydrochloride, treatment may be initiated at either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1 g tablet strength twice daily.

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

Treatment may be initiated with either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1 g tablet strength based on the dose of vildagliptin or metformin already being taken.

Starting dose for treatment of naïve patients

In naïve patients, treatment may be initiated at 50 mg/500 mg once daily and gradually titrated to a maximum dose of 50 mg/1 g twice daily after assessing the adequacy of therapeutic response.

Use in combination with SU (sulfonylurea) or with insulin

The dose 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.

General target population

Adults 18 years of age and above

Special Populations

Renal impairment

A GFR should be assessed before initiation of treatment with metformin-containing products (such as vildagliptin + metformin (ProglinMet®)) and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g., every 3 to 6 months.

The maximum daily dose of metformin should preferably be divided into 2 to 3 daily doses. Factors that may increase the risk of lactic acidosis (see section **WARNINGS AND PRECAUTIONS**) should be reviewed before considering initiation of metformin-containing products (such as vildagliptin + metformin (ProglinMet®)) in patients with GFR <60 mL/min. Vildagliptin + metformin (ProglinMet®) is contraindicated in patients with GFR <30 mL/min because of its metformin component (see section **CONTRAINDICATIONS**).

The following dosing recommendations apply to metformin and vildagliptin, used separately or in combination, in patients with renal impairment. If no adequate strength of vildagliptin + metformin (ProglinMet®) is available, individual components should be used instead of the fixed-dose combination.

Table 1: Dose adjustments in patients with renal impairment

GFR mL/min	Metformin	Vildagliptin
60-89	Maximum daily dose is 3,000 mg*. Dose reduction may be considered if renal function declines.	Maximal daily dose is 100 mg.
45-59	Starting dose should not be more than 1,000 mg with a maximum daily dose of 2,000 mg*.	Maximal daily dose is 50 mg.
30-44	Starting dose should not be more than 500 mg with a maximum daily dose of 1,000 mg.	
<30	Metformin is contraindicated.	

*If metformin doses higher than those achievable with vildagliptin + metformin (ProglinMet®) alone are considered necessary.

Hepatic impairment

Use is not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment ALT or AST >2.5x ULN (see section **WARNINGS AND PRECAUTIONS**).

Pediatric patients (below 18 years)

The safety and effectiveness in pediatric patients have not been established. Therefore, use is not recommended in children below 18 years of age.

Geriatric patients (65 years or above)

As metformin is excreted via the kidneys, and elderly patients tend to exhibit decreased renal function, elderly patients should have their renal function monitored regularly. The dosage for elderly patients should be adjusted based on renal function (see section **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Method of Administration

For oral use

Administer with meals to reduce the gastrointestinal side effects associated with metformin hydrochloride.

If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

CONTRAINDICATIONS

Hypersensitivity

Known hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients (see section **DESCRIPTION AND COMPOSITION**, sub-section **Excipients**).

Patients with renal impairment

Use is contraindicated in patients with severe renal impairment (<30 mL/min) (see section **DOSAGE REGIMEN AND ADMINISTRATION** and section **WARNINGS AND PRECAUTIONS**).

Congestive heart failure

Use is contraindicated in patients with congestive heart failure requiring pharmacologic treatment (see **WARNINGS AND PRECAUTIONS**).

Metabolic acidosis

Use is contraindicated in patients with acute or chronic metabolic acidosis, including lactic acidosis or diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

WARNINGS AND PRECAUTIONS

Vildagliptin/Metformin

Vildagliptin + metformin (ProglinMet®) is not a substitute for insulin in patients requiring insulin. It should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Vildagliptin

Patients with hepatic impairment

Vildagliptin is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >2.5x ULN.

Hepatic 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. Not recommended in patients with a pre-treatment ALT or AST >2.5X the upper limit of normal. LFTs should be monitored at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed up thereafter with frequent liver function tests until the abnormality/abnormalities return to normal. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue treatment and contact their physician immediately. Following withdrawal of treatment and LFT normalization, treatment should not be reinitiated. Vildagliptin + metformin (ProglinMet®) is not recommended in patients with hepatic impairment.

Heart failure

A clinical study of vildagliptin in patients with New York Heart Association (NYHA) functional class I-III showed that treatment with vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive (see section **CLINICAL STUDIES**).

There is no experience of vildagliptin use in clinical studies in patients with NYHA functional class IV and therefore use is not recommended in these patients.

