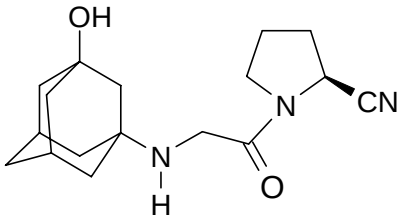
GALVUS®
Vildagliptin

NAME OF THE MEDICINE

The active ingredient of GALVUS is vildagliptin.
Chemical name: 1-[(3-Hydroxy-adamant-1-ylamino)acetyl]-pyrrolidine-2(S)-carbonitrile
Chemical structure:



Molecular formula: $C_{17}H_{25}N_3O_2$
Molecular weight: 303.40
CAS registry no. 274901-16-5

DESCRIPTION

Vildagliptin is a white to slightly yellowish or slightly greyish crystalline powder with a melting point/range of approximately 150°C. It is freely soluble in water.

Each GALVUS tablet contains 50 mg vildagliptin, lactose anhydrous, magnesium stearate, cellulose – microcrystalline and sodium starch glycollate.

PHARMACOLOGY

Pharmacodynamics

Vildagliptin, a member of the class that enhances islet cell insulin secretion via an augmented incretin effect, is a high affinity dipeptidyl-peptidase-4 (DPP-4) inhibitor that improves glycaemic control.

The administration of vildagliptin results in rapid and near-complete inhibition of DPP-4 activity. Vildagliptin shows weak inhibition of, and rapid dissociation from DPP-8 and DPP-9, compared to DPP-4. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. 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).

The degree of improvement in beta-cell function is dependent on the initial degree of impairment; in non-diabetic (normal glycaemic) 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 reduced glucagon secretion. There is a reduction in inappropriate glucagon release during meals. The increase in the insulin/glucagon ratio with hyperglycaemia, due to increased incretin hormone levels, may thus be expected to decrease postprandial hepatic glucose production, leading to reduced glycaemia.

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

Pharmacokinetics

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.

Absorption:

Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.75 hours. Coadministration 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 distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady state after intravenous administration (Vss) is 71 L, suggesting extravascular distribution.

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.

Excretion and Elimination:

Following oral administration of [14C] - vildagliptin, approximately 85% of the dose is excreted into the urine and 15% of the dose is recovered in the faeces. 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 L/hour and 13 L/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 dose.

Special Populations

Age:

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.

Paediatric:

No pharmacokinetic data available.

Obesity:

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

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 the upper limit of normal.

Chronic kidney disease:

In subjects with mild, moderate, and severe chronic kidney disease, and End Stage Renal Disease (ESRD) patients on haemodialysis, systemic exposure to vildagliptin was increased (Cmax 8% to 66%; AUC 32% to 134%) compared to subjects with normal renal function. Exposure to the inactive metabolite (LAY151) increased with increasing severity of chronic kidney disease (AUC 1.6- to 6.7-fold). Changes in exposure to vildagliptin did not correlate with severity of chronic kidney disease, whereas changes in exposure to the inactive metabolite did correlate. Elimination half-life of vildagliptin was not affected by chronic kidney disease. No dosage adjustment is required in patients with mild chronic kidney disease. Due to limited experience, the use of vildagliptin is not recommended in patients with moderate or severe chronic kidney disease or in patients with ESRD on haemodialysis (See **PRECAUTIONS**, **Chronic kidney disease**).

Race:

There is no evidence that race affects the pharmacokinetics of vildagliptin.

CLINICAL TRIALS

More than 15,000 patients with type 2 diabetes participated in double-blind, placebo- or active-controlled clinical trials including some studies of 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 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. Monotherapy studies suggested that vildagliptin on its own had slightly less efficacy compared to sulfonylureas or pioglitazone. The role of vildagliptin in dual therapy with sulfonylureas and pioglitazone is incompletely defined. No morbidity or mortality data are available.

