NOVARTIS

Regulatory Affairs

GALVUS® (vildagliptin)
50 mg Tablets

International Package Leaflet (IPL)

CDS Version 4.2

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Galvus®

Drugs used in diabetes, dipeptidyl peptidase 4 (DPP-4) inhibitors

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Galvus 50 mg tablets: white to light yellowish, round flat faced with beveled edges, unscored tablet. One side is debossed with "NVR", and the other side with "FB".

Active substance(s)

Vildagliptin

One tablet of Galvus contains 50 mg of vildagliptin.

Excipients

Lactose anhydrous, microcrystalline cellulose, sodium starch glycolate, magnesium stearate.

Pharmaceutical formulations may vary between countries.

INDICATIONS

Galvus is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM).

- **as monotherapy.**
- **in dual combination**
  - with metformin, when diet, exercise and metformin alone do not result in
  - adequate glycemic control.
  - with a sulfonylurea (SU), when diet, exercise and a SU alone do not result in
  - adequate glycemic control.
  - with a thiazolidinedione (TZD) when diet, exercise and a TZD do not result in
  - adequate glycemic control.
- **in triple combination**
  - with a sulfonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycemic control.

Galvus is also indicated in combination with insulin (with or without metformin) when diet, exercise and a stable dose of insulin do not result in adequate glycemic control.

Galvus is also indicated as initial combination therapy with metformin in patients with T2DM whose diabetes is not adequately controlled by diet and exercise alone.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage Regimen

The use of antidiabetic therapy in the management of diabetes should be individualized based on effectiveness and tolerability.

The recommended dose of Galvus is 50 mg once or twice daily. The maximum daily dose of Galvus is 100 mg.

For monotherapy, and for combination with metformin, with a thiazolidinedione (TZD) or with insulin (with or without metformin), the recommended dose of Galvus is 50 mg or 100 mg daily.

When used in dual combination with a sulfonylurea, the recommended dose of vildagliptin is 50 mg once daily. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg once daily.

For triple combination with metformin and a sulfonylurea (SU), the recommended dose of Galvus is 100 mg daily.

If tighter glycemic control is required on the top of the maximum recommended daily dose of vildagliptin, the addition of other antidiabetic drugs such as metformin, an SU, a TZD or insulin may be considered.

General target population

Adults 18 years of age and above

Special populations

Renal impairment

No dosage adjustment of Galvus is required in patients with mild renal impairment. In patients with moderate or severe renal impairment or End Stage Renal Disease (ESRD), the recommended dose of Galvus is 50 mg once daily (see section PHARMACOKINETICS under Special Populations).

Hepatic impairment

Galvus is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >2.5x the upper limit of normal (ULN) (see section PHARMACOKINETICS under Special Populations).

Pediatric patients (below 18 years)

Galvus has not been studied in patients under 18 years of age; therefore, the use of Galvus in pediatric patients is not recommended (see section PHARMACOKINETICS under Special Populations).

Geriatric patients (65 years or above)

In patients treated with Galvus ≥65 years of age and ≥75 years of age, no differences were observed in the overall safety, tolerability, or efficacy between this elderly population and younger patients. No dosage adjustments are therefore necessary in the elderly patients (see section PHARMACOKINETICS under Special Populations).

Method of administration

For oral use

Galvus can be administered with or without meals (see section PHARMACOKINETICS, absorption).

The 50 mg dose should be administered once daily in the morning. The 100 mg dose should be administered as two divided doses of 50 mg given in the morning and evening.

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

CONTRAINDICATIONS

Galvus is contraindicated in patients with known hypersensitivity to vildagliptin or to any of the excipients (see section DESCRIPTION AND COMPOSITION under subsection Excipients).

WARNINGS AND PRECAUTIONS

General

Galvus is not a substitute for insulin in patients requiring insulin. Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Special populations

Patients with Hepatic impairment

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

Hepatic enzyme monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported. 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 Galvus. LFTs should be monitored during Galvus treatment at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of therapy with Galvus is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus and contact their physician immediately. Following withdrawal of treatment with Galvus and LFT normalization, vildagliptin treatment should not be reinitiated.