Metformin Hydrochloride

Lactic acidosis

Lactic acidosis is a very rare but serious metabolic complication that most often occurs with acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs with acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (e.g., due to severe diarrhea or vomiting, fever or reduced fluid intake), the patient should stop taking metformin-containing products (such as vildagliptin + metformin (ProglinMet®)) and seek immediate medical attention.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in patients treated with metformin-containing products (such as vildagliptin + metformin (ProglinMet®)). Other risk factors for lactic acidosis are excessive alcohol intake, hepatic impairment, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see section **CONTRAINDICATIONS** and section **INTERACTIONS**).

Diagnosis of lactic acidosis

Patients and/or caregivers should be informed of the risk of lactic acidosis. Lactic acidosis is characterized by acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. If suspected symptoms occur, the patient should stop taking metformin-containing products (such as vildagliptin + metformin (ProglinMet®)) and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (<7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with metformin-containing products (such as vildagliptin + metformin (ProglinMet®)) should be discontinued and the patient should be immediately hospitalized (see section **OVERDOSAGE**).

Monitoring of renal function

GFR should be assessed before treatment initiation and regularly thereafter (see section **DOSAGE REGIMEN AND ADMINISTRATION**). Metformin-containing products (such as vildagliptin + metformin (ProglinMet®)) are contraindicated in patients with GFR <30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function (see section **CONTRAINDICATIONS**). Metformin hydrochloride is known to be substantially excreted by the kidney, and the risk of metformin hydrochloride accumulation and lactic acidosis increases with the degree of renal function impairment. Since advancing age is associated with reduced renal function, careful dose titration is needed in the elderly to establish the minimum dose for adequate glycemic effect, and renal function should be monitored regularly. (see section **DOSAGE REGIMEN AND ADMINISTRATION** and section **CONTRAINDICATIONS**).

Interactions

Concomitant medications that may affect renal function or metformin hydrochloride disposition

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

Administration of intravascular iodinated contrast materials

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Metformin-containing products (such as vildagliptin + metformin (ProglinMet®)) should be discontinued prior to or at the time of the imaging procedures and not restarted until 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be stable (see section **DOSAGE REGIMEN AND ADMINISTRATION** and section **INTERACTIONS**).

Hypoxic states

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. If such events occur, the medication should be promptly discontinued.

Surgical procedures

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

Alcohol intake

Alcohol is known to potentiate the effect of metformin hydrochloride on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving metformin-containing products (such as vildagliptin + metformin (ProglinMet®)).

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

Patients with hepatic impairment

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

Vitamin B_{12} levels

Metformin has been associated with a decrease in serum vitamin B_{12} levels without clinical manifestations, in approximately 7% of patients. Such a decrease is very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride and/or vitamin B_{12} supplementation. Measurement of hematological parameters on at least an annual basis is advised for patients receiving metformin-containing products (such as vildagliptin + metformin (ProglinMet®)) and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (e.g., those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at minimally two- to three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes

A patient with type 2 diabetes previously well-controlled on vildagliptin + metformin (ProglinMet®) who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should promptly be evaluated for ketoacidosis and/or lactic acidosis. If acidosis of either form occurs, vildagliptin + metformin (ProglinMet®) must be stopped immediately and appropriate measures initiated.

Hypoglycemia

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

Loss of control of blood glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, surgery, etc., a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold vildagliptin + metformin (ProglinMet®) and temporarily administer insulin. Vildagliptin + metformin (ProglinMet®) may be reinstituted after the acute episode is resolved.

ADVERSE DRUG REACTIONS

Summary of the safety profile

Vildagliptin/Metformin

The data presented here relate to the administration of vildagliptin and metformin as a free or fixed-dose combination.

Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin-converting enzyme inhibitor (ACE inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy studies lasting up to 24 weeks, the incidence of ALT or AST elevations ≥3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for vildagliptin 50 mg daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

In clinical studies with the combination of vildagliptin + metformin, 0.4% of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily + metformin treatment group, and no withdrawal due to adverse reactions was reported in either the vildagliptin 50 mg twice daily + metformin or the placebo + metformin treatment groups.

In clinical studies, the incidence of hypoglycemia was uncommon in patients receiving vildagliptin 50 mg once daily in combination with metformin (0.9%), patients receiving vildagliptin 50 mg twice daily in combination with metformin (0.5%) and in patients receiving placebo and metformin (0.4%). No severe hypoglycemic events were reported in the vildagliptin arms.