Overall, vildagliptin improved glycaemic control when given as monotherapy or when used in combination with metformin, a sulfonylurea, or a thiazolidinedione as measured by clinically relevant reductions in HbA_{1c} from baseline at study endpoint (see **Table 1**). Long-term extension studies with vildagliptin as add-on therapy to metformin, glimepiride, or pioglitazone generally demonstrated continued glycaemic benefit at week 52. However, results were variable across studies. Therefore, the individual long-term response may vary.

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

Table 1 Key efficacy results of vildagliptin in placebo-controlled monotherapy and in combination therapy trials (primary efficacy ITT population)

	Primary endpoint (weeks)	**Mean baseline HbA_{1c} (%)**	**Mean change from baseline in HbA_{1c} (%)**	**Difference from placebo group (95%CI)**	**Patients achieving a ≥ 0.7% reduction in A1c (%)**
Monotherapy studies					
Vildagliptin 50 mg once daily (N=104) [Study 2301]	24	8.2	-0.8	-0.5** (-0.8, -0.1)	62 (60%)
Vildagliptin 50 mg twice daily (N=90) [Study 2301]	24	8.6	-0.8	-0.5** (-0.8, -0.1)	59 (66%)
Vildagliptin 50 mg once daily (N=84) [Study 2384]	24	8.3	-0.5	-0.5** (-0.9, -0.1)	37 (44%)
Vildagliptin 50 mg twice daily (N=79) [Study 2384]	24	8.4	-0.7	-0.7** (-1.1, -0.4)	43 (54%)
Combination studies					
Vildagliptin 50 mg once daily + metformin (N=143)	24	8.4	-0.5	-0.7* (-1.0, -0.5)	66 (46%)

[Study 2303]					
Vildagliptin 50 mg twice daily + metformin (N=143) [Study 2303]	24	8.4	-0.9	-1.1* (-1.4, -0.8)	86 (60%)
Vildagliptin 50 mg once daily + pioglitazone (N=124) [Study 2304]	24	8.6	-0.8	-0.5* (-0.7, -0.2)	67 (54%)
Vildagliptin 50 mg twice daily + pioglitazone (N=136) [Study 2304]	24	8.7	-1.0	-0.7* (-0.9, -0.4)	93 (68%)
Vildagliptin 50 mg once daily + glimepiride (N=132) [Study 2305]	24	8.5	-0.6	-0.6* (-0.9, -0.4)	62 (47%)

* $p < 0.05$ for comparison versus placebo + background therapy
** $p < 0.05$ for comparison versus placebo

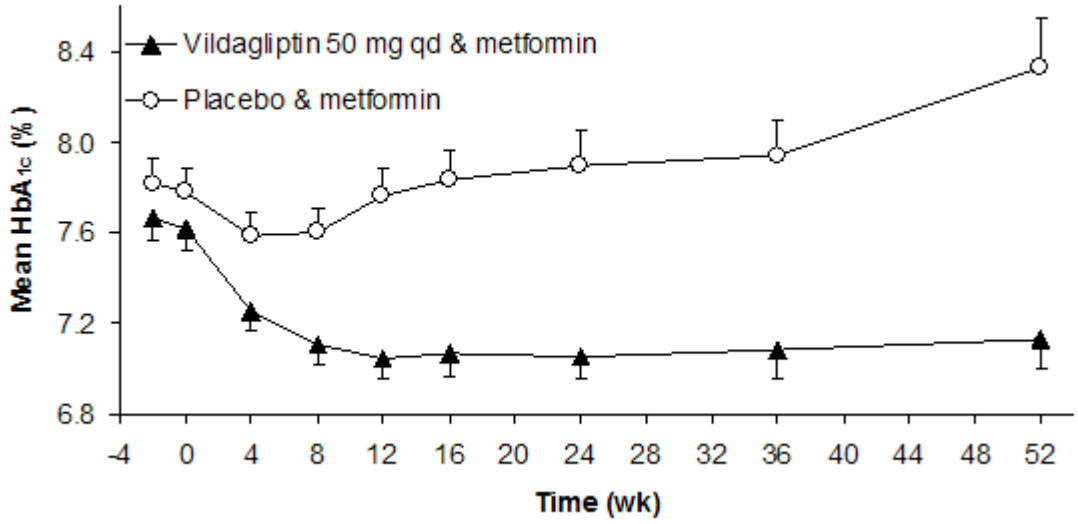
Combination with Metformin:

