GALVUS®

(Vildagliptin) 50 mg Tablets

Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Galvus 50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of vildagliptin.

Excipient: Each tablet contains 47.82 mg lactose anhydrous.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to light yellowish, round , flat-faced, bevelled-edge tablet. One side is debossed with “NVR”, and the other side with “FB”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Galvus is indicated as an adjunct to diet and exercise in patients with type 2 diabetes mellitus

- As monotherapy, if diet and exercise are not sufficient, or
- In combination with metformin, or a sulfonylurea if treatment with these oral antidiabetics does not offer sufficient control of blood glucose.
- In combination with a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

As triple oral therapy in combination with

- a sulfonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

Galvus is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.

4.2 Posology and method of administration

Adults

The management of antidiabetic therapy should be individualized.

The recommended dose of Galvus is 50 mg or 100 mg daily for monotherapy.

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 combination with metformin, in combination with thiazolidinedione, in combination with metformin and a SU or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening.

When used in dual combination with a sulfonylurea, 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.

When used in combination with a sulfonylurea, a lower dose of the sulfonylurea may be considered to reduce the risk of hypoglycaemia.

Daily doses higher than 100 mg are not recommended.

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

Additional information on special populations

Renal impairment

No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). In patients with moderate or severe renal impairment or End Stage Renal Disease (ESRD), the recommended dose of Galvus is 50 mg once daily.

Hepatic impairment

Galvus should not be used in patients with hepatic impairment, including patients with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x the upper limit of normal (ULN) (see also sections 4.4 and 5.2).

Elderly (≥ 65 years)

No dose adjustments are necessary in elderly patients. (see also sections 5.1 and 5.2).

Pediatric population

Galvus is not recommended for use in children and adolescents *(< 18 years)* due to a lack of data on safety and efficacy.

Method of administration

Oral use

Galvus can be administered with or without a meal (see also section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General

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

Renal impairment
There is limited experience in patients with ESRD on haemodialysis. Therefore Galvus should be used with caution in these patients (see also sections 4.2 and 5.2).

Hepatic impairment
Galvus should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3x ULN (see also sections 4.2 and 5.2).

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 test results returned to normal after discontinuation of treatment. Liver function tests should be performed prior to the initiation of treatment with Galvus in order to know the patient's baseline value. Liver function should be monitored during treatment with Galvus 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(s) to normal. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Galvus therapy is recommended.

Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus.

Following withdrawal of treatment with Galvus and LFT normalization, treatment with Galvus should not be reinitiated.

Heart Failure
A clinical trial of vildagliptin in patients with 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 CHF versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive(see section 5.1 Pharmacodynamic properties). 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.

Skin disorders
Skin lesions, including blistering and ulceration have been reported in extremities of monkeys in non-clinical toxicology studies (see section 5.3). Although skin lesions were not observed at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications. Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.

Acute pancreatitis
Use of vildagliptin has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis.
If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.

Hypoglycaemia
Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia.

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

4.5 Interaction with other medicinal products and other forms of interaction

Vildagliptin has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate and does not inhibit or induce CYP 450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes.

Combination with pioglitazone, metformin and glyburide
Results from studies conducted with these oral antidiabetics have shown no clinically relevant pharmacokinetic interactions.

Digoxin (Pgp substrate), warfarin (CYP2C9 substrate)
Clinical studies performed with healthy subjects have shown no clinically relevant pharmacokinetic interactions. However, this has not been established in the target population.

Combination with amlodipine, ramipril, valsartan or simvastatin
Drug-drug interaction studies in healthy subjects were conducted with amlodipine, ramipril, valsartan and simvastatin. In these studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin.

As with other oral antidiabetic medicinal products the hypoglycemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of vildagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Due to lack of human data, Galvus should not be used during pregnancy.
Lactation
It is unknown whether vildagliptin is excreted in human milk. Animal studies have shown excretion of vildagliptin in milk. Galvus should not be used during lactation.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Safety data were obtained from a total of 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 weeks duration. Of these patients, 2,264 patients received vildagliptin as monotherapy and 1,520 patients received vildagliptin in combination with another medicinal product. 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, ethnicity, duration of exposure or daily dose.

Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials of up to

24 weeks in duration, the incidence of ALT or AST elevations ≥ 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for vildagliptin 50 mg once daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

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

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 system organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Combination with metformin

In controlled clinical trials with the combination of vildagliptin 100 mg daily + metformin, no withdrawal due to adverse reactions was reported in either the vildagliptin 100 mg daily + metformin or the placebo + metformin treatment groups.