Vildagliptin is weight neutral when administered in combination with metformin. Gastrointestinal adverse reactions including diarrhea and nausea are known to occur very commonly during the introduction of metformin hydrochloride. In the vildagliptin monotherapy clinical program (n=2,264) where vildagliptin was administered 50 mg once daily, 50 mg twice daily, or 100 mg once daily, the rate of diarrhea was 1.2%, 3.5% and 0.8%, respectively, and the rate of nausea was

1.7%, 3.7% and 1.7%, respectively, as compared to 2.9% for both in the placebo group (n=347) and 26.2% and 10.3%, respectively, in the metformin hydrochloride group (n=252).

Overall, gastrointestinal symptoms were reported in 13.2% (50 mg once daily or twice daily) of patients treated with the combination of vildagliptin and metformin hydrochloride compared to 18.1% of patients treated with metformin hydrochloride alone.

Tabulated summary of adverse drug reactions from clinical studies

Adverse reactions reported in patients who received vildagliptin in double-blind studies as an add-on to metformin and as monotherapy, are listed below for each indication, by MedDRA system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 2: Other adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=233) or 50 mg twice daily (n=183) as add-on therapy to metformin compared to placebo plus metformin in double-blind studies

Nervous system disorders	
Common	Tremor, dizziness, headache

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

When vildagliptin was studied as an initial combination therapy with metformin, no additional safety signals or unforeseen risks were observed.

Combination with insulin

In controlled clinical studies 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 cases of withdrawal in the placebo group.

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

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

Table 3: Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with insulin (with or without metformin (n= 371))

Nervous system disorders	
Common	Headache
Gastrointestinal disorders	
Common	Nausea, gastroesophageal reflux disease
Uncommon	Diarrhea, flatulence
General disorders and administration site conditions	
Common	Chills
Investigations	
Common	Decreased blood glucose

Combination with SU

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

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

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

Table 4: Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with metformin and SU (n=157)

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

Vildagliptin

Adverse reactions for vildagliptin component from monotherapy double-blind studies are presented in Table 5.

Table 5: Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=409) or 50 mg twice daily (n=1,373) as monotherapy in double-blind studies

Nervous system disorders	
Common	Dizziness
Uncommon	Headache
Gastrointestinal disorders	
Uncommon	Constipation
General disorders and administration site conditions	
Uncommon	Peripheral edema

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

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

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

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

Adverse drug reactions from spontaneous reports and literature cases - post-marketing experience (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

- Hepatitis, reversible upon drug discontinuation (see also section **WARNINGS AND PRECAUTIONS**).
- Urticaria, bullous and exfoliative skin lesions, including bullous pemphigoid
- Pancreatitis
- Arthralgia, sometimes severe

Metformin Hydrochloride

Known adverse reactions for the metformin component are summarized in Table 6.

Table 6: Known adverse reactions for metformin

Metabolism and nutrition disorders	
Very common Very Rare	Decreased appetite Lactic acidosis
Nervous system disorders	
Common	Dysgeusia
Gastrointestinal disorders	
Very Common	Flatulence, nausea, vomiting, diarrhea, abdominal pain
Hepatobiliary disorders	
Very Rare	Hepatitis**
Skin and subcutaneous tissue disorders	
Very rare	Skin reactions such as erythema, pruritus, urticaria
Investigations	
Very rare	Decrease of vitamin B_{12} absorption*, abnormal liver function test

*A decrease of vitamin B_{12} absorption with decrease of serum levels has very rarely been observed in patients treated long-term with metformin and appears to generally not be of clinical significance. Consideration of such etiology is recommended if a patient presents with megaloblastic anemia.

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

Gastrointestinal adverse effects occur most frequently during initiation of therapy and resolve spontaneously in most cases.

INTERACTIONS

Vildagliptin/Metformin

No clinically relevant pharmacokinetic interactions have been observed when vildagliptin (100 mg once daily) was co-administered with metformin hydrochloride (1 g once daily). Drug interactions for each component have been extensively studied. However, the concomitant use of the active substances in patients in clinical studies and in widespread clinical use has not resulted in any unexpected interactions.

The following statements reflect the information available on the individual active substances (vildagliptin and metformin).

Vildagliptin

Vildagliptin has low potential for drug interactions. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit or induce CYP 450 enzymes, it is not likely to interact with co-medications that are substrates, inhibitors or inducers of these enzymes.

Furthermore, vildagliptin does not affect metabolic clearance of co-medications metabolized by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5. Drug-drug interaction studies were conducted with commonly co-prescribed medications for patients with type 2 diabetes or medications with a narrow therapeutic window. As a result of these studies, no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, metformin hydrochloride), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.