In a double-blind, placebo-controlled 24 week trial (Study 2303; n=544) in patients with type 2 diabetes whose hyperglycaemia was inadequately controlled on a maximal dose of metformin alone (mean metformin dose at baseline = 2100 mg/day), the addition of vildagliptin (50 mg once daily or 100 mg daily, as a divided dose of 50 mg in the morning and 50 mg in the evening) to metformin 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 were continued on metformin plus placebo. Group mean baseline HbA_{1c} ranged from 8.3% (placebo plus metformin) to 8.4% (in both vildagliptin plus metformin groups)(see **Table 1**). Vildagliptin combined with metformin 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 decrease of $\geq$0.7% in HbA_{1c} from baseline was statistically significantly higher in both vildagliptin plus metformin groups (46% and 60%, respectively) versus the metformin plus placebo group (20%). Patients on the combination of vildagliptin plus metformin did not experience a meaningful change in body weight compared to baseline. The incidence of gastrointestinal side effects ranged from 10% to 15% in the vildagliptin plus metformin groups as compared to 18% in the metformin plus placebo group. Vildagliptin added to metformin significantly reduced FPG compared to metformin plus placebo (-0.8 mmol/L for 50 mg once daily, and -1.7 mmol/L for 50 mg twice daily).

The effect of vildagliptin in combination with metformin was evaluated in another, double-blind, placebo-controlled add-on clinical trial (Study 2204E1) of 52 weeks total duration (12-week core study plus a 40-week extension) involving 132 patients with type 2 diabetes on stable doses of metformin (1500 mg-3000 mg daily). The addition of vildagliptin (50 mg once daily) to metformin resulted in an additional statistically significant reduction in mean HbA_{1c} (between group difference of -0.6%) from baseline compared to placebo plus metformin (+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 versus patients continued on metformin plus placebo (between group difference of -1.1%).

These data indicate vildagliptin plus metformin provides a durable effect on glycaemic control over 52 weeks (See **Figure 1**). In contrast, glycaemic control in the metformin plus placebo group deteriorated over the course of the study.

Figure 1. Mean HbA_{1c} Over Time in a 52-Week Study (12-Week Core Study and 40-Week Extension) Comparing Vildagliptin Plus Metformin to Placebo Plus Metformin in Patients Inadequately Controlled with Metformin



In a double-blind, active-controlled 24 week trial (Study 2354; n=576), vildagliptin (100 mg/day; 50 mg in the morning and 50 mg in the evening) was compared to pioglitazone (30 mg once daily) in patients with type 2 diabetes inadequately controlled with metformin alone. 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 while those 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, double-blind, active-controlled trial of up to more than 2 years (Study 2308; n=3118), vildagliptin (100 mg/day; 50 mg in the morning and 50 mg in the evening) was compared to glimepiride (up to 6 mg/day) in patients with type 2 diabetes 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 hypoglycaemia was significantly lower in the vildagliptin group (1.7%) than in the glimepiride group (16.2%). At study endpoint (2 years), the HbA_{1c} was similar to baseline values in both treatment groups and the body weight changes and hypoglycaemia differences were maintained.

Combination with Glimepiride:

The benefit of vildagliptin as add-on therapy was investigated in a double-blind, placebo-controlled add-on trial (Study 2305; n=515), in patients with type 2 diabetes whose

hyperglycaemia was inadequately controlled after switching from half maximal recommended doses of a sulfonylurea to glimepiride (4 mg). The addition of vildagliptin (50 mg once daily or 100 mg daily, as a divided dose of 50 mg in the morning and 50 mg in the evening) for 24 weeks led to additional statistically significant reductions in HbA_{1c} from baseline versus patients continued on glimepiride plus placebo. The difference from placebo plus glimepiride was -0.64 in the 50 mg once daily group and -0.70% in the 50 mg twice daily group. Patients receiving vildagliptin in combination with glimepiride experienced either no increase in body weight (with vildagliptin 50 mg daily) or a slight increase (with vildagliptin 100 mg daily) relative to baseline values. Vildagliptin added to glimepiride reduced FPG compared to placebo plus glimepiride (-0.5 mmol/L for 50 mg once daily, and -0.6 mmol/L for 100 mg once daily, as divided dose of 50 mg in the morning and 50 mg in the evening).