Heart failure

A clinical trial 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 the results are inconclusive (see section CLINICAL STUDIES).

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

ADVERSE DRUG REACTIONS

Summary of the safety profile

The safety and tolerability of vildagliptin (50 mg qd, 50 mg bid and 100 mg qd) have been assessed by pooling data from more than 11,000 patients from 36 Phase II and III studies (including 3 open label studies) ranging in duration from 12 to more than 104 weeks. The studies used in this pooled analysis have assessed vildagliptin as monotherapy, add-on therapy to other oral anti-diabetic agents (metformin, TZD, SU and insulin) and as an initial combination therapy with metformin or pioglitazone. Patients not receiving vildagliptin (all comparators group) were taking only placebo or metformin, TZD, SU, acarbose or insulin. For the calculation of frequency of adverse drug reactions for the individual indications, safety data from a subset of pivotal controlled trials of at least 12 week's duration was considered. Safety data were obtained from patients exposed to vildagliptin at a daily dose of 50 mg (once daily) or 100 mg (50 mg twice daily or 100 mg once daily) who received vildagliptin as monotherapy or in combination with another agent.

The majority of adverse reactions in these trials 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 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. 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 trials 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 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.

Tabulated summary of adverse drug reactions from clinical trials

Adverse reactions reported in patients who received Galvus in double-blind studies as monotherapy and add-on therapies, are listed below, for each indication, by MedDRA system organ class and absolute frequency. Within each 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).

Monotherapy

The overall incidence of withdrawal from monotherapy trials 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.

Galvus is weight neutral when administered as monotherapy.

Table 1 Adverse reactions reported in patients who received Galvus 50 mg once daily (n=409) or 50 mg twice daily (n=1373) as monotherapy in double-blind studies

Nervous system disorders	
Common	Dizziness
Uncommon	Headache
Gastrointestinal disorders	
Uncommon	Constipation
General disorders and administration site conditions	
Uncommon	Oedema peripheral

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

Combination with metformin

In clinical trials 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 trials, 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 + metformin (0.4%). No severe hypoglycemic events were reported in the vildagliptin arms.

Galvus is weight neutral when administered in combination with metformin.

Table 2 Adverse reactions reported in patients who received Galvus 50 mg once daily (n=233) or 50 mg twice daily (n=183) in combination with metformin in double-blind studies

GALVUS IN DUAL ORAL THERAPY WITH METFORMIN	
Nervous system disorders	
Common	Tremor, dizziness, headache

Long-term clinical trials of up to more than 2 years did not show any additional safety signal or unforeseen risks when vildagliptin was added on to metformin**.**

When vildagliptin was studied as an initial combination therapy with metformin, no additional safety signal or unforeseen risk was observed.

Combination with a sulfonylurea

In clinical trials with the combination of vildagliptin 50 mg + glimepiride, the overall incidence of withdrawals due to adverse reactions was 0.6% in the vildagliptin 50 mg + glimepiride treatment group versus 0% in the placebo + glimepiride treatment group.

In clinical trials, the incidence of hypoglycemia when vildagliptin 50 mg once daily was added to glimepiride was 1.2% versus 0.6% for placebo + glimepiride. No severe hypoglycemic events were reported in the vildagliptin arms.

At the recommended dose of 50 mg, Galvus is weight neutral when administered in combination with glimepiride.

Table 3 Adverse reactions reported in patients who received Galvus 50 mg once daily in combination with a sulfonylurea in double-blind studies (n=170)

Nervous system disorders	
Common	Tremor, headache, dizziness
General disorders and administration site conditions	
Common	Asthenia

Combination with a thiazolidinedione

In clinical trials with the combination of vildagliptin and a thiazolidinedione, 0.7% of patients withdrew for adverse reactions in the vildagliptin 50 mg once daily + pioglitazone group, and there were no withdrawals due to adverse reactions reported in either the vildagliptin 50 mg twice daily + pioglitazone or the placebo + pioglitazone treatment groups.