Metformin Hydrochloride

The following is known about metformin:

Furosemide

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

Nifedipine

Nifedipine increased absorption, C_{max} and AUC of metformin, and increased excretion of metformin in urine. Metformin had minimal effects on nifedipine.

Glyburide

Glyburide produced no changes in metformin PK/PD parameters. Decreases in C_{max}, blood AUC of glyburide were observed, but were highly variable. Therefore the clinical significance of this finding was unclear.

Iodinated contrast agents

Metformin-containing products (such as vildagliptin + metformin (ProglinMet®)) 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 section **DOSAGE REGIMEN AND ADMINISTRATION** and section **WARNINGS AND PRECAUTIONS**).

Drugs that reduce metformin clearance

Concomitant use of drugs 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.

Other

Some drugs can adversely affect renal function which may increase the risk of lactic acidosis, e.g., NSAIDs, including selective cyclooxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin-containing products (such as vildagliptin + metformin (ProglinMet®)), close monitoring of renal function is necessary. Certain drugs tend to cause hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Close monitoring of glycemic control and metformin dose adjustments are recommended when such drugs are administered or withdrawn for these patients.

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to metformin. Avoid consumption of alcohol and medicinal products containing alcohol (see section **WARNINGS AND PRECAUTIONS**).

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There is insufficient experience with vildagliptin + metformin (ProglinMet®) in pregnant women. Embryo-fetal development (teratology) studies have been conducted in rats and rabbits with the combination of vildagliptin and metformin hydrochloride in a 1:10 ratio and produced no evidence of teratogenicity in either species. It should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Animal studies are not always predictive of human response.

Lactation

Risk summary

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

Females and males of reproductive potential

No studies on the effect on human fertility have been conducted for vildagliptin + metformin (ProglinMet®). Fertility studies have been performed with vildagliptin in rats at doses producing exposures equivalent to up to 200 times the human dose and have revealed no evidence of impaired fertility or early embryonic development due to vildagliptin. Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

OVERDOSAGE

Signs and symptoms

Vildagliptin

In healthy subjects (seven to fourteen subjects per treatment group), vildagliptin was administered in once-daily doses of 25, 50, 100, 200, 400, and 600 mg for up to 10 consecutive days. Doses up to 200 mg were well tolerated. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paresthesia, fever, edema and transient increase in lipase levels (2x ULN). At 600 mg, one subject experienced edema of the hands and feet, and an excessive increase in creatine phosphokinase (CPK) levels, accompanied by elevations of aspartate aminotransferase (AST), C-reactive protein, and myoglobin. Three additional subjects in this dose group presented with edema of both feet, accompanied by paresthesia in two cases. All symptoms and laboratory abnormalities resolved after study drug discontinuation.

Vildagliptin is not dialyzable, however the major hydrolysis metabolite (LAY151) can be removed by hemodialysis.

Metformin Hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin hydrochloride overdose cases. Metformin hydrochloride is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of the accumulated drug from patients in whom metformin hydrochloride overdosage is suspected.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

CLINICAL PHARMACOLOGY

Mechanism of Action (MOA)

Vildagliptin + metformin (ProglinMet®) combines two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: vildagliptin, a member of the DPP-4 (dipeptidyl-peptidase-4) inhibitor 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 that improves glycemic control. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase and increasing the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

Pharmacodynamics (PD)

Vildagliptin/Metformin

The efficacy and safety of the separate components have been previously established and the co-administration of the separate components have been evaluated for efficacy and safety in clinical studies. These clinical studies established an added benefit of vildagliptin in patients with inadequately controlled type 2 diabetes while on metformin hydrochloride therapy (see section **CLINICAL STUDIES**).

Vildagliptin

The administration of vildagliptin results in rapid and complete inhibition of DPP-4 activity. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period.

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with 50 to 100 mg daily in patients with type 2 diabetes significantly improved markers of beta-cell function. The degree of improvement in beta-cell function is dependent on the initial degree of impairment; in non-diabetic (normal glycemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion. The reduction in inappropriate glucagon during meals in turn attenuates insulin resistance.

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

The known effect of increased GLP-1 levels to delay gastric emptying is not observed with vildagliptin treatment. In addition, a reduction in postprandial lipemia that is not associated with vildagliptin's incretin mediated effect to improve islet function, has been observed.