Combination with Pioglitazone:

In a double-blind, placebo-controlled add-on trial (Study 2304; n=463) in patients with type 2 diabetes whose hyperglycaemia was inadequately controlled with prior thiazolidinedione monotherapy, patients were randomized to either continued thiazolidinedione monotherapy (pioglitazone 45 mg once daily plus placebo) or to the combination of the thiazolidinedione (pioglitazone 45 mg) plus vildagliptin (either 50 mg once daily or 50 mg twice daily) for 24 weeks. Group mean baseline HbA_{1c} ranged from 8.6% (vildagliptin 50 mg daily plus pioglitazone) to 8.7% (vildagliptin 50 mg twice daily plus pioglitazone, or placebo plus pioglitazone).

The addition of vildagliptin 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 were continued on the thiazolidinedione alone. Vildagliptin combined with pioglitazone resulted in additional statistically significant mean reductions in HbA_{1c} compared to pioglitazone plus placebo (between group differences of -0.5% to -0.7% for vildagliptin 50 mg once daily and twice daily, respectively). The proportion of patients who achieved a decrease of $\geq$0.7% in HbA_{1c}, from baseline was statistically significantly higher in both vildagliptin plus pioglitazone groups (54% and 68%, respectively) versus the pioglitazone plus placebo group (38%). Patients on the combination experienced either no increase in body weight (those receiving vildagliptin 50 mg daily plus pioglitazone) or a slight increase (those receiving vildagliptin 50 mg twice daily plus pioglitazone) relative to pioglitazone plus placebo.

Vildagliptin added to pioglitazone reduced FPG compared to placebo plus pioglitazone (-0.3 mmol/L for 50 mg vildagliptin once daily, and -0.7 mmol/L for 100 mg vildagliptin once daily, as divided dose of 50 mg in the morning and 50 mg in the evening).

Fasting Plasma Glucose:

When administered as monotherapy and add-on therapy, vildagliptin produced clinically relevant and consistent mean reductions from baseline in fasting plasma glucose (FPG) concentrations.

INDICATIONS

Treatment of diabetes mellitus type 2 in persons 18 years of age and older, as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes

with one of metformin, a sulfonylurea or pioglitazone when diet, exercise and the single agent do not result in adequate glycaemic control.

CONTRAINDICATIONS

Hypersensitivity to vildagliptin or to any of the excipients.

PRECAUTIONS

General

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

Chronic kidney disease

There is limited experience in patients with moderate or severe chronic kidney disease and in patients with End Stage Renal Disease (ESRD) on haemodialysis. Therefore, the use of vildagliptin is not recommended in these patients.

Hepatic impairment

Vildagliptin is not recommended in patients with hepatic impairment, including patients with a pre-treatment ALT or AST > 2.5X the upper limit of normal.

Liver 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 vildagliptin. Vildagliptin is not recommended in patients with a pre-treatment ALT or AST > 2.5X the upper limit of normal. LFTs should be monitored during vildagliptin 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 3 X upper limit of normal or greater persist, withdrawal of therapy with vildagliptin is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue vildagliptin and contact their physician immediately. Following withdrawal of treatment with vildagliptin and LFT normalisation, vildagliptin should not be reinitiated.

Other

Vildagliptin tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Carcinogenicity

Long-term oral studies with vildagliptin in rats and mice showed evidence of haemangiosarcomas at high exposures. Tumour incidence was increased at exposure levels 46-235 times (mice) and 150 times (rats) human exposure at the maximum clinical dose, based on AUC. No significant increase in incidence was observed at 15 to 80 (females) times human exposure in mice. No effect levels of ca 80 to 160 times human exposure were established in rats.

