UNILAB

Vildagliptin

Proglin®

50 mg Tablet
hypoglycemic agent

Rx

DESCRIPTION AND COMPOSITION
Pharmaceutical form
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
Vildagliptin: 1-[(3-Hydroxy-adamant-1-yamino)-acetyl]-pyrrolidine-2(S)-carbonitrile

Each tablet contains 50 mg of vildagliptin.

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

INDICATIONS
Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM).
- **as monotherapy**
- **as combination therapy**
  - initial combination with metformin when diabetes is not adequately controlled by diet and exercise alone
  - in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycemic control (see section **WARNINGS AND PRECAUTIONS**, section **INTERACTIONS** and section **CLINICAL STUDIES** for available data on different combinations)

DOSAGE REGIMEN AND ADMINISTRATION
Dosage regimen
The management of antidiabetic therapy should be individualized.

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

If tighter glycemic control is required on 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 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 is 50 mg once daily (see section **PHARMACOKINETICS** under **Special populations**).

Hepatic impairment
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)
Vildagliptin (Proglin®) has not been studied in patients under 18 years of age; therefore, the use in pediatric patients is not recommended (see section **PHARMACOKINETICS** under **Special populations**).

Geriatric patients (65 years or above)
In patients treated that are ≥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
Administer 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 is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

CONTRAINDICATIONS
Patients with known hypersensitivity to vildagliptin or to any of the excipients (see section **DESCRIPTION AND COMPOSITION** under subsection **Excipients**).

WARNINGS AND PRECAUTIONS
General
Vildagliptin (Proglin®) 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.

Special populations
Patients with hepatic impairment
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. LFTs should be monitored during 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 ALT or AST 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, 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 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 vildagliptin (Proglin®) 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.

Vildaglitin is weight neutral when administered as monotherapy.

Table 1 Adverse reactions reported in patients who received vildagliptin (Proglin®) 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	Peripheral edema

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

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.

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Vildaglitin is weight neutral when administered as monotherapy.

Table 1 Adverse reactions reported in patients who received vildagliptin (Proglin®) 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	Peripheral edema

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.

Vildaglitin (Proglin®) is weight neutral when administered in combination with metformin.

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

VILDAGLIPTIN 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, vildagliptin (Proglin®) is weight neutral when administered in combination with glimepiride.

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

Nervous system disorders	
Common	Headache, chills
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 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 vildagliptin (Proglin®) 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 vildagliptin (Proglin®) 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

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 MALES OF REPRODUCTIVE POTENTIAL
Pregnancy
Risk summary
There is insufficient experience with vildagliptin (Proglin®) in pregnant women. Vildagliptin was not teratogenic in either rats or rabbits. Vildagliptin (Proglin®) 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, vildagliptin (Proglin®) 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 vildagliptin (Proglin®). 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), 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 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
Vildagliptin 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 ilsteer 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 is approximately 3 hours and is independent of the dose.

Linearity/Non-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
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) 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**).

Vildaglitin 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) after a single dose in subjects with mild and moderate hepatic impairment was decreased

(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 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.

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 HbA_{1c} from baseline at the study endpoint (see **Table 7**).

In clinical trials, the magnitude of HbA_{1c} reductions with vildagliptin was greater in patients with higher baseline HbA_{1c}.

In a 52-week trial (LAF2309), vildagliptin (100 mg/day) reduced baseline HbA_{1c} by 1.5% 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 HbA_{1c} of 8.7%. Patients receiving rosiglitazone experienced a mean increase in weight (+1.6 kg) while those receiving vildagliptin experienced no weight gain (-0.1 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 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 24-week extension, HbA_{1c} 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 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 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 HbA_{1c} 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 glclazide (up to 320 mg/day) in patients inadequately controlled with metformin. After one year, mean reductions in HbA_{1c} were -0.81% with vildagliptin added to metformin (mean baseline HbA_{1c} 8.4%) and -0.85% with glclazide 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 glclazide. 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 glclazide 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 HbA_{1c} reductions were significantly greater with vildagliptin plus metformin combination therapy compared to either monotherapy. Vildagliptin/metformin 50 mg/1,000 mg 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).

In a 24-week double-blind placebo-controlled trial, vildagliptin (50 mg once daily) reduced HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} compared with placebo: In the overall population, the placebo-adjusted mean reduction from 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 mean baseline HbA_{1c} 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 HbA_{1c} (%)	Mean change from baseline in HbA_{1c} (%) at week 24	Placebo-corrected mean change in HbA_{1c} (%) 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 + glimepride (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 23132: 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 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 vildaglitpin 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=598) 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