Metformin Hydrochloride

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Unlike sulfonylureas, metformin hydrochloride does not cause hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances), and does not cause hyperinsulinemia. With metformin hydrochloride therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

In humans, metformin hydrochloride has favorable effects on lipid metabolism, independent of its action on glycemia. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDLc and triglyceride levels.

Pharmacokinetics (PK)

Absorption

Vildagliptin/Metformin

In the bioequivalence studies at three dose strengths (50 mg/500 mg, 50 mg/850 mg and 50 mg/1 g), versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses, the area under the curve (AUC) and maximum concentration (C_{max}) of both the vildagliptin component and the metformin hydrochloride component were demonstrated to be bioequivalent to that of free combination tablets.

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

Vildagliptin

Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.75 hours. Co-administration with food slightly decreases the rate of absorption of vildagliptin, as characterized by a 19% decrease in peak concentrations, and a delay in the time to peak plasma concentration to 2.5 hours. There is no change in the extent of absorption, and food does not alter the overall exposure (AUC).

Metformin Hydrochloride

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

Distribution

Vildagliptin

The plasma protein binding of vildagliptin is low (9.3%), and vildagliptin is distributed equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady state after intravenous administration (V_{ss}) is 71 liters, suggesting extravascular distribution.

Metformin Hydrochloride

The apparent volume of distribution (V/F) of metformin hydrochloride following single oral doses of 850 mg averaged 654 ± 358 L. Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein-bound. Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride, steady-state plasma concentrations of metformin hydrochloride are reached within 24 to 48 hours and are generally <1 microgram/mL. During controlled clinical studies of metformin hydrochloride, maximum metformin hydrochloride plasma levels did not exceed 5 micrograms/mL, even at maximum doses.

Biotransformation/metabolism

Vildagliptin

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite, LAY151, is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the amide hydrolysis product (4% of the dose). DPP-4 contributes partially to the hydrolysis of vildagliptin as shown in an *in vivo* study using DPP-4 deficient rats. Vildagliptin is not metabolized by cytochrome P450 enzymes to any quantifiable extent. *In vitro* studies demonstrated that vildagliptin does not inhibit or induce cytochrome P450 enzymes.

Metformin Hydrochloride

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

Elimination

Vildagliptin

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

Metformin Hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin hydrochloride is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Linearity

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

Special Populations

Gender

Vildagliptin

No differences in the pharmacokinetics of vildagliptin were observed between male and female subjects with a diverse range of age and body mass index (BMI). DPP-4 inhibition by vildagliptin was unaffected by gender.

Metformin Hydrochloride

Metformin hydrochloride pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin hydrochloride was comparable in males and females.

Obesity

Vildagliptin

BMI does not show any impact on the pharmacokinetic parameters of vildagliptin. DPP-4 inhibition by vildagliptin was unaffected by BMI.

Hepatic impairment

Vildagliptin

The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in subjects with mild, moderate, and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison to subjects with normal hepatic function. The exposure to vildagliptin (100 mg) after a single dose in subjects with mild and moderate hepatic impairment decreased (20% and 8%, respectively), while the exposure to vildagliptin for subjects with severe impairment increased by 22%. The maximum change (increase or decrease) in the exposure to vildagliptin is ~30%, which is not considered to be clinically relevant. There was no correlation between the severity of hepatic function impairment and changes in exposure to vildagliptin.

The use of vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >2.5x ULN.

Metformin Hydrochloride

No pharmacokinetic studies of metformin hydrochloride have been conducted in subjects with hepatic impairment.

Renal impairment

Vildagliptin

Vildagliptin AUC increased on average 1.4, 1.7 and 2-fold in patients with mild, moderate and severe renal impairment, respectively, compared to normal healthy subjects. The AUC of the metabolites LAY151 increased 1.6, 3.2 and 7.3-fold and that of BQS867 increased on average about 1.4, 2.7 and 7.3-fold in patients with mild, moderate and severe renal impairment, respectively, compared to healthy volunteers. Limited data from patients with end stage renal disease (ESRD) indicate that vildagliptin exposure is similar to that in patients with severe renal impairment. LAY151 concentrations in ESRD patients were approximately 2-3-fold higher than in patients with severe renal impairment.

Vildagliptin was removed by hemodialysis to a limited extent (3% over a 3-4 hour hemodialysis session starting 4 hours post dose).

Metformin Hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin hydrochloride is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Geriatric patients (65 years or above)

Vildagliptin

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

Metformin Hydrochloride

Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin hydrochloride is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function.

Treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Pediatric patients (below 18 years)

No pharmacokinetic data available.