Mammary tumour incidence was increased in female mice at approximately 185 times the maximum anticipated human exposure to vildagliptin, but was not increased at ca 80 times. The tumours are thought to result from species-specific hormonal disturbances.

Based on the available data vildagliptin is not anticipated to present a carcinogenic risk at clinically relevant exposures.

Genotoxicity

Vildagliptin was not mutagenic in a bacterial reverse mutation assay and a human lymphocyte chromosomal aberration assay. Some clastogenic potential was exhibited in an in vitro micronucleus test in V79 Chinese hamster cells after long exposure to high, cytotoxic concentrations. However, no clastogenicity was observed in either mouse or rat micronucleus tests in vivo at up to ca 400 times the maximum human exposure, based on AUC. Furthermore, an in vivo mouse liver comet assay using the same dose was also negative. The weight of evidence indicates vildagliptin is unlikely to be genotoxic in humans at clinically relevant doses.

Effects on fertility

Vildagliptin did not impair male or female fertility or early embryonic development in rats at oral doses corresponding to 160 times human exposure at the maximum clinical dose.

Effects on skin

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at all oral doses administered (5 to 160 mg/kg/day). These were consistently located on the extremities (hands, feet, ears, scrotum and tail), and included flaking skin, peeling skin, scabs, tail sores and blisters. At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), lesions were reversible despite continued treatment. Necrotic lesions of the tail were observed at ≥ 80 mg/kg/day (18 times human AUC exposure at the maximum recommended clinical dose). Skin lesions were not reversible in monkeys treated at 160 mg/kg/day (35 times human AUC exposure) during a 4-week recovery period. Skin lesions have not been observed in other animal species and no excess of skin lesions with vildagliptin treatment relative to comparator treatments have been observed in the human clinical trials programme.

Use in pregnancy (Category B3)

Vildagliptin was not teratogenic in either rats or rabbits at exposures up to ca 115 times and 40 times the maximum expected human exposure, respectively. A slight treatment-related increase in the incidence of fetal rib abnormalities was observed in the fetuses of rats at oral doses of 225 mg/kg/day (approximately 30 times the human AUC exposure at the 100 mg dose). There are no adequate and well-controlled studies in pregnant women. Vildagliptin should not be used during pregnancy unless the benefit to the mother outweighs the potential

risk to the foetus. Attainment of strict normoglycaemia during pregnancy may require conversion to insulin monotherapy.

Use in lactation

Vildagliptin is excreted in the milk of lactating rats. As it is not known whether vildagliptin is excreted in human milk, vildagliptin should not be administered to breastfeeding mother.

Use in children

The safety and effectiveness of vildagliptin in paediatric patients have not been established.

Use in elderly

Of the 2900 patients treated with vildagliptin, 543 (18.9%) were ≥65 years of age and 109 (3.8%) were ≥75 years of age. There were no differences observed in overall safety, tolerability, or efficacy between these patients and younger patients.

Interaction with other drugs

Vildagliptin has a low potential for drug interaction. Since vildagliptin is not a cytochrome (CYP) P450 enzyme substrate and does not inhibit or induce CYP P450 enzymes, it is not likely to interact with the concomitant medications that are substrates, inhibitors or inducers of these enzymes.

Furthermore, vildagliptin is not likely to interact with the concomitant medications that are substrates, inhibitors or inducers of CYP P450 enzymes nor does it affect metabolic clearance of co-medications metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. Drug-drug interaction studies were conducted with the following commonly co-prescribed medications for patients with type 2 diabetes or medications with a narrow therapeutic window.

Glibenclamide

Coadministration of vildagliptin (100 mg twice daily) with glibenclamide (10 mg once daily) had no significant effect on the steady-state pharmacokinetics of vildagliptin. Vildagliptin did not alter the steady-state pharmacokinetics of glibenclamide.

Pioglitazone

Coadministration of vildagliptin (100 mg once daily) with pioglitazone (45 mg once daily) did not alter the steady-state pharmacokinetics of vildagliptin. Vildagliptin had no effect on the steady-state pharmacokinetics of pioglitazone measured by the parent pioglitazone and its two active metabolites, MIII and MIV.