In clinical trials, no hypoglycemia events were reported in patients receiving vildagliptin 50 mg once daily + pioglitazone 45 mg, hypoglycemia was uncommon in patients receiving vildagliptin 50 mg twice daily + pioglitazone 45 mg (0.6%) but common in patients receiving placebo + pioglitazone 45 mg (1.9%). No severe hypoglycemic events were reported in the vildagliptin arms.

In the pioglitazone add-on study, the change in body weight compared to placebo was +0.1 kg and +1.3 kg for Galvus 50 mg daily and Galvus 50 mg twice daily, respectively.

The incidence of peripheral edema when vildagliptin was added to a maximum dose of background pioglitazone (45 mg once daily) was 8.2% as 50 mg once daily and 7.0%, as 50 mg twice daily compared to 2.5% for background pioglitazone alone. The incidence of edema when vildagliptin was added to pioglitazone as dual initial therapy in drug naïve patients was, however, less than for pioglitazone alone (50 mg once daily 3.5%, 50 mg twice daily 6.1% vs. pioglitazone 30 mg 9.3%).

Table 4 Adverse reactions reported in patients who received Galvus 50 mg once daily (n= 146) or 50 mg twice daily (n=158) in combination with a thiazolidinedione in double-blind studies

General disorders and administration site conditions	
Common	Oedema peripheral
Investigations	
Common	Weight increase

Combination with insulin

In controlled clinical trials using vildagliptin 50 mg twice daily in combination with insulin, with or without concomitant metformin, the overall incidence of withdrawal 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 versus 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 5 Adverse reactions reported in patients who received Galvus 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	Diarrhoea, flatulence
General disorders and administration site conditions		
	Common	Chills
Investigations		
	Common	Blood glucose decreased

Combination with metformin and 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 6 Adverse reactions reported in patients who received Galvus 50 mg twice daily in combination with metformin and SU (n=157)

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

Common	Asthenia

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 with Galvus 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.
- Cutaneous vasculitis
- Pancreatitis.
- Arthralgia, sometimes severe.
- Cholecystitis

INTERACTIONS

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), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.

PREGNANCY, LACTATION, FEMALES AND MALE OF REPRODUCTIVE POTENTIALS

Pregnancy

Risk summary

There is insufficient experience with Galvus in pregnant women. Vildagliptin was not teratogenic in either rats or rabbits. Galvus should not be used during pregnancy unless the benefit to the mother outweighs the potential risk to the fetus.

Lactation

Risk summary

As it is not known whether vildagliptin is excreted in human milk, Galvus should not be administered to breast-feeding women.

Females and males of reproductive potential

No studies on the effect on human fertility have been conducted for Galvus. Fertility studies have been performed in rats at doses up to 200 times the human dose and have revealed no evidence of impaired fertility or early embryonic development due to vildagliptin.

OVERDOSAGE

Signs and symptoms

In healthy subjects (seven to fourteen subjects per treatment group), Galvus 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 feet and hands, 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.

Management

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

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

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).

Pharmacodynamics (PD)

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.

Pharmacokinetics (PK)

Absorption

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).

Distribution

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.

Biotransformation/metabolism

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.

Elimination

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 unchanged vildagliptin accounts for 23% of the dose after oral administration. After 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 of Galvus tablets is approximately 3 hours and is independent of the dose.

Linearity/non-linearity

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

Special populations

Pediatric patients (below 18 years)

No pharmacokinetic data available.

Geriatric patients (65 years or above)

In otherwise healthy elderly subjects (≥70 years), the overall exposure to vildagliptin (100 mg once daily IR tablet) was 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.

Gender

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.

Obesity

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

Ethnicity

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

Renal impairment

The AUC of vildagliptin 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 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 to 3-fold higher than in patients with severe renal impairment. Dosage adjustment may be required in patients with renal impairment. (see section DOSAGE REGIMEN AND ADMINISTRATION).