In clinical trials, the incidence of hypoglycemia was common in patients receiving vildagliptin 100 mg daily in combination with metformin (1%) and uncommon in patients receiving placebo + metformin (0.4%). No severe hypoglycemic events were reported in the vildagliptin arms.

In clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was added to metformin (+0.2 kg and -1.0 kg for vildagliptin and placebo, respectively).

Table 1 Adverse reactions reported in patients who received Galvus 100 mg daily in combination with metformin in double-blind studies (N=208)

Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness
Uncommon	Fatigue
Gastrointestinal disorders	
Common	Nausea
Metabolism and nutrition disorders	
Common	Hypoglycemia

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

Combination with a sulfonylurea

In controlled clinical trials with the combination of vildagliptin 50 mg + a sulfonylurea, the overall incidence of withdrawals due to adverse reactions was 0.6% in the vildagliptin 50 mg + sulfonylurea vs 0% in the placebo + sulfonylurea 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.

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

Table 2 Adverse reactions reported in patients who received Galvus 50 mg in combination with a sulfonylurea in double-blind studies (N=170)

Infections and infestations	
Very rare	Nasopharyngitis
Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness
Common	Asthenia
Gastrointestinal disorders	
Uncommon	Constipation
Metabolism and nutrition disorders	
Common	Hypoglycemia

Combination with a thiazolidinedione

In controlled clinical trials with the combination of vildagliptin 100 mg daily + a thiazolidinedione, no withdrawal due to adverse reactions was reported in either the vildagliptin 100 mg daily + thiazolidinedione or the placebo + thiazolidinedione treatment groups.

In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin + pioglitazone (0.6%) but common in patients receiving placebo + pioglitazone (1.9%). No severe hypoglycaemic events were reported in the vildagliptin arms.

In the pioglitazone add-on study, the absolute weight increases with placebo, Galvus 100 mg daily were 1.4 and 2.7 kg, respectively.

The incidence of peripheral oedema when vildagliptin 100 mg daily was added to a maximum dose of background pioglitazone (45 mg once daily) was 7.0%, compared to 2.5% for background pioglitazone alone.

Table 3 Adverse reactions reported in patients who received Galvus 100 mg daily in combination with a thiazolidinedione in double-blind studies (N=158)

Metabolism and nutrition disorders	
Common	Weight increase
Uncommon	Hypoglycemia
Nervous system disorders	
Uncommon	Headache
Uncommon	Asthenia
Vascular disorders	
Common	Oedema peripheral

Monotherapy

In addition, in controlled monotherapy trials with vildagliptin the overall incidence of withdrawals due to adverse reactions was no greater for patients treated with vildagliptin at doses of 100 mg daily (0.3%) than for placebo (0.6%) or comparators (0.5%).

In comparative controlled monotherapy studies, hypoglycaemia was uncommon, reported in 0.4% (7 of 1,855) of patients treated with vildagliptin 100 mg daily compared to 0.2% (2 of 1,082) of patients in the groups treated with an active comparator or placebo, with no serious or severe events reported.

In clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was administered as monotherapy (-0.3 kg and -1.3 kg for vildagliptin and placebo, respectively).

Table 4 Adverse reactions reported in patients who received Galvus 100mg daily as monotherapy in double-blind studies (N=1,855)

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

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

Combination with metformin and SU

Table 5 Adverse reactions reported in patients who received Galvus 50mg twice daily in combination with metformin and a sulfonylurea (N=157)

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

There were no withdrawals reported due to adverse reactions in the vildagliptin + metformin + glimepiride treatment group. vs. 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 group). One severe hypoglycemic event was reported in the vildagliptin group.

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

Combination with insulin

Table 6 Adverse reactions reported in patients who received Galvus 100 mg daily in combination with insulin (with or without metformin) in double-blind studies (n=371)

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

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

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

At the end of the study, 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).

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

Table 7 Post-marketing adverse reactions

Gastrointestinal disorders	
Not known*	Pancreatitis
Hepatobiliary disorders	
Not known*	Hepatitis (reversible upon discontinuation of the medicinal product) Abnormal liver function tests (reversible upon discontinuation of the medicinal product)
Musculoskeletal and connective tissue disorders	
Not known*	Myalgia
Skin and subcutaneous tissue disorders	
Not known*	Urticaria Bullous or exfoliative skin lesions

*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".