Ethnic Group

Vildagliptin

There was no evidence that ethnicity affects the pharmacokinetics of vildagliptin.

Metformin Hydrochloride

No studies of metformin hydrochloride pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin hydrochloride in patients with type 2 diabetes, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51) and Hispanics (n=24).

CLINICAL STUDIES

Vildagliptin/Metformin

In a double-blind, placebo-controlled study in patients with type 2 diabetes whose hyperglycemia was inadequately controlled on a maximum dose of metformin hydrochloride alone, the addition of vildagliptin (50 mg once daily or 100 mg in divided doses) for 24 weeks led to statistically significant reductions in HbA_{1c} and increased the proportion of patients achieving at least a 0.7% reduction in HbA_{1c} when compared to patients who continued on metformin hydrochloride alone. Group mean baseline HbA_{1c} (%) ranged from 8.3% (placebo plus metformin hydrochloride) to 8.4% (in both vildagliptin plus metformin hydrochloride groups). Vildagliptin combined with metformin hydrochloride resulted 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 clinically meaningful and robust decrease in HbA_{1c} (defined as a decrease ≥0.7% from baseline) was statistically significantly higher in both vildagliptin plus metformin hydrochloride groups (46% and 60%, respectively) versus the metformin hydrochloride plus placebo group (20%). Patients on the combination of vildagliptin plus metformin hydrochloride did not experience a meaningful change in body weight compared to baseline. After 24 weeks, there was a decrease from baseline for both systolic and diastolic blood pressure in the vildagliptin treatment groups combined with metformin hydrochloride. Mean changes from baseline were -2.0/-0.8 mmHg, -3.5/-2.2 mmHg, and -0.8/-0.1 mmHg, in patients receiving metformin hydrochloride combined with vildagliptin 50 mg once daily, vildagliptin 50 mg twice daily or placebo, respectively. The incidence of gastrointestinal side effects ranged from 10% to 15% in the vildagliptin plus metformin hydrochloride groups as compared to 18% in the metformin hydrochloride plus placebo group.

The effect of vildagliptin in combination with metformin hydrochloride was evaluated in another double-blind, placebo-controlled clinical study of lasting 52 weeks in total (12-week core study plus a 40-week extension) involving 132 patients with type 2 diabetes on stable doses of metformin hydrochloride (1,500 mg to 3,000 mg daily). The addition of vildagliptin (50 mg once daily) to metformin hydrochloride resulted in an additional statistically significant reduction in mean HbA_{1c} (-0.6%) from baseline compared to placebo plus metformin hydrochloride (+0.1%) at the end of the 12-week study interval (mean baseline HbA_{1c} of 7.7% and 7.9%, respectively). Of these patients, 71 continued add-on treatment with vildagliptin or placebo for an additional

40 weeks (placebo-controlled, double-blind extension). At 52 weeks, mean change from baseline in HbA_{1c} was statistically significantly greater and sustained with vildagliptin (50 mg) plus metformin hydrochloride versus patients continued on metformin hydrochloride alone (between group difference of -1.1%) indicating a durable effect on glycemic control. In contrast, glycemic control in the metformin hydrochloride plus placebo group deteriorated over the course of the study.

In a 24-week study (LAF2354) vildagliptin (50 mg twice daily) was compared to pioglitazone (30 mg once daily) in patients inadequately controlled with metformin. 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. The decrease in HbA_{1c} from baseline >9.0% was greater (-1.5%) in both treatment groups. Patients receiving pioglitazone in addition to metformin experienced an increase in weight of 1.9 kg. Patients receiving vildagliptin in addition to metformin experienced an increase in weight of 0.3 kg. In a 28-week extension, HbA_{1c} reductions were similar between treatment groups and the body weight difference further increased.

In a long-term study of up to more than 2 years (LAF2308), vildagliptin (100 mg/day) was compared to glimepiride (up to 6 mg/day) in patients treated with metformin. After 1 year, mean reductions in HbA_{1c} were -0.4% with vildagliptin added to metformin and -0.5% with glimepiride added to metformin. Body weight change with vildagliptin was -0.2 kg vs +1.6 kg with glimepiride. The incidence of hypoglycemia 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 hypoglycemia differences were maintained.

In a 52-week study (LAF237A2338), vildagliptin (50 mg twice daily) was compared to gliclazide (up to 320 mg/day) in patients inadequately controlled with metformin. 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. Body weight change with vildagliptin was +0.1 kg compared to a weight gain of +1.4 kg with gliclazide. The number of patients experiencing hypoglycemic events was the same in both treatment groups, however the number of patients experiencing two or more hypoglycemic events was higher in the gliclazide plus metformin group (0.8%) than in the vildagliptin plus metformin group (0.2%).