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

Hepatic impairment

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 IR tablet) after a single dose in subjects with mild and moderate hepatic impairment was decreased by (20% and 8%, respectively), while the exposure to vildagliptin for subjects with severe impairment was increased by 22%. The maximum change (increase or decrease) in the exposure to vildagliptin was ~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 the ULN.

CLINICAL STUDIES

More than 15,000 patients with type 2 diabetes participated in double-blind, placebo- or active-controlled clinical trials of up to more than 2 years of 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 trials, 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, a sulfonylurea, a thiazolidinedione, with insulin, or in triple combination with metformin and a sulfonylurea as measured by clinically relevant reductions in HbA1c from baseline at the study endpoint (see Table 7).

In clinical trials, the magnitude of HbA1c reductions with vildagliptin was greater in patients with higher baseline HbA1c.

In a 52-week trial (LAF2309), vildagliptin (100 mg/day) reduced baseline HbA1c by -1% compared to -1.4% for metformin (titrated to 2 g/day). Patients treated with vildagliptin reported significantly lower incidences of gastrointestinal adverse reactions versus those treated with metformin.

In a 24-week trial (LAF2327), vildagliptin (100 mg/day) was compared to rosiglitazone (8 mg once daily). Mean reductions were -1.1% with vildagliptin and -1.3% with rosiglitazone in patients with mean baseline HbA1c of 8.7%. Patients receiving rosiglitazone experienced a mean increase in weight (+1.6 kg) while those receiving vildagliptin experienced no weight gain (-0.3 kg). The incidence of peripheral edema was lower in the vildagliptin group than in the rosiglitazone group (2.1% vs. 4.1%, respectively).

In a 24-week trial (LAF2354) vildagliptin (50 mg twice daily) was compared to pioglitazone (30 mg once daily) in patients inadequately controlled with metformin. Mean reductions from baseline HbA1c of 8.4% were -0.9% with vildagliptin added to metformin and -1.0% with pioglitazone added to metformin. The decrease in HbA1c 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, HbA1c reductions were similar between treatment groups and the difference in body weight further increased.

In a long-term trial 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 one year mean reductions in HbA1c 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 HbA1c was similar to baseline values in both treatment groups and the body weight changes and the differences in hypoglycemia were maintained.

In a long-term trial of 2 years (LAF2310), vildagliptin (50 mg twice daily) was compared to gliclazide (up to 320 mg/day). After two years, mean reduction in HbA1c was -0.5% for vildagliptin and -0.6% for gliclazide. Vildagliptin had less of a weight gain (0.75 kg) and fewer hypoglycemic events (0.7%) than gliclazide (1.6 kg and 1.7%, respectively).

In a 52-week trial (LAF237A2338), vildagliptin (50 mg twice daily) was compared to gliclazide (up to 320 mg/day) in patients inadequately controlled with metformin. After one-year, mean reductions in HbA1c were -0.81% with vildagliptin added to metformin (mean baseline HbA1c 8.4%) and -0.85% with gliclazide added to metformin (mean baseline HbA1c 8.5%); statistical non-inferiority was achieved. 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 trial (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/1,000 mg twice daily) as initial therapy in drug-naïve patients was evaluated. The mean HbA1c reductions were significantly greater with vildagliptin plus metformin combination therapy compared to either monotherapy. Vildagliptin/metformin 50 mg/1,000 mg twice daily reduced HbA1c by -1.82% and vildagliptin/metformin 50 mg/500 mg twice daily by -1.61% from a mean baseline HbA1c of 8.6%. The decrease in HbA1c 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).

In a 24-week, double-blind placebo-controlled trial, vildagliptin (50 mg once daily) reduced HbA1c by -0.74% from a mean baseline of 7.9% in patients with moderate renal impairment and -0.88% from a mean baseline of 7.7% in patients with severe renal impairment. Vildagliptin significantly decreased HbA1c when compared to placebo (reductions in patients with moderate and severe renal impairment in the placebo group were -0.21% and -0.32% respectively, from similar mean baseline values).