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

4.9 Overdose

Information regarding overdose with vildagliptin is limited.

Symptoms
Information on the likely symptoms of overdose was taken from a rising dose tolerability study in healthy subjects given Galvus for 10 days. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paresthesia, fever, edema and a transient increase in lipase levels. At 600 mg, one subject experienced edema of the feet and hands, and increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C-reactive protein (CRP) and myoglobin levels. Three other subjects experienced edema of the feet, with paresthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product.

Management
In the event of an overdose, supportive management is recommended. Vildagliptin cannot be removed by hemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH02

Vildagliptin, a member of the islet enhancer class, is a potent and selective DPP-4 inhibitor.

The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity, resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with vildagliptin 50-100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function including HOMA-β (Homeostasis Model Assessment–β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion.

The enhanced increase in the insulin/glucagon ratio during 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 delaying gastric emptying is not observed with vildagliptin treatment.

Clinical Experience

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 year’s 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 study endpoint (see Table 7 and below data).

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

In a 52-week double-blind controlled trial, vildagliptin (50 mg twice daily) reduced baseline HbA_{1c} by -1% compared to -1.6% for metformin (titrated to 2 g/day) statistical non-inferiority was not achieved. Patients treated with vildagliptin reported significantly lower incidences of gastrointestinal adverse reactions versus those treated with metformin.

In a 24-week double-blind controlled trial, vildagliptin (50 mg twice daily) was compared to rosiglitazone (8 mg once daily). Mean reductions were -1.20% with vildagliptin and -1.48% 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 (-0.3 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, vildagliptin (50 mg twice daily) was compared to pioglitazone (30 mg once daily) in patients inadequately controlled with metformin (mean daily dose: 2020 mg). Mean reductions from baseline HbA_{1c} of 8.4% were - 0.9% with vildagliptin added to metformin and -1.0% with pioglitazone added to metformin. The decrease in HbA_{1c} from baseline >9.0% was greater (-1.5%) in both treatment groups. A mean weight gain of +1.9 kg was observed in patients receiving pioglitazone added to metformin compared to +0.3 kg in those receiving vildagliptin added to metformin.

In a clinical trial of 2 years' duration, vildagliptin (50 mg twice daily) was compared to glimepiride (up to 6 mg/day – mean dose at 2 years: 4.6 mg) in patients treated with metformin (mean daily dose: 1894 mg). After 1 year mean reductions in HbA_{1c} were -0.4% with vildagliptin added to metformin and -0.5% with glimepiride added to metformin, from a mean baseline HbA1c of 7.3%. 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 the study endpoint (2 years), the HbA_{1c} was similar to baseline values in both treatment groups and the body weight changes and hypoglycemia differences were maintained.

In a long-term trial of 2 years, 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, from mean baseline HbA1c of 8.6%. Statistical non-inferiority was not achieved. Vildagliptin was associated with fewer hypoglycemic events (0.7%) than gliclazide (1.7%).

In a 52-week trial, vildagliptin (50 mg twice daily) was compared to gliclazide (mean daily dose: 229.5 mg) in patients inadequately controlled with metformin (metformin dose at baseline 1928 mg/day). After 1 year, mean reductions in 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 (95% CI -0.11 – 0.20). Body weight change with vildagliptin was +0.1 kg compared to a weight gain of +1.4 kg with gliclazide.

In a 24-week trial the efficacy of the fixed dose combination of vildagliptin and metformin (gradually titrated to a dose of 50 mg/500 mg twice daily or 50 mg/1000 mg twice daily) as initial therapy in drug-naïve patients was evaluated. Vildagliptin/metformin 50 mg/1000 mg twice daily reduced HbA1c by -1.82%, vildagliptin/metformin 50 mg/500 mg twice daily by -1.61%, metformin 1000 mg twice daily by -1.36% and vildagliptin 50 mg twice daily by -1.09% from a mean baseline HbA1c of 8.6%. The decrease in HbA1c observed in patients with a baseline ≥ 10.0% was greater.

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 concomitant use of metformin (N = 276) or without concomitant metformin (N = 173). Vildagliptin in combination with insulin significantly decreased HbA1c compared with placebo. In the overall population, the placebo-adjusted mean reduction from a 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. Patients receiving vildagliptin experienced no weight gain (+0.2 kg) while those receiving placebo experienced weight reduction (-0.7kg).