In a 24-week study (LMF237A2302) 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/1 g twice daily) as initial therapy in drug-naïve patients was evaluated. The mean HbA_{1c} reductions were significantly greater with vildagliptin plus metformin combination therapy compared to either monotherapy. Vildagliptin/metformin 50 mg/1 g twice daily reduced HbA_{1c} by - 1.82% and vildagliptin/metformin 50 mg/500 mg twice daily by -1.61% from a mean baseline HbA_{1c} of 8.6%. The decrease in HbA_{1c} observed in patients with a baseline ≥10.0% was greater. Body weight decreased in all groups, with a mean reduction of -1.2 kg for both vildagliptin plus metformin combinations. The incidence of hypoglycemia was similar across treatment groups (0% with vildagliptin plus metformin combinations and 0.7% with each monotherapy).

A five year multi-center, randomized, double-blind study (VERIFY) was conducted in patients with type 2 diabetes to evaluate the durability 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=1003) in newly diagnosed patients with type 2 diabetes. The initiation of an early combination regimen of vildagliptin 50 mg bid plus metformin resulted in a statistically and clinically significant reduction in the relative risk for "time to confirmed initial treatment failure" (HbA_{1c} value ≥7%) vs metformin monotherapy in treatment-naïve patients with T2DM over the 5-year study duration. 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 (HR [95%CI]: 0.51 [0.45, 0.58]; p<0·001).

Consistently lower HbA_{1c} was observed with the combination treatment group compared with the sequential treatment group throughout the study duration. An early combination treatment approach with vildagliptin plus metformin in patients with newly diagnosed type 2 diabetes significantly and consistently improved long-term glycemic durability compared with sequential treatment. The incidence of adverse events (AE) was comparable between the treatment groups (83.5% in the early combination therapy group vs. 83.2% in the sequential treatment group, respectively). The proportion of newly diagnosed patients who experienced hypoglycemic events over the entire study was low in both treatment groups (1.1% in early combination group and 0.6% in sequential treatment group). Both the treatment groups reported microvascular or macrovascular complications in a comparable proportion of patients (30.5% of patients in the early combination group, and 33.1% of patients in the sequential treatment group). The overall safety and tolerability profile was similar between treatment approaches, with no unexpected safety findings reported.

A 24-week randomized, double-blind, placebo-controlled study 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 U), with (N=276) or without (N=173) concomitant metformin. 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 hypoglycemia in the overall population was 8.4% and 7.2% in the vildagliptin and placebo groups, respectively. Changes in weight were +0.2 kg and -0.7 kg in the vildagliptin and placebo groups, respectively.

A 24-week randomized, double-blind, placebo-controlled study was conducted in 318 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with metformin (≥1,500 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} 8.8% was -0.76%.

Vildagliptin

More than 15,000 patients with type 2 diabetes participated in double-blind, placebo- or active-controlled clinical studies of up to more than 2 years treatment duration. In these studies, vildagliptin was administered to more than 9,000 patients at daily doses of 50 mg once daily, 50 mg twice daily or 100 mg once daily. More than 5,000 male and more than 4,000 female patients received vildagliptin 50 mg once daily or 100 mg daily. More than 1,900 patients receiving vildagliptin 50 mg once daily or 100 mg daily were ≥65 years of age. In these studies, vildagliptin was administered as monotherapy in drug-naïve patients with type 2 diabetes or in combination in patients not adequately controlled by other antidiabetic medicinal products.

Overall, vildagliptin improved glycemic control when given as monotherapy or when used in combination with metformin hydrochloride, as measured by clinically relevant reductions in HbA_{1c} and fasting plasma glucose from baseline at the study endpoint. When given as monotherapy or in combination with metformin hydrochloride in studies of up to 52 weeks in duration, these improvements in glucose homeostasis were durable.

A 52-week multi-center, randomized, double-blind study was conducted in patients with type 2 diabetes and congestive heart failure (NYHA class I-III) to evaluate the effect of vildagliptin 50 mg bid (N=128) compared to placebo (N=126) on left ventricular ejection fraction (LVEF). Vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing CHF. Adjudicated cardiovascular events were overall balanced. There were slightly more cardiac events in vildagliptin-treated patients with NYHA class III heart failure compared to placebo. However, there were imbalances in baseline CV risk favoring placebo and the number of events was low, precluding firm conclusions. Vildagliptin significantly decreased HbA_{1c} compared with placebo (difference of 0.6%) from a mean baseline of 7.8%. The incidence of hypoglycemia in the overall population was 4.7% and 5.6% in the vildagliptin and placebo groups, respectively.