Metformin

Coadministration of vildagliptin (100 mg once daily) with metformin (1000 mg once daily) did not alter the steady-state pharmacokinetics of metformin. Metformin (1000 mg once daily) did not affect total exposure to vildagliptin at steady state. The Cmax of vildagliptin was decreased by 18%, which is not considered to be clinically relevant.

Amlodipine

Coadministration of vildagliptin (100 mg once daily) with amlodipine (5 mg once daily) given in combination to healthy subjects, did not alter the steady-state pharmacokinetics of amlodipine (5 mg once daily). Similarly, the steady-state pharmacokinetics of vildagliptin were unaffected by coadministration of amlodipine.

Valsartan

Coadministration of vildagliptin (100 mg once daily) with valsartan (320 mg once daily) did not alter the steady-state pharmacokinetics of vildagliptin. Coadministration of vildagliptin with valsartan resulted in an increased exposure to valsartan (AUC by 24% and Cmax by 14%). However, these changes are not considered to be clinically relevant.

Ramipril

Coadministration of vildagliptin (100 mg once daily) with ramipril (5 mg once daily) to healthy subjects, did not alter the steady-state pharmacokinetics of ramipril and its active metabolite, ramiprilat. Similarly, ramipril did not affect the steady-state pharmacokinetics of vildagliptin.

Simvastatin

Coadministration of vildagliptin (100 mg once daily) with simvastatin (80 mg once daily) did not alter the steady-state pharmacokinetics of simvastatin and its active metabolite, simvastatin hydroxyacid. Similarly, simvastatin did not influence the steady-state pharmacokinetics of vildagliptin.

Digoxin

Coadministration of vildagliptin (100 mg once daily) with digoxin (0.5 mg loading dose on Day 1 and a 0.25 mg maintenance dose from Day 2 to Day 7) did not affect the pharmacokinetics of digoxin at steady state, and digoxin did not alter the pharmacokinetics of vildagliptin.

Warfarin

Coadministration of vildagliptin (100 mg once daily) with warfarin (25 mg single dose) did not alter the pharmacokinetics of warfarin and warfarin did not influence the pharmacokinetics of vildagliptin (100 mg once daily). Coadministration of vildagliptin did not affect the pharmacodynamic parameters of prothrombin times such as AUC_{PT}, PT_{max}, AUC_{INR}, INR_{max} following administration of warfarin 25 mg in comparison with coadministration of placebo.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who may experience dizziness should therefore avoid driving vehicles or using machines.

ADVERSE REACTIONS

Safety data were obtained from 3,784 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) in controlled trials of at least 12 week's duration. Of these patients, 2,264 patients received vildagliptin as

monotherapy and 1,520 patients receiving vildagliptin in combination with another agent. 2,682 patients were treated with vildagliptin 100 mg daily (2,027 with 50 mg twice daily and 655 with 100 mg once daily) and 1,102 patients were treated with vildagliptin 50 mg once daily.

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, gender, 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.

Adverse reactions reported in patients who received vildagliptin in double blind studies as monotherapy and add-on therapy are listed below, for each indication, by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); or common (≥ 1/100, < 1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Monotherapy

The overall incidence of withdrawals 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 50mg twice daily (0.1%) than for placebo (0.6%) or comparators (0.5%).

In monotherapy studies, hypoglycaemia was uncommon, reported in 0.5% (2 of 409) of patients treated with vildagliptin 50 mg once daily and 0.3% (4 of 1373) of patients treated with vildagliptin 50mg 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.

Table 2 Adverse reactions reported in patients who received vildagliptin 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 plus metformin, 0.4% of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily plus metformin, and no withdrawal due to adverse reactions was reported in either the vildagliptin 50mg bid plus metformin or the placebo plus metformin treatment groups.

In clinical trials, the incidence of hypoglycaemia 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 plus metformin (0.4%). No severe hypoglycaemic events were reported in the vildagliptin arms.

Vildagliptin is weight neutral when administered in combination with metformin.