A 24-week randomized, double-blind, placebo-controlled trial was conducted in 318 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with metformin (≥ 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 a mean baseline HbA1c of 8.8% was -0.76%.

In another 24-week study in patients with more advanced type 2 diabetes not adequately controlled on insulin (short or longer acting, average insulin dose 80 IU/day), the mean reduction in HbA1c when vildagliptin (50 mg twice daily) was added to insulin was statistically significantly greater than with placebo plus insulin (0.5% vs. 0.2%). The incidence of hypoglycaemia was lower in the vildagliptin group than in the placebo group (22.9% vs. 29.6%).

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 twice daily (N=90)	8.6	-0.8	-0.5* (-0.8, -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			
Vildagliptin 50 mg twice daily + metformin (N=143)	8.4	-0.9	-1.1* (-1.4, -0.8)
Vildagliptin 50 mg daily + glimepiride (N=132)	8.5	-0.6	-0.6* (-0.9, -0.4)
Vildagliptin 50 mg twice daily + pioglitazone (N=136)	8.7	-1.0	-0.7* (-0.9, -0.4)
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 + comparator	

A 52-week multi-center, randomized, double-blind trial was conducted in patients with type 2 diabetes and congestive heart failure (NYHA class I - III) to evaluate the effect of vildagliptin 50 mg bid (N=128) compared to placebo (N=126) on left ventricular ejection fraction (LVEF). Vildagliptin was not associated with a change in left ventricular function or worsening of pre-existing CHF. Adjudicated cardiovascular events were overall balanced. There were slightly more cardiac events in vildagliptin treated patients with NYHA class III heart failure compared to placebo. However there were imbalances in baseline CV risk favoring placebo and the number of events was low, precluding firm conclusions. Vildagliptin significantly decreased HbA1c compared with placebo (difference of

0.6%) from a mean baseline of 7.8% at week 16. In the subgroup with NYHA class III, the decrease in HbA_{1c} compared to placebo was lower (difference 0.3%) but this conclusion is limited by the small number of patients (n=44). The incidence of hypoglycemia in the overall population was 4.7% and 5.6% in the vildagliptin and placebo groups, respectively.

Cardiovascular risk

A meta-analysis of independently and prospectively adjudicated cardiovascular events from 25 phase III clinical studies of up to more than 2 years duration was performed. It involved 8956 patients with type 2 diabetes treated with vildagliptin and showed that vildagliptin treatment was not associated with an increase in cardiovascular risk. The composite endpoint of adjudicated cardio and cerebrovascular (CCV) events [acute coronary syndrome (ACS, stroke or CCV death], was similar for vildagliptin versus combined active and placebo comparators [Mantel–Haenszel risk ratio 0.84 (95% confidence interval 0.63-1.12)] supporting the cardiovascular safety of vildagliptin. In total, 99 out of 8956 patients reported an event in the vildagliptin group vs 91 out of 6061 patients in the comparator group.

5.2 Pharmacokinetic properties

Absorption

Following oral administration in the fasting state, vildagliptin is rapidly absorbed, with peak plasma concentrations observed at 1.7 hours. Food slightly delays the time to peak plasma concentration to 2.5 hours, but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased C_{max} (19%). However, the magnitude of change is not clinically significant, so that Galvus can be given with or without food. The absolute bioavailability is 85%.

Distribution

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

Biotransformation

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite (LAY 151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the amide hydrolysis product (4% of dose). In vitro data in human kidney microsomessuggest that the kidney may be one of the major organs contributing to the hydrolysis of vildagliptin to its major inactive metabolite, LAY151. DPP-4 contributes partially to the hydrolysis of vildagliptin based on an *in vivo* study using DPP-4 deficient rats. Vildagliptin is not metabolized by CYP 450 enzymes to any quantifiable extent. Accordingly, the metabolic clearance of vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. *In vitro* studies demonstrated that vildagliptin does not inhibit/induce CYP 450 enzymes. Therefore, vildagliptin is not likely to affect metabolic clearance of co-medications metabolized by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

Elimination

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

Linearity / non-linearity

The C_{max} for vildagliptin and the area under the plasma concentrations versus time curves (AUC) increased in an approximately dose proportional manner over the therapeutic dose range.

Characteristics in patients

Gender

No clinically relevant differences in the pharmacokinetics of vildagliptin were observed between male and female healthy subjects within a wide range of age and body mass index (BMI). DPP-4 inhibition by vildagliptin is not affected by gender.