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 in duration was performed. It involved 9,599 patients with type 2 diabetes treated with vildagliptin 50 mg qd or 50 mg bid and showed that vildagliptin treatment was not associated with an increase in cardiovascular risk. The composite endpoint of adjudicated major adverse cardiovascular events (MACE) including acute myocardial infarction, stroke or CV death was similar for vildagliptin versus combined active and placebo comparators [Mantel–Haenszel risk ratio (M-H RR) 0.82 (95% confidence interval 0.61-1.11)] supporting the cardiovascular safety of vildagliptin. 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 HF events defined as HF requiring hospitalization 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) showing no increased risk of HF in vildagliptin-treated patients.

Metformin Hydrochloride

The prospective randomized (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 hydrochloride after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin hydrochloride 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 sulfonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034
- a significant reduction of the absolute risk of diabetes-related mortality: metformin hydrochloride 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017
- a significant reduction of the absolute risk of overall mortality: metformin hydrochloride 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years (p=0.011), and versus the combined sulfonylurea 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 hydrochloride 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years (p=0.01)

NON-CLINICAL SAFETY DATA

No new toxicities associated with the combination were identified during animal studies of up to 13 weeks. The following data are findings from studies performed with vildagliptin or metformin individually.

Vildagliptin

Carcinogenicity and mutagenicity

A two-year carcinogenicity study was conducted in rats at oral doses of up to 900 mg/kg (approximately 200 times the human exposure at the maximum recommended dose). No increases in tumor incidence attributable to vildagliptin were observed. A two-year carcinogenicity study was conducted in mice at oral doses of up to 1,000 mg/kg (up to 240 times the human exposure at the maximum recommended dose). Mammary tumor incidence increased in female mice at approximately 150 times the maximum anticipated human exposure to vildagliptin; it did not increase at approximately 60 times the maximum human exposure. The incidence of hemangiosarcoma increased in male mice treated at 42 to 240 times the maximum human exposure to vildagliptin and in female mice at 150 times the maximum human exposure. No significant increases in hemangiosarcoma incidences were observed at approximately 16 times the maximum human exposure to vildagliptin in males and approximately 60 times the maximum human exposure in females.

Vildagliptin was not mutagenic in a variety of mutagenicity tests including a bacterial reverse mutation Ames assay and a human lymphocyte chromosomal aberration assay. Oral bone marrow micronucleus tests in both rats and mice did not reveal clastogenic or aneugenic potential up to 2,000 mg/kg or approximately 400 times the maximum human exposure. An *in vivo* mouse liver comet assay using the same dose was also negative.

Safety pharmacology and repeat dose toxicity

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. It should be noted that vildagliptin exhibits a significantly higher pharmacological potency in monkeys compared with humans. Skin lesions were not reversible in the monkeys treated at 160 mg/kg/day during a 4-week recovery period. Skin lesions have not been observed in other animal species or in humans treated with vildagliptin.

Metformin Hydrochloride

Preclinical 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.

Carcinogenicity

Long-term carcinogenicity studies with metformin hydrochloride have been performed in rats (dosing duration 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin hydrochloride was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin hydrochloride in male rats.

Reproductive toxicity

There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day. This is a frequent spontaneous reproductive tract lesion in rats and its relevance in terms of toxicological and carcinogenicity study outcomes for humans is uncertain.

Mutagenicity

There was no evidence of mutagenic potential of metformin hydrochloride in the following *in vitro* tests: Ames test (*S. typhimurium*), and gene mutation test (mouse lymphoma cells) or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

INCOMPATIBILITIES

Not applicable.

STORAGE

Store at temperatures not exceeding 30°C. Protect from moisture. Drugs must be kept out of the reach and sight of children.

AVAILABILITY

Vildagliptin + Metformin (ProglinMet®) 50 mg/500 mg Film-Coated Tablet, in alu/alu blister pack x 10s (box of 30s)

Vildagliptin + Metformin (ProglinMet®) 50 mg/850 mg Film-Coated Tablet, in alu/alu blister pack x 10s (box of 30s)

Vildagliptin + Metformin (ProglinMet®) 50 mg/1 g Film-Coated Tablet, in alu/alu blister pack x 10s (box of 30s)

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