Table 3 Additional adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=233) or 50 mg twice daily (n=183) in combination with metformin in double-blind studies

Nervous system disorders	
Common	Headache, tremor, dizziness

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.

Combination with glimepiride

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

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

In clinical trials, weight did not change from baseline when vildagliptin 50 mg daily was added to glimepiride (-0.1kg and -0.4 kg for vildagliptin and placebo, respectively).

Table 4 Adverse reactions reported in patients who received vildagliptin 50mg once daily in combination with a sulphonylurea in double-blind studies (n=170)

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

Combination with pioglitazone

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

In clinical trials, no hypoglycaemia events were reported in patients receiving vildagliptin 50 mg once daily plus pioglitazone 45 mg, hypoglycaemia was uncommon in patients receiving vildagliptin 50 mg twice daily plus pioglitazone 45 mg (0.6%) but common in patients receiving placebo plus pioglitazone 45 mg (1.9%). No severe hypoglycaemic 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 oedema 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 oedema 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 5 Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n= 290) or 50mg twice daily (n=158) daily in combination with a thiazolidinedione in double-blind studies

Investigations	
Common	Weight increase
Vascular disorders	
Common	Oedema peripheral

Post-marketing Experience

During post-marketing experience the following additional adverse drug reactions have been reported:

- Rare cases of hepatitis reversible upon drug discontinuation
- Frequency not known: urticaria, pancreatitis.

DOSAGE AND ADMINISTRATION

The management of antidiabetic therapy should be individualised.

When used in dual combination with metformin, a thiazolidinedione (clinical experience is with pioglitazone as dual therapy), the recommended dose of vildagliptin is 50 mg or 100 mg daily. 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.

When used in dual combination with a sulphonylurea (clinical experience is with glimepiride as dual therapy), the recommended dose of vildagliptin is 50 mg once daily administered in

the morning. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg once daily and was associated with a higher rate of hypoglycaemia than the 50 mg dose.

Doses greater than 100 mg are not recommended.

Vildagliptin can be administered with or without a meal.

Patients with hepatic impairment

Vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST > 2.5X the upper limit of normal.

Patients with chronic kidney disease

Glomerular Filtration Rate (GFR) is to be estimated prior to commencement of therapy.
No dosage adjustment of vildagliptin is required in patients with mild chronic kidney disease (eGFR 60-89 mL/min/1.73m^2). Vildagliptin is, however, not recommended in patients with moderate (eGFR 30-59 mL/min/1.73m^2) or severe (eGFR 15-29 mL/min/1.73m^2) chronic kidney disease or End Stage Renal Disease (ESRD) on haemodialysis (See **PRECAUTIONS**, **Chronic kidney disease** and **PHARMACOLOGY**, **Special populations**).

Elderly patients

In patients treated with vildagliptin ≥ 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 **Pharmacokinetics**, **Special Populations**). Experience in patients aged 75 years and older is limited and caution should be exercised when treating this population.

Paediatric patients

Vildagliptin has not been studied in patients under 18 years of age; therefore, the use of vildagliptin in paediatric patients is not recommended (see **Pharmacokinetics**, **Special Populations**).

OVERDOSAGE

In healthy subjects (seven to fourteen subjects per treatment group), GALVUS (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 600 mg, one subject experienced oedema 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 oedema of both feet, accompanied by paraesthesia in two cases. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and transient increase in lipase levels (twice the upper limit of normal). All adverse events and laboratory abnormalities resolved after study drug discontinuation.

GALVUS is not dialysable, however the major hydrolysis metabolite (LAY151) can be removed by haemodialysis.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION

GALVUS (vildagliptin) is available as a 50 mg tablet.

50 mg: white to light yellowish, round, flat-faced, bevelled edge tablet. One side is debossed with "NVR" and the other side with "FB".

GALVUS is available in blisters packs containing 7, 10, 14, 28, 30, 56, 60 or 112 tablets.

Not all pack sizes may be marketed.

Storage: Store below 30°C. Protect from moisture.

Poison Schedule: S4

SPONSOR

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