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

Hepatic impairment
The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in patients with mild, moderate and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison with healthy subjects. The exposures to vildagliptin after a single dose in patients with mild and moderate hepatic impairment was decreased (20% and 8%, respectively), while the exposure to vildagliptin for patients 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 the hepatic disease and changes in the exposure to vildagliptin.

Renal impairment
A multiple-dose, open-label trial was conducted to evaluate the pharmacokinetics of the lower therapeutic dose of vildagliptin (50 mg once daily) in patients with varying degrees of chronic renal impairment defined by creatinine clearance (mild: 50 to <80 ml/min, moderate: 30 to <50 ml/min and severe: <30 ml/min) compared to normal healthy control subjects.
Vildagliptin AUC increased on average 1.4, 1.7 and 2-fold in patients with mild, moderate and severe renal impairment, respectively, compared to normal healthy subjects. AUC of the metabolites LAY151 and BQS867 increased on average about 1.5, 3 and 7-fold in patients with mild, moderate and severe renal impairment, respectively. 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 were approximately 2-3-fold higher than in patients with severe renal impairment. Vildagliptin was removed by haemodialysis to a limited extent (3% over a 3-4 hour haemodialysis session starting 4 hours post dose).

Ethnic group
Limited data suggest that race does not have any major influence on vildagliptin pharmacokinetics.

5.3 Preclinical safety data

Intra-cardiac impulse conduction delays were observed in dogs with a no-effect dose of 15 mg/kg (7-fold human exposure based on C_{max}).

Accumulation of foamy alveolar macrophages in the lung was observed in rats and mice. The no-effect dose in rats was 25 mg/kg (5-fold human exposure based on AUC) and in mice 750 mg/kg (142-fold human exposure).

Gastrointestinal symptoms, particularly soft feces, mucoid feces, diarrhoea and, at higher doses, faecal blood were observed in dogs. A no-effect level was not established.

Vildagliptin was not mutagenic in conventional *in vitro* and *in vivo* tests for genotoxicity.
A fertility and early embryonic development study in rats revealed no evidence of impaired fertility, reproductive performance or early embryonic development due to vildagliptin. Embryo-foetal toxicity was evaluated in rats and rabbits. An increased incidence of wavy ribs was observed in rats in association with reduced maternal body weight parameters, with a no-effect dose of 75 mg/kg (10-fold human exposure). In rabbits, decreased foetal weight and skeletal variations indicative of developmental delays were noted only in the presence of severe maternal toxicity, with a no-effect dose of 50 mg/kg (9-fold human exposure). A pre- and postnatal development study was performed in

rats. Findings were only observed in association with maternal toxicity at ≥ 150 mg/kg and included a transient decrease in body weight and reduced motor activity in the F1 generation.

A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times human exposure at the maximum recommended dose). No increases in tumour incidence attributable to vildagliptin were observed. Another two-year carcinogenicity study was conducted in mice at oral doses up to 1,000 mg/kg. An increased incidence of mammary adenocarcinomas and hemangiosarcomas was observed with a no-effect dose of 500 mg/kg (59-fold human exposure) and 100 mg/kg (16-fold human exposure), respectively. The increased incidence of these tumours in mice is considered not to represent a significant risk to humans based on the lack of genotoxicity of vildagliptin and its principal metabolite, the occurrence of tumours only in one species and the high systemic exposure ratios at which tumours were observed.

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at doses ≥ 5 mg/kg/day. These were consistently located on the extremities (hands, feet, ears and tail). At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), only blisters were observed. They were reversible despite continued treatment and were not associated with histopathological abnormalities. Flaking skin, peeling skin, scabs and tail sores with correlating histopathological changes were noted at doses ≥ 20 mg/kg/day (approximately 3 times human AUC exposure at the 100 mg dose). Necrotic lesions of the tail were observed at ≥ 80 mg/kg/day. Skin lesions were not reversible in the monkeys treated at 160 mg/kg/day during a 4-week recovery period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, anhydrous
Cellulose, microcrystalline
Sodium starch glycolate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Store below 30°C. Store in the original package in order to protect from moisture.

6.4 Nature and contents of container

Aluminium/Aluminium (PA/Al/PVC/Al) blister.

6.6 Special precautions for disposal

No special requirements.

Manufacturer:

Novartis -Farmaceutica SA, Spain
For Novartis Pharma AG, Basel, Switzerland

Registration Holder:

Novartis Israel Ltd.,
36 Shacham St., Petach-Tikva.

Registration Number: 139 87 31692