A 24-week randomized, 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 U), with (N = 276) or without (N = 173) concomitant metformin. Vildagliptin in combination with insulin significantly decreased HbA1c compared with placebo: in the overall population, the placebo-adjusted mean reduction from mean baseline HbA1c 8.8% was -0.72%. In the subgroups treated with insulin with or without concomitant metformin the placebo-adjusted mean reduction in HbA1c 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 HbA1c compared with placebo: the placebo-adjusted mean reduction from mean baseline HbA1c 8.8% was -0.76%.

Table 7 Key efficacy results of vildagliptin in placebo-controlled monotherapy trials and in add-on combination therapy trials (primary efficacy ITT population)

Monotherapy placebo controlled studies	Mean baseline HbA1c (%)	Mean change from baseline in HbA1c (%) at week 24	Placebo-corrected mean change in HbA1c (%) at week 24 (95% CI)

Study 2301: Vildagliptin 50 mg once daily (N=104)	8.2	-0.8	-0.5* (-0.8, -0.1)
Study 2301: Vildagliptin 50 mg twice daily (N=90)	8.6	-0.8	-0.5* (-0.8, -0.1)
Study 2384: Vildagliptin 50 mg once daily (N=84)	8.3	-0.5	-0.5* (-0.9, -0.1)
Study 2384: Vildagliptin 50 mg twice daily (N=79)	8.4	-0.7	-0.7* (-1.1, -0.4)
		* p< 0.05 for comparison versus placebo	
Add-on / Combination studies			
Study 2303: Vildagliptin 50 mg once daily + metformin (N=143)	8.4	-0.5	-0.7* (-1.0, -0.5)
Study 2303: Vildagliptin 50 mg twice daily + metformin (N=143)	8.4	-0.9	-1.1* (-1.4, -0.8)
Study 2305: Vildagliptin 50 mg daily + glimepiride (N=132)	8.5	-0.6	-0.6* (-0.9, -0.4)
Study 2304: Vildagliptin 50 mg daily + pioglitazone (N=124)	8.6	-0.8	-0.5* (-0.7, -0.2)
Study 2304: Vildagliptin 50 mg twice daily + pioglitazone (N=136)	8.7	-1.0	-0.7* (-0.9, -0.4)
Study 2311: Vildagliptin 50 mg twice daily + insulin (N=125)	8.5	-0.5	-0.3* (-0.5, -0.0)
Study 23135: Vildagliptin 50 mg twice daily + insulin	8.8	-0.8	-0.7* (-0.9, -0.5)
Study 23152: Vildagliptin 50 mg twice daily + metformin + glimepiride (N=152)	8.8	-1.0	-0.8* (-1.0, -0.5)
		* p< 0.05 for comparison versus placebo + background therapy	

A 52-week multi-center, randomized, double-blind trial was conducted in patients with type 2 diabetes and congestive heart failure (CHF) (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 HbA1c 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.

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" (HbA1c value ≥ 7%) vs metformin monotherapy in treatment-naïve patients with T2DM over the 5-year study duration. The incidence of initial treatment failure (HbA1c value ≥ 7%) was 429 (43.6%) patients in the combination treatment group and 614 (62.1%) patients in the sequential treatment group (HR [95%CI]: 0.51 [0.45, 0.58]; p<0·001).

Consistently lower HbA1c 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 glycaemic 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.

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 cardio-vascular 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.

NON-CLINICAL SAFETY DATA

Carcinogenicity and mutagenicity

A two-year carcinogenicity study was conducted in rats at oral doses 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 up to 1,000 mg/kg (up to 240 times the human exposure at the maximum recommended dose). Mammary tumor incidence was increased in female mice at approximately 150 times the maximum anticipated human exposure to vildagliptin; it was not increased at approximately 60 times the maximum human exposure. The incidence of hemangiosarcoma was 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 number 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.

INCOMPATIBILITIES

Not applicable.

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